UCSF

25th ANNUAL

MANAGEMENT OF THE HOSPITALIZED PATIENT

Hyatt Regency San Francisco • San Francisco, CA

Thursday - Saturday

October 21-23, 2021

Praise from past attendees...

"The best conference ever! By far!!!"

COURSE CHAIR
Robert M. Wachter, MD
Professor and Chair, Department of Medicine
University of California, San Francisco

2021

REMOTE LEARNING OPTIONS AVAILABLE

shm
Society of Hospital Medicine

The course that started it all returns for its 25th year! This course serves as the West Coast Regional Meeting of the Society of Hospital Medicine.

Table of Contents

Friday, October 22, 2021

Saturday, October 23, 2021

Presented by the Division of Hospital Medicine • Department of Medicine •
University of California, San Francisco

25th Annual Management of the Hospitalized Patient

October 21 - 23, 2021

Course Chair
Robert M. Wachter, MD
Professor and Chair, Department of Medicine
University of California, San Francisco

Exhibitors

Alexion

Astellas

AstraZeneca

Baylor Scott & White Health

Boehringer Ingelheim

Genentech

Janssen

Theravance

UCSF University of California, San Francisco School of Medicine

25th Annual
Management of the Hospitalized Patient

We are thrilled that you're joining us for the Management of the Hospitalized Patient CME course

Overview

This course, chaired by Dr. Robert Wachter, covers the clinical issues most relevant to hospitalists and other clinicians who care for inpatients. Taught by UCSF's top teachers and selected guest faculty, the course – now in its 25th year – highlights recent advances and current controversies. To promote active learning, the course uses a mobile audience response system and features multiple workshops in a variety of disciplines to allow for small group discussions. The course will be offered both in-person and virtually.

The course includes broad content in critical care, perioperative care, patient safety, hospital neurology, cardiology, GI, hematology, oncology, nephrology, and infectious diseases (including Covid).

This course is presented by the UCSF Division of Hospital Medicine and is sponsored by the Office of Continuing Medical Education, University of California, San Francisco School of Medicine. It also serves as the West Coast regional meeting of the Society of Hospital Medicine.

Educational Objectives

An attendee completing the Management of the Hospitalized Patient course should be able to:

- Improve diagnosis of common inpatient clinical presentations;
- Perform an evidence-based work-up for common inpatient clinical presentations;
- Apply modern therapeutic approaches to common inpatient disorders;
- More effectively respond to patients questions in hospital medicine using the latest clinical literature.

ACCREDITATION

The University of California, San Francisco School of Medicine (UCSF) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

UCSF designates this educational activity for a maximum of **18.50** AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity meets the requirements under California Assembly Bill 1195, continuing education and cultural and linguistic competency.

Geriatric Medicine:
The approved credits shown above include **2.50** Geriatric Credits toward meeting the requirement under California Assembly Bill 1820, Geriatric Medicine.

ABIM Maintenance of Certification Points:
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to **18.50** MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Family Physicians:
The AAFP has reviewed 25th Annual Management of the Hospitalized Patient and deemed it acceptable for up to **18.50** In-Person, Live (could include online) AAFP Prescribed credit. Term of Approval is from 10/21/2021 to 10/23/2021. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses:
For the purpose of recertification, the American Nurses Credentialing Center accepts AMA PRA Category 1 Credit TM issued by organizations accredited by the ACCME.

Pharmacotherapeutics CEUs for Nurses:
This activity is designated for a maximum of **2.50** pharmacotherapeutic credits towards meeting the requirement for nursing pharmacology continuing education. Nurses should claim 0.1 CEUs for each contact hour of participation in designated pharmacotherapeutic continuing education.

Pharmacists:
The California Board of Pharmacy accepts as continuing professional education those courses that meet the standard of relevance to pharmacy practice and have been approved for AMA PRA Category 1 Credit™.

Physician Assistants
AAPA accepts category 1 credit from AOACCME, Prescribed credit from AAFP, and AMA PRA Category 1 credit™ for organizations accredited by the ACCME.

GENERAL INFORMATION

ATTENDANCE VERIFICATION

Please remember to sign-in on the sign-in sheet when you check in on your first day at the UCSF Registration Desk, located in the Market Street Foyer on the Street Level. *You only need to sign-in once for the course, when you first check in.*

Those attending virtually will be verified upon logging into the Live Stream.

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EVALUATIONS / CREDITS / MOC

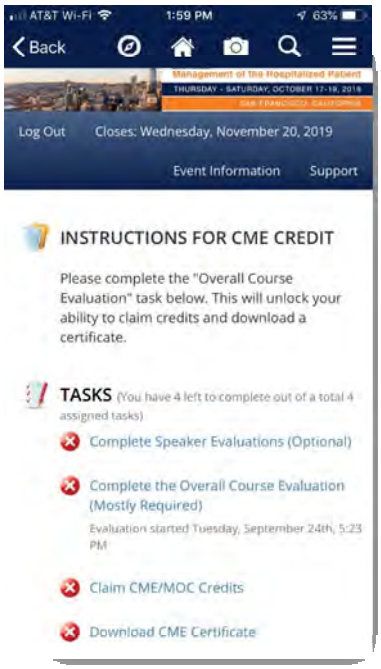
Visit the MHP Evaluation Site to do all of these things!

Tap the **Evaluation** tile from the app's home screen. OR
Visit https://tinyurl.com/MHP21Eval from a web browser.

If asked to login, use the email address and access key you used for the app. *If you didn't use the mobile app, click the **Create Account** button.*

Select a "Task" to complete it:

- ✓ Speaker Evaluations
- ✓ Course Evaluation (required for credit)
- ✓ Claim CME / MOC
- ✓ Download Certificate
  - Print it
  - Save it as a PDF
  - Email it



CONTINENTAL BREAKFAST AND COFFEE BREAKS

Breakfasts and coffee breaks provided for the registered attendees will be served in the Grand Ballroom Foyer on the Street Level along with the exhibits and have been ordered according to registration numbers. You name badge will be required to access the exhibitor and meal service area. Guests and travel companions are not permitted.

LUNCH

Lunch is on your own on Thursday 10/21. A list of are restaurants is provided in the MHP2021 app along with a map.

On Friday 10/22, a boxed lunch will be provided. If you have any dietary restrictions that you did not list when you registered, please be sure to let us know as soon as possible so we may prepare accordingly. We will have vegetarian as well as a limited number of vegan and vegan/gluten-free options available. You will have 30 minutes (12:10PM- 12:40PM) to collect your boxed lunch before the start of the small group workshop sessions.

COURSE RECEPTION

On Thursday 10/21, we will host the course reception on the east end of the Atrium Lobby located on the Lobby Level and is for registered attendees only. Please make sure to wear your course name badge.

Due to San Francisco Vaccine Verification protocols, we are not able to accommodate guests this year.

GENERAL SESSION

The general session will take place in the Grand Ballroom. We will provide a warning bell during breakfasts and coffee breaks to allow you ample time to re-enter the room before the course reconvenes.

Federal and State Law
Regarding Linguistic Access and Services for Limited English Proficient Persons

I. Purpose.

This document is intended to satisfy the requirements set forth in California Business and Professions code 2190.1. California law requires physicians to obtain training in cultural and linguistic competency as part of their continuing medical education programs. This document and the attachments are intended to provide physicians with an overview of federal and state laws regarding linguistic access and services for limited English proficient ("LEP") persons. Other federal and state laws not reviewed below also may govern the manner in which physicians and healthcare providers render services for disabled, hearing impaired or other protected categories

II. Federal Law – Federal Civil Rights Act of 1964, Executive Order 13166, August 11, 2000, and Department of Health and Human Services ("HHS") Regulations and LEP Guidance.

The Federal Civil Rights Act of 1964, as amended, and HHS regulations require recipients of federal financial assistance ("Recipients") to take reasonable steps to ensure that LEP persons have meaningful access to federally funded programs and services. Failure to provide LEP individuals with access to federally funded programs and services may constitute national origin discrimination, which may be remedied by federal agency enforcement action. Recipients may include physicians, hospitals, universities and academic medical centers who receive grants, training, equipment, surplus property and other assistance from the federal government.

HHS recently issued revised guidance documents for Recipients to ensure that they understand their obligations to provide language assistance services to LEP persons. A copy of HHS's summary document entitled "Guidance for Federal Financial Assistance Recipients Regarding Title VI and the Prohibition Against National Origin Discrimination Affecting Limited English Proficient Persons – Summary" is available at HHS's website at: http://www.hhs.gov/ocr/lep/ .

As noted above, Recipients generally must provide meaningful access to their programs and services for LEP persons. The rule, however, is a flexible one and HHS recognizes that "reasonable steps" may differ depending on the Recipient's size and scope of services. HHS advised that Recipients, in designing an LEP program, should conduct an individualized assessment balancing four factors, including: (i) the number or proportion of LEP persons eligible to be served or likely to be encountered by the Recipient; (ii) the frequency with which LEP individuals come into contact with the Recipient's program; (iii) the nature and importance of the program, activity or service provided by the Recipient to its beneficiaries; and (iv) the resources available to the Recipient and the costs of interpreting and translation services.

Based on the Recipient's analysis, the Recipient should then design an LEP plan based on five recommended steps, including: (i) identifying LEP individuals who may need assistance; (ii) identifying language assistance measures; (iii) training staff; (iv) providing notice to LEP persons; and (v) monitoring and updating the LEP plan.

A Recipient's LEP plan likely will include translating vital documents and providing either on-site interpreters or telephone interpreter services, or using shared interpreting services with other Recipients. Recipients may take other reasonable steps depending on the emergent or non-emergent needs of the LEP individual, such as hiring bilingual staff who are competent in the skills required for medical translation, hiring staff interpreters, or contracting with outside public or private agencies that provide interpreter services. HHS's guidance provides detailed examples of the mix of services that a Recipient should consider and implement.
HHS's guidance also establishes a "safe harbor" that Recipients may elect to follow when determining whether vital documents must be translated into other languages. Compliance with the safe harbor will be strong evidence that the Recipient has satisfied its written translation obligations.

In addition to reviewing HHS guidance documents, Recipients may contact HHS's Office for Civil Rights for technical assistance in establishing a reasonable LEP plan.

III. California Law – Dymally-Alatorre Bilingual Services Act.

The California legislature enacted the California's Dymally-Alatorre Bilingual Services Act (Govt. Code 7290 *et seq.*) in order to ensure that California residents would appropriately receive services from public agencies regardless of the person's English language skills. California Government Code section 7291 recites this legislative intent as follows:

> "The Legislature hereby finds and declares that the effective maintenance and development of a free and democratic society depends on the right and ability of its citizens and residents to communicate with their government and the right and ability of the government to communicate with them.
>
> The Legislature further finds and declares that substantial numbers of persons who live, work and pay taxes in this state are unable, either because they do not speak or write English at all, or because their primary language is other than English, effectively to communicate with their government. The Legislature further finds and declares that state and local agency employees frequently are unable to communicate with persons requiring their services because of this language barrier. As a consequence, substantial numbers of persons presently are being denied rights and benefits to which they would otherwise be entitled.
>
> It is the intention of the Legislature in enacting this chapter to provide for effective communication between all levels of government in this state and the people of this state who are precluded from utilizing public services because of language barriers."

The Act generally requires state and local public agencies to provide interpreter and written document translation services in a manner that will ensure that LEP individuals have access to important government services. Agencies may employ bilingual staff, and translate documents into additional languages representing the clientele served by the agency. Public agencies also must conduct a needs assessment survey every two years documenting the items listed in Government Code section 7299.4, and develop an implementation plan every year that documents compliance with the Act. You may access a copy of this law at the following url: http://www.spb.ca.gov/bilingual/dymallyact.htm

FACULTY LIST

Course Chair

Robert M. Wachter, MD
Professor and Chair, Department of Medicine
University of California, San Francisco

Visiting Faculty

Linda DeCherrie, MD
Professor of Geriatrics and Palliative Medicine; Associate Professor of Medicine, General Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Course Faculty (University of California, San Francisco, School of Medicine)

Jennifer Babik, MD, PhD
Associate Professor of Medicine, Division of Infectious Diseases; Associate Program Director, Internal Medicine Residency

Danielle Brandman, MD, MAS
Associate Professor of Clinical Medicine; Program Director, Transplant Hepatology Fellowship, Division of Gastroenterology/Liver Transplant

Sam Brondfield, MD, MA
Assistant Professor of Medicine, Division of Hematology/Oncology

H. Quinny Cheng, MD
Professor of Medicine; Medical Director, Medicine Consultation Service and Neurosurgery Co-Management Service

Gurpreet Dhaliwal, MD
Professor of Medicine, Medicine Clerkship Site Director, San Francisco VA Health Care System

Vanja Douglas, MD
Associate Professor of Neurology; Sara & Evan Williams Foundation Endowed Neurohospitalist Chair

Brett M. Elicker, MD
Professor of Radiology & Biomedical Imaging; Chief, Cardiac & Pulmonary Imaging

Monica Gandhi, MD, MPH
Professor of Medicine; Associate Division Chief, Division of HIV, Infectious Diseases, and Global Medicine, UCSF/San Francisco General Hospital; Director of the UCSF Center for AIDS Research; Medical Director, HIV Clinic at SFGH

Sarah Goglin, MD
Assistant Professor of Medicine, Department of Rheumatology

Antonio Gomez, MD
Associate Professor of Medicine

Trevor Jensen, MD, MS
Assistant Professor of Medicine, Division of Hospital Medicine

S. Andrew Josephson, MD
Carmen Castro Franceschi and Gladyne K. Mitchell Neurohospitalist Distinguished Professor and Chair, Department of Neurology

Course Faculty (University of California, San Francisco, School of Medicine)

Lowell Lo, MD
Assistant Professor of Medicine, Division of Nephrology

Gregory M. Marcus, MD
Professor of Medicine, Division of Cardiology

Marlene Martin, MD
Associate Professor of Medicine, Division of Hospital Medicine

Tracy Minichiello, MD
Professor of Medicine; Chief, Anticoagulation and Thrombosis Service,
San Francisco VA Health Care System

Bradley Monash, MD
Associate Professor of Medicine and of Pediatrics; Chief of Medicine Service

Craig Munroe, MD
Associate Professor of Medicine, Division of Gastroenterology; Associate Chief for Clinical Innovation

Erika Price, MD, MPH
Associate Clinical Professor
VA Medicine Home, Hospital Medicine, Hospital Medicine VA

George Rutherford, III, MD
Professor of Epidemiology & Biostatistics
Director, Prevention and Public Health

Lekshmi Santhosh, MD
Assistant Professor of Pulmonary and Critical Care Medicine

Anne Schafer, MD
Associate Professor of Medicine and of Epidemiology & Biostatistics;
Chief of Endocrinology and Metabolism, San Francisco VA Health Care System

Bradley A. Sharpe, MD
Professor of Medicine; Chief, Division of Hospital Medicine

Krishan Soni, MD, MBA, FACC
Assistant Professor, Division of Cardiology

DISCLOSURES

The following faculty speakers, moderators, and planning committee members have disclosed they have no financial interest/arrangement or affiliation with any commercial companies who have provided products or services relating to their presentation(s) or commercial support for this continuing medical education activity:

Jennifer Babik, MD, PhD
H. Quinny Cheng, MD
Linda DeCherrie, MD
Gurpreet Dhaliwal, MD
Vanja Douglas, MD
Brett M. Elicker, MD
Monica Gandhi, MD, MPH
Sarah Goglin, MD
Antonio Gomez, MD
S. Andrew Josephson, MD
Lowell Lo, MD
Marlene Martin, MD
Tracy Minichiello, MD
Bradley Monash, MD
Craig Munroe, MD
Erika Price, MD, MPH
George Rutherford, III, MD
Lekshmi Santhosh, MD
Bradley A. Sharpe, MD
Krishan Soni, MD

The following faculty speakers have disclosed a financial interest/arrangement or affiliation with a commercial company who has provided products or services relating to their presentation(s) or commercial support for this continuing medical education activity. All conflicts of interest have been resolved in accordance with the ACCME Standards for Commercial Support:

Danielle Brandman, MD, MAS	Allergan Gilead Genentech Grifols NGM	Grant/Research Support Grant/Research Support Grant/Research Support Grant/Research Support Grant/Research Support
Sam Brondfield, MD, MA	Doximity PAI Pharmaceuticals Blackstone Gemini Health IDEO American Physician Institute	Honorarium Recipient Consultant Consultant Consultant Consultant Consultant
Trevor Jensen, MD	Caption Health	Consultant
Gregory M. Marcus, MD	Johnson & Johnson InCarda Baylis Medical	Advisor/Reviewer Consultant Stock Shareholder (excluding mutual funds) Grant/Research Support
Anne Schafer, MD	Amgen	Grant/Research Support
Robert M. Wachter, MD	Curai EarlySense	Consultant Consultant

This UCSF CME educational activity was planned and developed to uphold academic standards to ensure balance, independence, objectivity, and scientific rigor; adhere to requirements to protect health information under the Health Insurance Portability and Accountability Act of 1996 (HIPAA); and, include a mechanism to inform learners when unapproved or unlabeled uses of therapeutic products or agents are discussed or referenced.

This activity has been reviewed and approved by members of the UCSF CME Governing Board in accordance with UCSF CME accreditation policies. Office of CME staff, planners, reviewers, and all others in control of content have disclosed no relevant financial relationships.

COURSE PROGRAM

Thursday, October 21, 2021

7:00 AM		*Registration and Continental Breakfast*	
8:00		**Welcome and Overview**	Robert M. Wachter, MD
8:10	**Rx**	**Diagnosis and Management of VTE in the Hospitalized Patient**	Tracy Minichiello, MD
9:00		**Update on Clinical Manifestations and Inpatient Management of Covid-19**	Jennifer Babik, MD, PhD
9:50		*Break*	
10:15	**GRx**	**Managing Anticoagulation in the Hospitalized Patients**	Tracy Minichiello, MD
11:10	**GRx**	**Update in Diagnosis and Management of Stroke**	S. Andrew Josephson, MD
12:00 PM		*Lunch Break*	
1:30		**Small Group Workshops: Session I**	
		1. The Neurological Exam	S. Andrew Josephson, MD
		2. Tough Cases in the Hospitalized Patient with Liver Disease	Danielle Brandman, MD, MAS
		3. Thromboembolism Q&A: Cases and Controversies	Tracy Minichiello, MD Erika Price, MD, MPH
		4. Tough Cases in Inpatient Pulmonary Medicine	Lekshmi Santhosh, MD
		5. Common Hospital Consults in Infectious Disease	Jennifer Babik, MD, PhD
		6. Caring for the Hospitalized Patient with Addictions	Marlene Martin, MD
		7. Meet the Professor	Robert M. Wachter, MD
2:50		*Break*	
3:15		**ICU Management Pearls for the Hospitalist**	Lekshmi Santhosh, MD
4:10		**Setting Up a Successful Hospital at Home Program**	Linda DeCherrie, MD
5:00 PM		*Adjourn*	

P = Pain Credit **G** = Geriatric Credit

Rx = Meets Requirements for Pharmacotherapeutics CEUs for NPs/Nurses

Friday, October 22, 2021

7:00 AM	*Continental Breakfast*	
8:00	**Clinical Problem-Solving Exercise**	Gurpreet Dhaliwal, MD
9:00	**Covid-19: Update on Vaccines and Variants**	Monica Gandhi, MD, MPH
9:55	*Break*	
10:20	**The State of the Covid-19 Pandemic**	George Rutherford, MD
11:15	**Advances in Interventional Endoscopy**	Craig Munroe, MD
12:10 PM	*Lunch Break*	
12:40	**Small Group Workshops: Session II**	
	8. The Neurological Exam (repeat)	Vanja Douglas, MD
	9. Radiology Refresher: Chest Imaging	Brett M. Elicker, MD
	10. Fundamentals of Preoperative Evaluation	H. Quinny Cheng, MD
	11. Interesting Cases in Hospital Rheumatology	Sarah Goglin, MD
	12. Bedside Ultrasound for Diagnosis	Trevor Jensen, MD, MS
	13. The Art of Diagnostic Reasoning: An Interactive Case	Gurpreet Dhaliwal, MD
2:00	*Session Break- Transition to Next Workshop*	
2:10	**Small Group Workshops: Session III**	
	14. The Neurological Exam (repeat #2)	Vanja Douglas, MD
	15. Radiology Refresher: Chest Imaging (repeat)	Brett M. Elicker, MD
	16. Thromboembolism Q&A: Cases and Controversies (repeat)	Tracy Minichiello, MD Erika Price, MD, MPH
	17. Tough Cases in Medical Consultation	H. Quinny Cheng, MD
	18. Bedside Ultrasound for Diagnosis (repeat)	Trevor Jensen, MD, MS
	19. Management of COVID-19 Patients in the ICU	Antonio Gomez, MD
	20. Diagnosis and Management of Acute Kidney Injury	Lowell Lo, MD
3:30	*Break*	
3:50	**Current Controversies in Medical Consultation**	H. Quinny Cheng, MD
4:40	**Cardiology Pearls for the Hospitalist**	Krishan Soni, MD
5:30 PM	*Adjourn*	

P = Pain Credit **G =** Geriatric Credit

Rx = Meets Requirements for Pharmacotherapeutics CEUs for NPs/Nurses

Saturday, October 23, 2021

7:00 AM		*Continental Breakfast*	
8:00		**How Has the Pandemic Changed Healthcare?**	Robert M. Wachter, MD
8:50		**Neurological Emergencies**	S. Andrew Josephson, MD
9:45	G	**Key Arrhythmia Topics for Hospitalists**	Gregory M. Marcus, MD
10:30		*Break*	
10:50		**Oncologic Emergencies in Hospital Medicine**	Sam Brondfield, MD
11:35		**The Year in Review in Hospital Medicine**	Bradley A. Sharpe, MD Bradley Monash, MD
12:20 PM		*Adjourn*	

P = Pain Credit **G =** Geriatric Credit

Rx = Meets Requirements for Pharmacotherapeutics CEUs for NPs/Nurses

Diagnosis and Management of VTE in the Hospitalized Patient

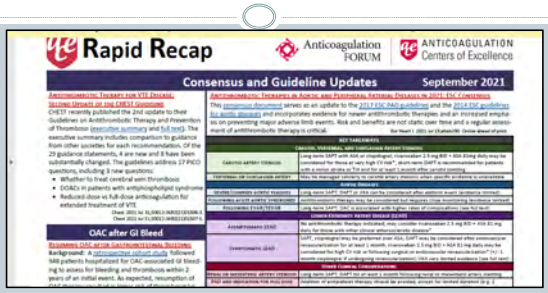
Tracy Minichiello, MD
Professor of Medicine
University of California, San Francisco
Chief, Anticoagulation and Thrombosis Services
San Francisco, VA Medical Center

Conflicts of Interest

- I have no actual or potential conflicts of interest in relation to this program or presentation to disclose.

AC FORUM Literature Updates & Rapid Resources

https://acforum-excellence.org/



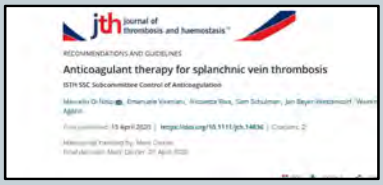
Objectives

- Splanchnic vein thrombosis
- Calf vein thrombosis
- Outpatient management of PE
- DOACs for VTE in obesity
- Management of anticoagulation in recurrent VTE

A 62 year old man with **cirrhosis** and history of alcohol use presents with abdominal pain. On exam vitals are stable but abdomen is tender in right upper quadrant. Labs are significant for **PLT count of 105K**, creatinine 0.8, AST/ALT: 60/30 normal bili, INR 1.0. ultrasound of RUQ shows thrombosis in left and right portal veins. **What anticoagulation regimen do you recommend?**

1) None-we always see portal vein thrombosis in cirrhosis
2) DOAC
3) LMWH
4) LMWH→warfarin
5) I really don't like any of these options

Anticoagulation for splanchnic thrombosis



Di Nisio et al. JTN 2020 https://doi.org/10.1111/jth.14836

Splanchnic Vein Thrombosis

Table 1 Risk Factors For Splanchnic Vein Thrombosis

Risk Factors For SVT		
Persistent Acquired Risk Factors	Transient Acquired Risk Factors	Inherited Risk Factors
Liver cirrhosis	Intra-abdominal Inflammations/Infections	Factor V Leiden mutation
Solid cancer	Abdominal surgery	Prothrombin G20210A mutation
Myeloproliferative neoplasm	Hormonal therapy	JAK2V617F mutation
Inflammatory bowel disease	Pregnancy or puerperium	Protein C deficiency
Antiphospholipid syndrome		Protein S deficiency
Other hematologic disease (e.g. PNH)		Antithrombin deficiency
Autoimmune disease (e.g. Behçet's disease)		

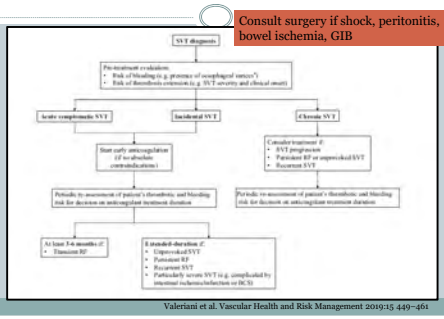
10 %

- 10 % of cirrhotic have PVT
- 10% of all splanchnic vein thrombosis cases have myeloproliferative disorder
- 10% of cancer associated splanchnic vein thrombosis is due to pancreatic CA
  - Up to 15% of those with "unprovoked" PVT are diagnosed with cancer in subsequent 1.5 years

Valeriani et al. Vascular Health and Risk Management 2019:15 449–461

Splanchnic Vein Thrombosis Management

Consult surgery if shock, peritonitis, bowel ischemia, GIB



Valeriani et al. Vascular Health and Risk Management 2019:15 449–461

Splanchnic Vein Thrombosis

WHO TO TREAT?

- Acute SVT
  - Goal is to prevent bowel ischemia and portal HTN
  - Consider GI eval prior to anticoagulation-particularly in chronic PVT due to varices, portal HTN GIB risk
- Chronic SVT
  - Goal is to prevent progression
  - Risk benefit less clear

Splanchnic Vein Thrombosis-Anticoagulation

HOW TO TREAT?

- Non cirrhotic SVT→ DOAC
- Cancer associated symptomatic SVT→LMWH or DOAC
  - Favor LMWH if high bled risk
- Cirrhotic→LMWH and then switch to DOAC or warfarin if able
- Above assumes not high bleed risk. If high bleed risk multidisciplinary discussion. Consider delay, low intensity AC, witholding

Di Nisio et al. JTN 2020 https://doi.org/10.1111/jth.14836

Case

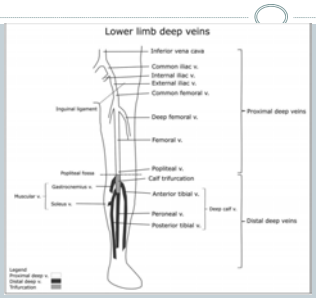
A 62 year old man with **cirrhosis** and history of alcohol use presents with abdominal pain. On exam vitals are stable but abdomen is tender in right upper quadrant. Labs are significant for **PLT count of 105K**, creatinine 0.8, AST/ALT: 60/30 normal bili, INR 1.0. ultrasound of RUQ shows thrombosis in left and right portal veins. **What anticoagulation regimen do you recommend?**

1) None-we always see portal vein thrombosis in cirrhosis
2) DOAC
3) LMWH
4) LMWH→warfarin
5) I really don't like any of these options

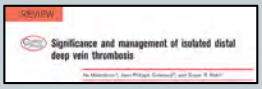
A 79-year-old man is diagnosed with a **posterior tibial vein DVT**. He is started on therapeutic anticoagulation but a week later he returns to ED with **upper gastrointestinal bleed**. EGD shows gastric ulcer. **Should anticoagulation be resumed on discharge?**

1) Yes, he had a DVT one week ago
2) No, let's just get a follow up ultrasound
3) I like these options even less than the last case

CALF VEIN DVT



Calf trifurcation:
the popliteal vein distal to the knee crease where it divides into the anterior tibial, posterior tibial and peroneal veins



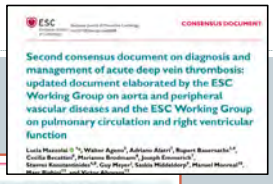
Makedonov et al CO-Hematology 2021

CALF VEIN DVT

- Calf trifurcation DVT (the popliteal vein distal to the knee crease, where it divides into the anterior tibial, posterior tibial and peroneal veins) like proximal DVTs, have annual recurrence risk of 4.7%
- Muscular DVTs (e.g. in the gastrocnemius and soleus veins) have a similar risk of recurrence to deep calf DVT (1.7% vs. 1.6% annual recurrence)
- Proximal DVTs tend to recur more commonly as proximal DVTs and distal DVTs tend to recur more commonly as IDDVT

Makedonov et al CO-Hematology 2021

CALF VEIN DVT



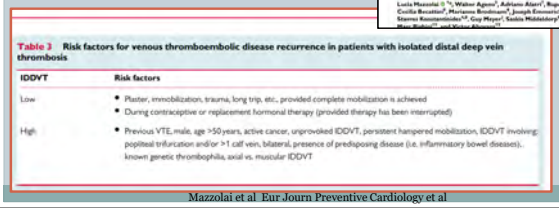


Table 3 Risk factors for venous thromboembolic disease recurrence in patients with isolated distal deep vein thrombosis

IDDVT	Risk factors
Low	• Plaster, immobilization, trauma, long trip, etc., provided complete mobilization is achieved • During contraceptive or replacement hormonal therapy (provided therapy has been interrupted)
High	• Previous VTE, male, age >50 years, active cancer, unprovoked IDDVT, persistent hampered mobilization, IDDVT involving popliteal trifurcation and/or >1 calf vein, bilateral, presence of predisposing disease (i.e. inflammatory bowel diseases), known genetic thrombophilia, axial vs. muscular IDDVT

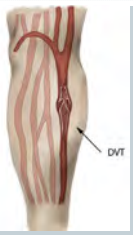
Mazzolai et al Eur Journ Preventive Cardiology et al

CALF VEIN DVT-CHEST 2016

Whether and How to Anticoagulate Isolated Distal DVT

13. In patients with acute isolated distal DVT of the leg and (i) without severe symptoms or risk factors for extension (see text), we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (Grade 2C) or (ii) with severe symptoms or risk factors for

extension (see text), we suggest anticoagulation over serial imaging of the deep veins (Grade 2C).



Risk factors for extension: d-dimer +, extensive thrombosis close to proximal veins; active cancer, prior VTE, inpatient

CHEST VTE GUIDELINES 2021: suggest serial u/s over anticoagulation (weak evidence) if no severe symptoms or risk factors for extension

Kearon et al. Chest. 2016;149(2):315-352.

CALF VEIN DVT

DVT	TREATMENT/DURATION
Cancer associated calf vein DVT	Full dose anticoagulation at least 3 months and continue while cancer active
Unprovoked calf vein DVT	Full dose anticoagulation for 3 months
Provoked/transient risk factor calf vein DVT	Full dose anticoagulation for 6 weeks. May consider intermediate dose AC. Continue if risk factor still present
Trifurcation DVT	Treat with full dose anticoagulation, duration as with proximal DVT

If high risk of bleeding it is reasonable to withhold anticoagulation and do serial ultrasound (1 week and 2 weeks)

Makedonov et al CO-Hematology 2021, Stevens et all CHEST 2021 Mazzolai et al Eur Journ Preventive Cardiology et al

Case

A 79-year-old man is diagnosed with a **posterior tibial vein DVT.** He is started on therapeutic anticoagulation but a week later he returns to ED with **upper gastrointestinal bleed**. EGD shows gastric ulcer. **Should anticoagulation be resumed on discharge?**

1) Yes, he had a DVT one week ago
2) No, let's just get a follow up ultrasound
3) I like these options even less than the last case

A 65 year old man with HTN, **weight 130 kg,** presents with pleuritic chest pain. He is hemodynamically stable, O2 sat 95% on RA. CTPE shows segmental PE in RLL. Trop & BNP neg. PESI=O Hestia score NEGATIVE. **Should this patient be admitted?**

1) Yes, he has a PE
2) No, looks like he can head home

PESI & HESTIA RULE

Table 1 The simplified Pulmonary Embolism Severity Index

sPESI criteria	Points
Age >80 years	1
History of cancer	1
Chronic cardiopulmonary disease	1
Systolic blood pressure <100 mmHg	1
Heart rate ≥110 b.p.m.	1
Arterial oxygen saturation <90%	1

Table 2 The Hestia rule

Checklist questions of the Hestia rule

- Is the patient haemodynamically unstable?*
- Is thrombolysis or embolectomy necessary?
- Active bleeding or high risk of bleeding?*
- More than 24 h of oxygen supply to maintain oxygen saturation >90%?
- Is pulmonary embolism diagnosed during anticoagulant treatment?
- Severe pain needing intravenous pain medication for more than 24 h?
- Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?
- Does the patient have a creatinine clearance of <30 mL/min?
- Does the patient have severe liver impairment?*
- Is the patient pregnant?
- Does the patient have a documented history of heparin-induced thrombocytopenia?

HOME PE STUDY

Eur Heart J, ehab373, https://doi.org/10.1093/eurheartj/ehab373

HOME PE STUDY

- More than a third of PE patients were treated at home using either the Hestia rule or the sPESI, with a low 30-day rate of complicationsAll had timely follow-up/clear instructions for discharged patients.
- **All had timely follow-up/clear instructions for discharged patients .**This may have contributed to the low rate of complications.

Case

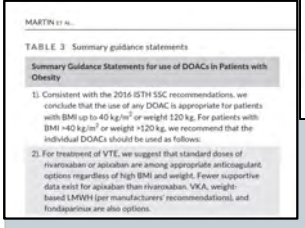
A 65 year old man with HTN, **weight 130 kg**, presents with pleuritic chest pain. He is hemodynamically stable, O2 sat 95% on RA. CTPE shows segmental PE in RLL. Trop & BNP neg. PESI=O Hestia score NEGATIVE. **Should this patient be admitted?**

"In patients with low risk PE we recommend outpatient treatment over hospitalization provided access to medication, ability to access outpatient care,and home circumstance are adequate (strong recommendation)"

A 65 year old man with HTN, **weight 130 kg**, presents with pleuritic chest pain. He is hemodynamically stable, O2 sat 95% on RA. CTPE shows segmental PE in RLL. Trop & BNP neg. PESI=O Hestia score NEGATIVE. **He will be sent home with close follow up with AC clinic** and his PCP. **What anticoagulation regimen do you recommend?**

1) LMWH→warfarin
2) Rivaroxaban
3) Apixaban
4) IV heparin→DOAC
5) Any of the above would work for me

DOACS in VTE & OBESITY



MARTIN ET AL.

TABLE 3 Summary guidance statements

Summary Guidance Statements for use of DOACs in Patients with Obesity
1). Consistent with the 2016 ISTH SSC recommendations, we conclude that the use of any DOAC is appropriate for patients with BMI up to 40 kg/m^2 or weight 120 kg. For patients with BMI >40 kg/m^2 or weight >120 kg, we recommend that the individual DOACs should be used as follows:
2). For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA, weight-based LMWH (per manufacturers' recommendations), and fondaparinux are also options.

jth

RECOMMENDATIONS AND GUIDELINES

Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation

Karlyn A. Martin | Jan Beyer-Westendorf | Bruce L. Davidson | Menno V. Huisman | Per Morten Sandset | Stephan Moll

DOAC levels not recommended
Avoid dabigatran/edoxaban due to
Use LMWH for 1st 4 weeks after bariatric surgery

Martin et al J Thromb Haemst 2021

DOACS in BARIATRIC SURGERY

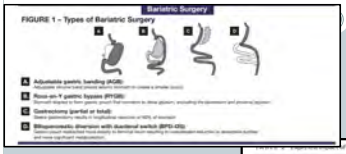
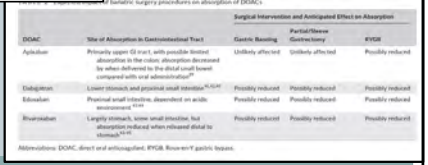


FIGURE 1 – Types of Bariatric Surgery

Bariatric Surgery

A Adjustable gastric banding (AGB)
B Roux-en-Y gastric bypass (RYGB)
C Gastrectomy (partial or total)
D Biliopancreatic diversion with duodenal switch (BPD-DS)



Surgical Intervention and Anticipated Effect on Absorption

DOAC	Site of Absorption in Gastrointestinal Tract	Gastric Banding	Partial/Sleeve Gastrectomy	RYGB
Apixaban	Primarily upper GI tract, with possible limited absorption in the colon; absorption decreased by when delivered to the distal small bowel compared with oral administration[39]	Unlikely affected	Unlikely affected	Possibly reduced
Dabigatran	Lower stomach and proximal small intestine[40,41,44]	Possibly reduced	Possibly reduced	Possibly reduced
Edoxaban	Proximal small intestine, dissolved on acidic environment[42,44]	Possibly reduced	Possibly reduced	Possibly reduced
Rivaroxaban	Largely stomach, some small intestine, but absorption reduced when released distal to stomach[43,45]	Possibly reduced	Possibly reduced	Possibly reduced

Abbreviations: DOAC, direct oral anticoagulant; RYGB, Roux-en-Y gastric bypass.

Martin et al J Thromb Haemst 2021

https://acforum-excellence.org/Resource-Center/resource_files/-2021-09-11-103024.pdf

DOACS in BARIATRIC SURGERY

6). We suggest not to use DOAC for treatment or prevention of VTE in the acute setting after bariatric surgery (because of concerns of decreased absorption), and instead, to initiate such patients on parenteral anticoagulation in the early postsurgical phase.

We suggest that switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability.

Martin et al J Thromb Haemst 2021

CASE

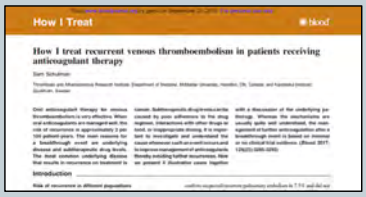
A 65 year old man with HTN, **weight 130 kg**, presents with pleuritic chest pain. He is hemodynamically stable, O2 sat 95% on RA. CTPE shows segmental PE in RLL. Trop & BNP neg. PESI=O Hestia score NEGATIVE. He will be sent home with close follow up with AC clinic and his PCP. **What anticoagulation regimen do you recommend?**

1) LMWH→warfarin
2) Rivaroxaban
3) Apixaban
4) IV heparin→DOAC
5) Any of the above would work for me

51 yo man with *diffuse b cell lymphoma* undergoing chemotherapy presents with LUEswelling. He has **PICC line** on that side. U/S **shows DVT in brachial→subclavian vein**. He is started on enoxaparin 1mg/kg BID. One week later he returns with increased LUE swelling and dilated venous pattern over shoulder and chest and pleuritic chest pain. CT shows **thrombosis up to brachiocephlic vein** and **<u>2 sub segmental pulmonary emboli</u>**. **What do you recommend?**

1) Pull PICC and continue dalteparin at current dose
2) Pull PICC and increase dalteparin dose
3) Pull PICC and switch to rivaroxaban

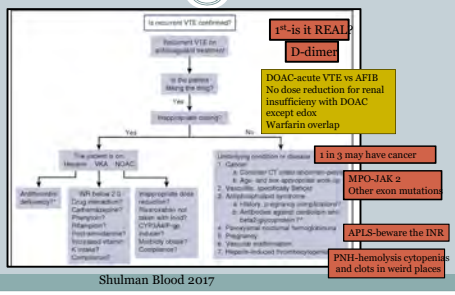
VTE Recurrence on Anticoagulation


How I Treat

How I treat recurrent venous thromboembolism in patients receiving anticoagulant therapy

Shulman Blood 2017

VTE Recurrence on Anticoagulation



Shulman Blood 2017

CHEST 2016:VTE Recurrence While on AC

Anticoagulant Therapy

***29. In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily** (Grade 2C).

***30. In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third** (Grade 2C).

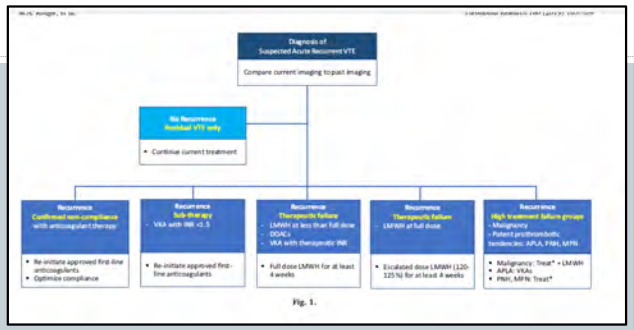


Fig. 1.

Rodgers et al Thrombosis Research 2019

Case

51 year old man with *diffuse b cell lymphoma* undergoing chemotherapy presents with left upper extremity swelling. He has **PICC line** on that side. u/s **shows DVT in brachial→subclavian vein**. He is started on dalteparin 200 IU/kg/day. One week later he returns with increased LUE swelling and dilated venous pattern over shoulder and chest as well as pleuritic chest pain. CT shows **thrombosis up to brachiocephlic vein** but not into SVC as well as 2 sub segmental pulmonary emboli. **What do you recommend?**

1) Pull PICC and continue dalteparin at current dose
2) Pull PICC and increase dalteparin dose
3) Pull PICC and switch to rivaroxaban

Case

65 year old man with **lung cancer** undergoing chemo presents with sudden onset chest pain and SOB. BP 130/80 HR 115, O2 sat 89%. He is found to have **bilateral lobar PE.** Trop and BNP are negative. U/S shows **DVT in right proximal femoral vein**. **What anticoagulant regimen do you start him on?**

1) DOAC-anyone will do
2) LMWH-this is 1st line in cancer associated thrombosis
3) IV heparin, I am thinking about thrombolysis
4) Are we done yet?

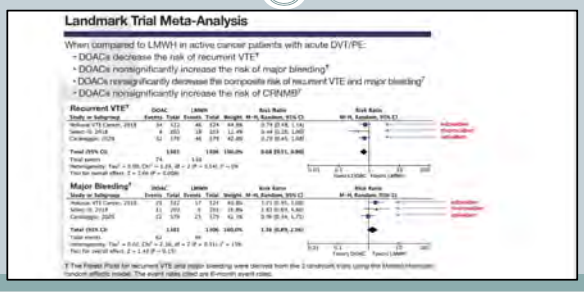
Anticoagulation for Cancer-Associated VTE

Guideline Recommendations

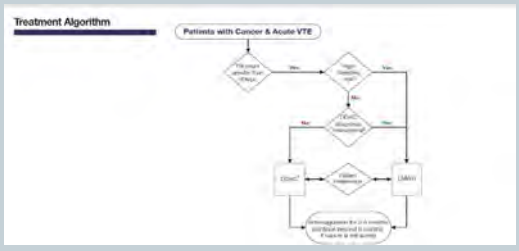
	2020 NCCN[1]	2020 ASCO[2,*]	2018 ISTH[3,*]
Acute VTE Treatment	DOAC (edoxaban, apixaban, and rivaroxaban) preferred for patients without gastric or gastroesophageal lesions	Initial anticoagulation (first 5-10 days): LMWH or rivaroxaban preferred Long-term (at least 6 months): LMWH, edoxaban or rivaroxaban preferred	DOACs (edoxaban and rivaroxaban) suggested for low risk of bleeding and no drug-drug interaction, LMWH suggested otherwise
GI/GU Cancer	LMWH preferred for patients with gastric or gastroesophageal lesions	There is an increase in major bleeding risk with DOACs, particularly observed in GI and potentially GU malignancies	LMWH suggested in patients with luminal GI cancers with an intact primary; patients at risk of bleeding from the GU tract, bladder, or nephrostomy tubes, or patients with active GI mucosal abnormalities

*The recommendations from ASCO and ISTH were made before apixaban was compared to LMWH

Anticoagulation for Cancer-Associated VTE



Anticoagulation for Cancer-Associated VTE



https://acforum-excellence.org/Resource-Center/resource_files/1638-2020-11-30-121425.pdf

Case

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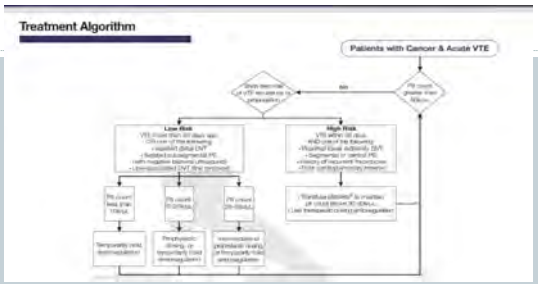
1) DOAC-any one will do
2) LMWH-this is 1st line in cancer associated thrombosis
3) Are we done yet?

Case

65 year old man with lung cancer undergoing chemo presents with sudden onset chest pain and SOB. BP 130/80 HR 115, O2 sat 91%. He is found to have bilateral lobar PE. Trop and BNP are negative. U/S shows DVT in right proximal femoral vein. **What anticoagulant regimen do you start him on if his PLT count is 50K?**



https://acforum-excellence.org/Resource-Center/resource_files/1638-2020-11-30-121425.pdf

Case

65 year old man with lung cancer undergoing chemo presents with sudden onset chest pain and SOB. BP 130/80 HR 115, O2 sat 91%. He is found to have bilateral lobar PE. Trop and BNP are negative. U/S shows DVT in right proximal femoral vein. **What anticoagulant regimen do you start him on if his PLT count is 50K?**

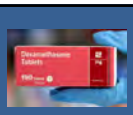
Objectives

- Splanchnic vein thrombosis
  - Timing dictates IF anticoag considered; explore etiology; DOACs reasonable in select patients
- Calf vein thrombosis
  - Low risk outpatients options include serial u/s, lower intensity, shorter period of time;For most hospitalized patients anticoagulation will be considered BUT know that serial u/s is option in very high bleeding risk patient, or perhaps lower intensity dosing
- Outpatient management of PE
- DOACs for VTE in obesity
  - Reasonable to use but when approaching BMI 50 we are in completely data free zone; always explore history of GI surgery/bariatric surgery-avoid use of DOACs first month post op at least and if used beyond that check trough level
- Management of anticoagulation in recurrent VTE
  - Make sure it is real. IF so ask why (patient factors, disease factors), situation dictates anticoagulation choice, maybe switching to DOAC, may be switching oral agents, maybe starting LMWH. THINK CANCER

Questions?

Tracy Minichiello, MD





Update on Clinical Manifestations and Inpatient Management of COVID-19

Management of the Hospitalized Patient
October 21, 2021

Jennifer Babik, MD, PhD
Associate Clinical Professor
Division of Infectious Diseases
University of California, San Francisco

Disclosures

- I have no disclosures.

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Learning Objectives

At the end of this lecture, you will be able to:

1. Recognize the diverse clinical manifestations of COVID
2. Identify the indications for COVID-specific and general diagnostic tests in patients admitted with COVID
3. Describe the evidence-based treatments for COVID

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Outline

- Clinical Manifestations
- Diagnostics
- Treatment

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Outline

- **Clinical Manifestations**
- Diagnostics
- Treatment

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Case #1

31 y/o man with no PMH admitted with fever, sore throat, conjunctival injection, N/V, and chest pain. Found to have elevated troponin (4.55), EF 25%, with course c/b cardiac arrest. Cardiac cath was negative. Chest CTA was negative. CRP was 327.

COVID PCR: initial test negative but repeat positive (Ct value 34)
COVID Ab: nucleocapsid Ab positive

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His Troponin Leak is Most Likely:

A. Cardiac injury from demand ischemia
B. Viral myocarditis
C. Pulmonary embolism
D. MIS-A

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Case Continued

He was thought to have fulminant myocarditis, possibly due to MIS-A given it seemed COVID infection may have been several weeks prior. He was treated with methylprednisone and IVIG. His cardiac function improved.

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Almost Every Organ System Can Be Affected

Neurologic: AMS, delirium, HA, stroke (rare), GBS (rare), encephalitis (rare)
Ocular: conjunctivitis (rare)
ENT: taste and/or smell disorders
Respiratory: cough, dyspnea > URI symptoms
Cardiac: arrhythmias, cardiac injury, myocarditis (rare)
Gastrointestinal: N/V, diarrhea
Renal: acute kidney injury, rhabdo (rare)
Hematologic: DVT/PE (?more common than other respiratory viruses)
Systemic: Fever, myalgias, fatigue, MIS-A (rare)
Dermatologic: rash (erythematous, urticarial, vesicular), ?COVID toes

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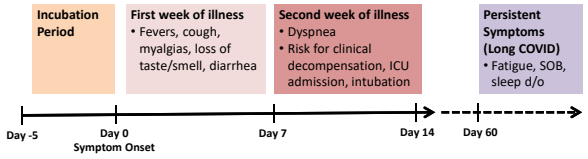
Clinical Course



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Multisystem Inflammatory Syndrome in Adults

Systematic review of 221 adults w/ MIS-A

- **Demographics**:
  - Median age 21, 70% M, 30% Latinx, 36% Black
  - 58% no underlying comorbidity
- **Clinical**
  - 68% prior (recovered) symptomatic COVID
  - Time from symptom onset to MIS-A = 28 days
  - *Systemic/Cardiac*: Fever 96%, hypotension 60%, cardiac dysfunction 54%, myocarditis 30%, SOB 52%
  - *GI/derm*: Diarrhea 52%, vomiting 44%, rash 38%, conjunctival injection 26%, mucocutaneous lesions 16%
- **Diagnostics**
  - Elevated CRP in 90%
  - (+) COVID Ab 40%, PCR 25%, both 32%
- **Treatment**
  - Steroids 74%, IVIG 55%, other immunomodulators 21%
  - 7% died

Think you have a case?
- CDC criteria for MIS-A: https://www.cdc.gov/mis/mis-a/hcp.html
- NIH Rx guidelines for MIS-C: IVIG+steroids first line, IL-1 antagonist if refractory
- Consult ID, peds ID, rheum, cards

Patel et al, JAMA Netw Open 2021, 4:e2126456.

Outline

- Clinical Manifestations
- **Diagnostics**
- Treatment

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Case #1 Revisited

31 y/o M with no PMH admitted with fever, sore throat, conjunctivitis, N/V, and chest pain. Found to have elevated troponin (4.55), EF 25%, with course c/b cardiac arrest. Cardiac cath was negative. Chest CTA was negative.

COVID PCR: initial test negative but repeat positive (Ct value 34)

COVID Ab: nucleocapsid Ab positive

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What Does a High Cycle Threshold Value Mean?

1. High Viral Load
2. Low Viral Load
3. Does Not Correlate with Viral Load

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Nucleocapsid Antibody Should Be Positive in:

1. Prior Natural Infection
2. Prior Vaccination
3. Both

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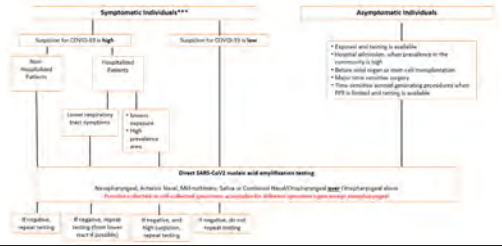
Molecular Testing Algorithm in IDSA Guidelines



Hanson et al, IDSA Guidelines on the Diagnosis of COVID-19: Molecular Testing, 12/2020.

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Molecular Testing: Highlights of IDSA Guidelines

- Avoid use of OP swab alone
- Patient collected samples acceptable unless NP swab
- Obtain an upper tract sample first → if negative and high suspicion, collect a lower tract sample
- Obtain repeat testing if initial test is negative only in patients where there is high suspicion

Hanson et al, IDSA Guidelines on the Diagnosis of COVID-19: Molecular Testing, 12/2020.

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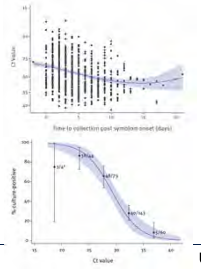
Primer on Cycle Threshold (Ct) Vaues

Ct value in PCR = number of amplification cycles required to amplify the target gene past a threshold level

In general, high Ct value = low viral load = less likely to be infectious = longer time from symptom onset

Beware: sampling technique can affect Ct value



Singanayagam et al, Euro Surveillance 2020.

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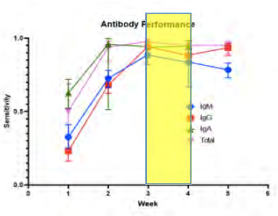
Serology: Timing of the Ab Response In Infection



- Abs become detectable in most patients >14d after symptom onset
- IDSA recommends against using Abs to diagnose COVID in first 2 weeks given risk of false (-)
- Note that IgM and IgG rise at the same time

Key point: Serology may have an adjunct role in diagnosis when suspicion is high and molecular tests are negative - optimal timing is 3-4 weeks after infection

Hanson et al, IDSA Guidelines on the Diagnosis of COVID-19: Serologic Testing, 8/2020.

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Serology Test Indications

1. To evaluate for COVID in patients where there is high suspicion but molecular testing is repeatedly negative (optimal timing 3-4 weeks after onset)
2. For assessment of MIS-C or MIS-A
3. Epidemiologic surveillance
4. To assess for vaccination response?

Hanson et al, IDSA Guidelines on the Diagnosis of COVID-19: Serologic Testing, 8/2020.

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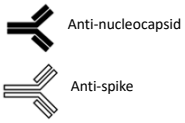
Nucleocapsid vs Spike Antibodies

Natural infection



Vaccine induced antibodies

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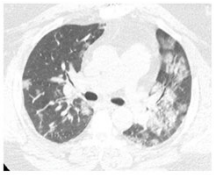
Case #2

65 y/o woman with asthma presents with 1 week of shortness of breath and is found to be hypoxic requiring 4L. She is COVID positive and admitted. What diagnostic testing does she need?



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What labs should you order?

A. Basic labs only (CBC, BMP, LFTs, coags)

B. Basic labs and CRP

C. Basic labs and CRP, D-dimer, ferritin, fibrinogen

D. #3 and trend q72 hours

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What Labs to Order in a COVID (+) Inpatient?

- **Initial Labs:**
  - All patients: CBC with diff, BMP, LFTs, coags
  - *Consider*: procalcitonin, troponin, BNP, lactate
  - *Consider* to estimate risk for severe disease: D-dimer, CRP, LDH, CK
- **Monitoring**
  - CBC with diff and BMP per usual practice
  - Trent LFTs at least q48h if abnormal at baseline or on remdesivir

UCSF

Other Microbiology Testing

- **Respiratory viral testing?**
  - Send during flu season (declared by infection control/hospital leadership based on Bay Area flu incidence – currently NOT in flu season)
  - Note, most studies show <6% viral coinfection at presentation
- **Blood cultures and sputum culture?**
  - If considering bacterial coinfection or starting antibiotics
  - Note, most studies show <1-3% bacterial coinfection at presentation
  - Secondary infections can occur (VAP, bloodstream infections, *Aspergillus*)
- **Send an HIV test if no recent testing**

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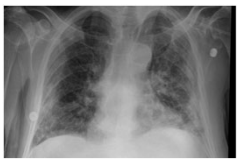
Imaging

- **All patients should have a baseline CXR**
- Chest CT not needed routinely but consider if there is concern for an additional process (e.g., PE, superimposed bacterial/fungal infection)



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Outline

- Clinical Manifestations
- Diagnostics
- **Treatment**

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Treatment Resources

****UCSF Health Internal Guidelines:**
https://infectioncontrol.ucsfmedicalcenter.org/coronavirus/clinical-guidance

****NIH Guidelines on Therapeutic Management of Adults with COVID**
https://www.covid19treatmentguidelines.nih.gov/management/therapeutic-management/

IDSA Guidelines on Treatment of Patients with COVID
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

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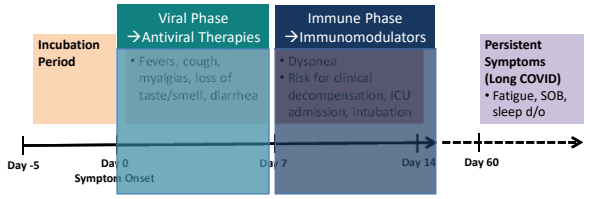
Clinical Course



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Treatment Overview in Hospitalized Patients

Antivirals
- Remdesivir

Immunomodulators
- Steroids
- Tocilizumab or Baricitinib

Antibodies
- Convalescent plasma
- Monoclonal Antibodies

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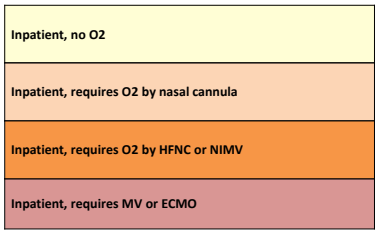
Treatment By Clinical Status



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Treatment Overview in Hospitalized Patients

Antivirals
- Remdesivir

Immunomodulators
- Steroids
- Tocilizumab or Baricitinib

Antibodies
- Convalescent plasma
- Monoclonal Antibodies

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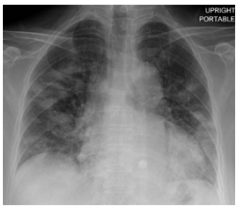
Case #3

39 y/o F with no PMH admitted with COVID pneumonia, requiring 2L O2.

She had been taking high doses of acetaminophen and is found to have AST 1250, ALT 1070. She also has AKI with a Cr of 3.5 (normal baseline).



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Would You Give Her Remdesivir?

A. Yes

B. No, she is not on enough O2

C. No, because of her LFTs

D. No, because of her AKI

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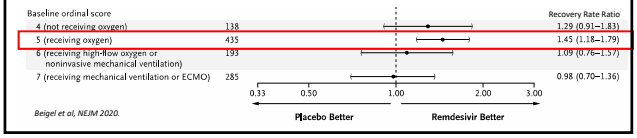
ACTT-1: Most RDV Benefit if only Supplemental O2?

- RCT of 1062 patients w/severe COVID (SaO2≤94%, CXR infiltrates, or on O2)
- RDV vs placebo x 10d
- Shortened recovery time from 15 to 10d (p<0.001)
- Benefit greatest if on supplemental O2 only - ? b/c this was largest group (confidence intervals wide in smaller groups) or b/c intubated patients require longer f/u



Beigel et al, NEJM 2020.

Remdesivir: Summary of Data/Guidelines

Disease Category	Clinical Benefit	Mortality Benefit	NIH Guidelines	UCSF Guidelines
Inpatient, no O2	May have modest benefit	None	Insufficient data to recommend for or against	Use in patients at high risk for progression or with radiographic e/o LRTI
Inpatient, requires O2 by nasal cannula	↓ time to recovery	Possible mortality benefit	Recommend use	Give remdesivir
Inpatient, requires O2 by HFNC or NIMV	No clear benefit	None	Recommend only with dex (not monotherapy)	Give remdesivir
Inpatient, requires MV or ECMO	No clear benefit	None	Recommend against use	Give remdesivir

Remdesivir: How to Use

Administration:

- 200mg IV x 1 then 100mg IV q24h for 4 additional days
- Do not need to stay inpatient to finish if otherwise ready for discharge
- May consider 10d course if not improving at 5d (usually HFNC, ICU)
- Watch for elevated ALT/AST (discontinue if > 5-10 times ULN)

Renal failure?

- Cyclodextrin vehicle can accumulate in renal failure but likely safe for short course
- Consider risk/benefit if CrCl<30 or HD/CRRT, but usually benefit > risk
- Dose adjustment not needed

UCSF

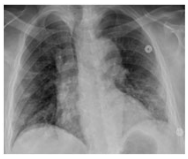
Treatment Overview in Hospitalized Patients

Antivirals	**Immunomodulators**	Antibodies
• Remdesivir	• Steroids • Tocilizumab • Baricitinib	• Convalescent plasma • Monoclonal Antibodies

UCSF

Case #4

92 y/o M with CAD, DM, dementia is admitted with COVID. He is satting 94% on 2L. Blood sugars are in the 300s. He is started on remdesivir.



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Would You Start Dexamethasone?

A. Yes

B. No

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Case Follow-Up

Steroids were initially held given he was on 2L and hyperglycemia, risk of delirium.

He then worsened to required 4L and steroids were started. Blood sugars went into the 400s-500s and steroids were held.

He recovered well and was eventually discharged.

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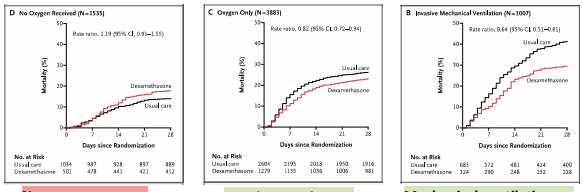
RECOVERY: Dexamethasone by Level of O2



No oxygen
Dex 17.8%
Usual care 14.0%

Supplemental O2
Dex 23.3%
Usual care 26.2%

Mechanical ventilation
Dex 29.3%
Usual care 41.4%

Recovery trial, NEJM 2020.

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Dexamethasone: Pooled Analysis/Guidelines

Disease Category	Mortality Benefit	NIH Guidelines	UCSF Guidelines
Inpatient, no O2	Trend towards harm	Recommend against	Do not give
Inpatient, requires O2 by nasal cannula	↓ mortality by 17% if on supplemental O2 (? level with most benefit)	Recommend use when patients require increasing amounts of O_2	Give dex when requiring >3-4L O2
Inpatient, requires O2 by HFNC or NIMV	↓ mortality by 17% if on supplemental O2 (? level with most benefit)	Recommend use	Give dex
Inpatient, requires MV or ECMO	↓ mortality by 34%	Recommend use	Give dex

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Dexamethasone: How to Use

- 6mg IV/PO x 10d or until hospital discharge, whichever comes first (PO preferred)
- If dexamethasone is unavailable, equivalent doses of other glucocorticoids may be used
- Factors to consider if you might withhold or stop steroids:
  - Uncontrolled invasive fungal infection
  - Uncontrolled hyperglycemia
  - Existing delirium
  - Active GI bleeding

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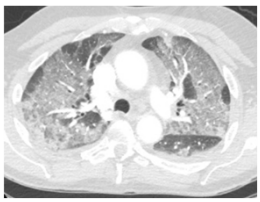
Case #5

71 y/o M with melanoma (not on chemo) admitted with COVID 2 days ago. On admission he was requiring 2-3L but has had rapid worsening since admission and is just now transferred to the ICU requiring 30L HFNC.



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What Treatments Would You Give?

A. Remdesivir, dexamethasone

B. Remdesivir, dexamethasone, baricitinib

C. Remdesivir, dexamethasone, tocilizumab

D. Remdesivir, dexamethasone, baricitinib, tocilizumab

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Tocilizumab (Anti-IL6R)

- Multiple smaller RCTs showed no mortality benefit
- The 2 largest RCTs (REMAP-CAP and RECOVERY) did show a mortality benefit
- May be due to differences in patient population or baseline steroid use
  - Benefit seen in sicker patients early in course with associated inflammatory response
  - Benefit seen in studies with high background steroid use

IDSA Guidelines on Treatment of Patients with COVID, Updated 6/3/2021. NIH Guidelines on Therapeutic Management of Adults with COVID, Updated 5/24/2021

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Tocilizumab: RCTs with Mortality Benefit

	Inclusion Criteria	Characteristics	Outcomes
RECOVERY (n=4116)	SaO2<92% RA or on O2 and CRP ≥ 75 mg/L	• 82% steroids • Median duration of hospitalization 2 days • 41% HFNC/NIMV, 14% MV	• Lower mortality - 29% toci vs 33% SOC (RR 0.86, CI 0.77-0.96) • Shorter time to d/c in toci group • 3 serious bacterial infections thought due to toci
REMAP-CAP (n=865)	Admitted to ICU within 24 hrs	• 90% steroids • Median duration of hospitalization 1.2d • 71 % HFNC/NIMV, 29% MV	• Lower mortality - 28% toci vs 36% SOC (OR 1.64, CI 1.14-2.35) • Shorter duration of organ support • 1 secondary bacterial infection in toci group

Abani et al, Lancet 2021. REMAP-CAP investigators, NEJM 2021.

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Baricitinib (JAK inhibitor): RCT Data

	Trial Design	Characteristics (note lack of data for MV)	Outcomes
ACTT-2 (n=1033)	RDV +bari vs RDV + placebo	• Only 12% got steroids • 14% RA, 55% supp O2, 21 % HFNC/NIMV, 11% MV	• Improved recovery 8 → 7d (most benefit if HFNC/NIMV), no difference in mortality • No increase in infections or VTE
COV-BARRIER (n=1525)	Bari v placebo - ↑CRP, LDH, ferritin, D-dimer	• 79% got steroids • 12% RA, 64% supp O2, 24% HFNC/NIMV • Excluded MV	• No diff in progression to HFNC/NIMV/MV • ↓ mortality by 38% overall (especially in HFNC/NIMV group) • No increase in infections or VTE
STOP-COVID (n=289)	Tofacitinib vs placebo - hospitalized <3d	• 89% got steroids • 25% RA, 63% supp O2, 13% HFNC • Excluded NIMV or MV	• ↓ risk death/resp failure 37% overall (in all baseline severity groups) • No increase in infections or VTE

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Tocilizumab and Baricitinib: Guidelines

Disease Category	NIH Guidelines	UCSF Guidelines
Inpatient, no O2	n/a	Do not give
Inpatient, requires O2 by nasal cannula	Insufficient evidence to clearly characterize subgroups who would benefit	Do not give
Inpatient, requires O2 by HFNC or NIMV	Recommend baricitinib or tocilizumab if recently hospitalized (eg <3d), rapidly increased O2, systemic inflammation	Baricitinib if recent hospitalization (eg 3-4d) and rapidly worsening
Inpatient, requires MV or ECMO	Recommend tocilizumab if within 24h of admission to the ICU	Tocilizumab if hospitalized <3d and in ICU <24h and rapidly progressing to MV or requiring MV

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Tocilizumab and Baricitinib: Notes

- Give one or the other, NOT both
- They should be given in combination with steroids
- If there are drug shortages, per NIH Guidelines can substitute tofacitinib (for baricitinib) or sarilumab (for tocilizumab)
- Consider screening for (or empirically treating for) Strongyloides before starting toci in patients from endemic areas
- Use with caution in immunocompromised patients (but we still usually give)
- Relatively contraindicated if a patient has a concomitant serious infection

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How to Give

Tocilizumab

- Tocilizumab 8mg/kg IV x 1 (based on actual body weight, max dose 800mg)
- Contraindicated if ANC < 500, platelets < 50, ALT > 5x ULN

Baricitinib

- Baricitinib 4 mg PO daily x 14d or until hospital d/c (whichever comes first)
- Renally dose if CrCl<60, contraindicated if CrCl<15
- Need to discontinue if ALC<200, ANC<500, or AST/ALT >10x ULN
- Give patient the EUA fact sheet (http://pi.lilly.com/eua/baricitinib-eua-factsheet-patient.pdf)

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Case #5: continued

Given ICU team's suspicion he would be intubated that evening, we gave tocilizumab x 1.

He was not actually intubated until several days later. He had a prolonged ICU stay with multiple complications and was eventually transitioned to comfort care.

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Treatment Overview in Hospitalized Patients

Antivirals	Immunomodulators	**Antibodies**
• Remdesivir	• Steroids • Tocilizumab • Baricitinib	• Convalescent plasma • Monoclonal Antibodies

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Convalescent Plasma

- **Data**:
  - Multiple RCTs, pooled analysis of 11 RCTs → no mortality benefit
  - One exception: Libster et al showed ↓risk progression if early, mild disease, high risk patient

- **Guidelines**
  - **NIH**: Recommends against
  - **UCSF**: <72h symptom onset + non-severe disease (~RA) + high risk for progression (criteria from Libster et al, rare to meet these in practice!)

IDSA Guidelines on Treatment of Patients with COVID, Updated 6/3/2021. NIH Guidelines on Therapeutic Management of Adults with COVID, Updated 5/27/2021. Libster et al, NEJM 2021. REMAP-CAP, JAMA 2021.

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Convalescent Plasma in Immunocompromised?

- **Data**
  - Little comparative data although in REMAP-CAP there was possible benefit (↑ organ support free days) in the subgroup of immunosuppressed patients (but only 6% of the trial)

- **Guidelines**
  - **NIH**: insufficient data to recommend for or against
  - **UCSF**: consider in patients with severe immunocompromise + not expected to mount Ab response

REMAP-CAP, JAMA 2021.

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Monoclonal Abs in Hospitalized Patients

- ACTIV-3 → no benefit of bamlanivimab in hospitalized patients
- Guidelines in hospitalized patients:
  - NIH: Monoclonal Abs not authorized for hospitalized patients unless patient is hospitalized for another reason and happens to have mild-mod COVID (e.g. admitted for hip fracture but then found to have midl-mod COVID)
- Recovery Trial (still in preprint):
  - Casirivimab/imdevimab combination reduced risk of death by 20% in hospitalized patients who were seronegative (24% vs 30%, RR 0.8, p=0.001)
  - Also led to shorter LOS and lower risk progression to MV/death
  - Stay tuned but not currently authorized for use in hospitalized patients

ACTIV-3 study group, NEJM 2020. Recovery Trial Group, MedRxiv, 2021.

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Molnupiravir

- Studied in <u>outpatients</u> with mild-moderate COVID with symptom onset <5 days → reduced risk of hospitalization or death by 50% (press release)
- EUA application filed with FDA → stay tuned

Mjolnir

Merck press release, October 1, 2021.

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Summary: NIH Treatment Guidelines

NIH Guidelines on Therapeutic Management of Adults with COVID, Updated 8/25/2021

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Summary: UCSF Treatment Guidelines

Disease Category	UCSF Guidelines
Inpatient, no O2	• Remdesivir if high risk for progression or radiographic e/o LRTI • No steroids, baricitinib, or toci
Inpatient, requires O2 by nasal cannula	• Remdesivir • Dexamethasone if >3-4L • No baricitinib or toci
Inpatient, requires O2 by HFNC or NIMV	• Remdesivir • Dexamethasone • Baricitinib if recent hospitalization (eg 3-4d) + rapidly worsening
Inpatient, requires MV or ECMO	• Remdesivir • Dexamethasone • Tocilizumab if hosp <3d <u>and</u> ICU <24h <u>and</u> rapidly progressing to MV or requiring MV

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Antibiotics

- Bacterial coinfection on admission to the hospital is very uncommon (<1-3% across multiple studies)
- Most patients do not need to be covered for CAP

Gerver et al, CMI 2021. Russell et al, Lancet Microbe 2021.

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Anticoagulation

- Prophylactic anticoagulation should be given unless contraindicated
- Therapeutic anticoagulation
  - **Critically ill**: No benefit, ↑ major bleeding – do not use
  - **Noncritically ill:**
    - REMAP-CAP, ACTIV-4, ATTACC (n=2231): ↑ survival without organ support (79% vs 75%); no difference survival; ↑ major bleeding (1.9% vs 0.9%)
    - HEP-COVID (n=253): ↓ composite thrombosis/death (but did asx screening for VTE, small study) , no difference in major bleeding
    - Jury still out here, could consider in patients with noncritical COVID and no contraindications

REMAP-CAP, ACTIV-4, ATTACC Investigators, NEJM 2021. Spyropoulos et al, HEP-COVID RCT, JAMA 2021.

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Take Home Points

- COVID can affect all organ systems
- Most admitted patients just need basic labs
- For most patients, consider if they need remdesivir, dexamethasone, and baricitinib vs tocilizumab
- Most patients do not need antibiotics

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Questions?

October 2020

October 2021

UCSF

MANAGEMENT OF ANTICOAGULATION IN THE HOSPITALIZED PATIENT

Tracy Minichiello, MD
Professor of Medicine
University of California, San Francisco
Chief, Anticoagulation and Thrombosis Services
San Francisco, VA Medical Center

Conflicts of Interest

- I have no actual or potential conflicts of interest in relation to this program or presentation to disclose.

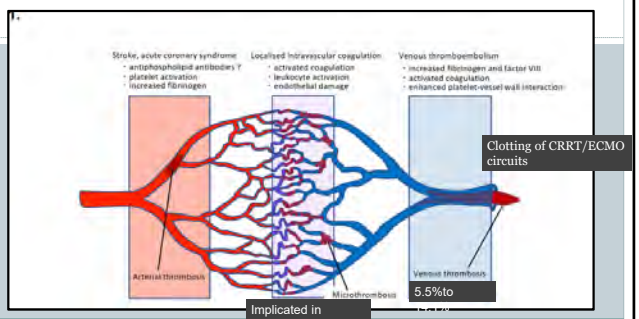
Objectives

- Anticoagulation in COVID 19
- ASA + anticoagulation
- Anticoagulation for AFIB in ESRD

62 yo admitted to hospital with COVID-19 requiring 3 L oxygen. Classic chest x-ray and inflammatory markers. Normal kidney and liver function. D-dimer elevated at 2000 ng/dL. He is admitted to the floor with telemetry monitoring.

What dose of anticoagulation prophylaxis do you recommend?

A. Prophylactic dose
B. Intermediate dose
C. Therapeutic dose
D. Yes



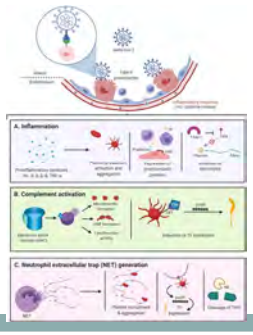
Clotting of CRRT/ECMO circuits

5.5%to

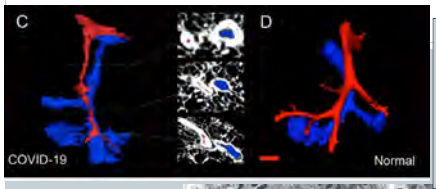
Implicated in disease

Iba et all CCMJ July 2020

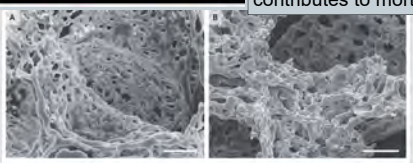
Immunothrombosis in COVID-19.



Joan Loo et al. Thorax 2021;76:412-420



Autopsy studies identified unsuspected VTE/ in situ pulmonary arterial thrombosis in more than 60% of pts w/COVID-19, suggesting thrombosis contributes to mortality.



Ackermann NEJM May 2020

Coagulation laboratory characteristics of COVID-19 infection

	Survivors	Non-survivors
Platelet count <150x10⁹/L	30-70%	45-80%
Platelet count <100x10⁹/L	0-1%	3-5%
Prothrombin time > 3 sec. prolonged	0-5%	15-25%
Fibrinogen < 1.0 g/L	0%	5-10%
Fibrinogen > 4.0 g/L	80-100%	80-100%
D-dimer > 1 mg/L (2x ULN)	15-25%	80-90%
D-dimer > 3 mg/L (6x ULN)	1-5%	50-70%
Antithrombin < 80%	0%	0-2%

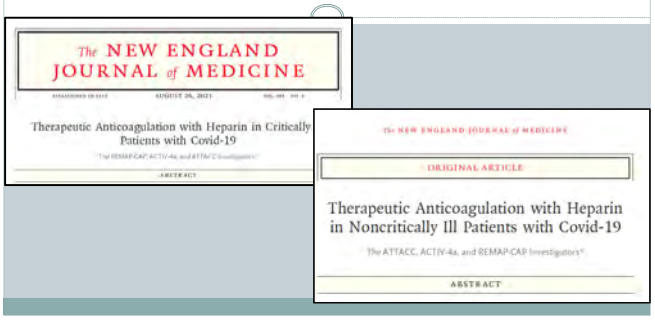
↑ D-dimer, especially > 4x ULN predict a more than 2-fold ↑risk of VTE/ mortality

Levi et al Res Pract Thromb Haemost. 2020;4:744–751

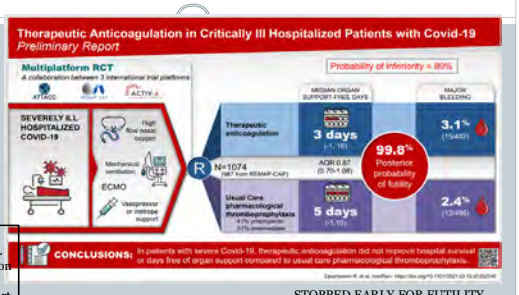
Anticoagulation for Thrombosis Prevention in COVID

- What dose of anticoagulation should be used in critically ill patients hospitalized with COVID
- What dose of anticoagulation should be used in moderately ill patients hospitalized with COVID
- Should patients hospitalized with COVID be discharged on anticoagulation for thrombosis prevention

MULTIPLATFORM TRIALS



What dose of anticoagulation in the Critically Ill COVID 19

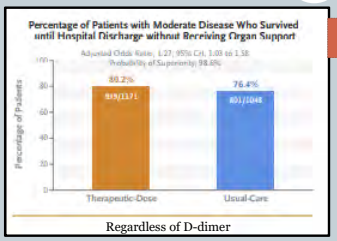


Support free, NO:
High flow nasal (20L
Mechanical ventilation
ECHO
Vascopresssor support

STOPPED EARLY FOR FUTILITY

REMAP-CAP, ACTIV-4a ATTACC NEJM 2021

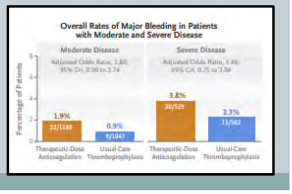
What Dose of Anticoagulation in Moderately Ill COVID



Regardless of D-dimer

Trial stopped early

Organ free support
High flow cannula
Noninvasive ventilation
Invasive ventilation
ECMO



ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators, Lawler PR. N Engl J Med. 2021 Aug 4. PMID: 34351721.

MULTIPLATFORM TRIALS

CRITICALLY ILL PATIENTS_
PROPHYLACTIC DOSING OF ANTICOAUGLATION

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

NONCRITICALLY ILL PATIENTS_
THERAPEUTIC DOSING OF ANTICOAUGLATION

Therapeutic Anticoagulation in Moderately Ill Covid

Survival to DC
- therapeutic anticoagulation 92.7%
- usual care 91.8%

Progression to intubation/death
- Therapeutic anticoagulation 10.9%
- Usual care 12.1 %

Major thrombosis or death
- Therapeutic anticoagulation 8%
- Usual care 9-9%

ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators, Lawler PR. N Engl J Med. 2021 Aug 4. PMID: 34351721.

ACTION TRIAL –Rivaroxaban in COVID 19

Is therapeutic anticoagulation with rivaroxaban effective in preventing complications in patients hospitalized with COVID (90% moderately ill) & ↑ D-dimer?

*In patients hospitalized with COVID-19 with elevated D-dimer levels, initial in-hospital **therapeutic anticoagulation with rivaroxaban 20 mg** once daily for stable patients or enoxaparin for unstable patients followed by rivaroxaban through 30 days **did not improve clinical outcomes** and increased bleeding compared with in-hospital prophylactic anticoagulation.*

Lopes RD et al Lancet 2021 https://doi.org/10.1016/S0140-6736(21)01203-4

Therapeutic Anticoagulation for Thromboprophylaxis in COVID 19

JAMA Internal Medicine | Original Investigation

Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19
The HEP-COVID Randomized Clinical Trial

Spyropolos AC et al JAMA Int Med 2021

Therapeutic Anticoagulation for Thromboprophylaxis in COVID 19

- 257 patient hospitalized with COVID 19
- Supplemental O2 and D-dimer > 4x ULN or SIC score ≥4.
- Primary outcome composite of VTE,ATE, and all-cause mortality within 30 days of hospitalization
- All had U/S at HD 10 + 4 or at discharge if sooner.

	standard	therapeutic		
Primary endpoint (VTE)	41.9% (29%)	28.7% (10.9%)	P=0.03	
ICU	55.3%	51.1%	NS	
Non ICU	36.1%	16.7%	P =.004	NON ICU: NNT 5 NNH 33
Death	25%	19.4% (NS)	NS	
Major bleeding	1.6%	4.7% (NS)	NS	

Spyropolos AC et al JAMA Int Med 2021

POST DISCHARGE PROPHYLAXIS FOR COVID

MICHELLE trial-publication pending

- Evaluate rivaroxaban 10 mg po daily vs control among discharged patients hospitalized for 3 + days WITHOUT CKD, dual antiplt, surgery/trauma in past month or any bleeding in past 3 months with COVID-19
- IMPROVE score ≥4 OR IMPROVE SCORE > 2-3 PLUS elevated d-dimer (> 500 ng/ml)
- Primary outcome symptomatic VTE, VTE death, ATE, MI., stroke
  - 3.1% rivaroxaban 9.4% control, no major bleeding in either arm

Ramaccioti et al Am Heart J 2021

COVID-19 and Thrombosis: Searching for Evidence - Anticoagulation

Example Randomized Trials	Completed • ACTT	Completed • ***ACCATT*** • ***ACTIV 4a*** • ***REMAP-CAP*** • ACTION	Completed • ACCATT • ACTIV 4a • REMAP-CAP • INPRIATION	Recruiting • ACTIV 4b
Environment of Care	"Pre-hospitalization"	Hospital Floor	ICU	Post Discharge
ASH Guidelines	No Prophylaxis	Prophylactic Dose	Prophylactic Dose	No Prophylaxis
How I Treat	No Prophylaxis **IF O2 + ↑D-dimer + low bleeding risk**	Prophylactic Dose Treatment Dose	Prophylactic Dose	FDA approved DOAC in highly selected patients *IF 3+ days and* IMPROVE ≥4 or 2-3 + D-dimer 2x ULN AND Low bleed

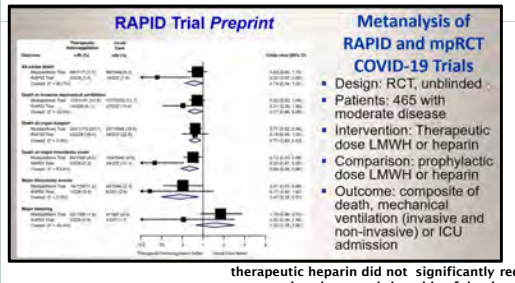
Case

62 yo admitted to hospital with **COVID-19 requiring 3 L oxygen** Classic chest x-ray and inflammatory markers. Normal kidney and liver function.**D-dimer elevated at 2000 ng/dL. What dose of anticoagulation prophylaxis do you recommend?**

A. Prophylactic dose
B. Intermediate dose
C. Therapeutic dose
D. Yes

MODERATELY ILL PATIENTS-
Consider D-dimer, Oxygen status, bleeding risk
PROPHYLACTIC vs. THERAPEUTIC ANTICOAGULATION

RAPID TRIAL-PREPRINT



g

therapeutic heparin did not significantly reduce the primary outcome but decreased the odds of death at 28 days.

A 75 year old man with HFpEF, DM, HTN is admitted with CHF exacerbation and new **AFIB**. You are going to start him on a **DOAC**. He is on ASA for primary CAD prevention. **Do you continue this in addition to his full dose DOAC?**

1) Yes, he has a lot of risk factors for CAD
2) No, I think the DOAC should cover it
3) I am going to defer this to the PCP

ASA & ANTICOAGULATION

MANY INDICATIONS FOR ASA

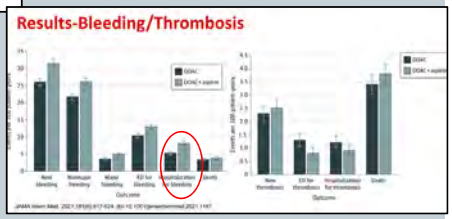
- Primary prevention of CAD
- PAD
- Secondary prevention of CAD, CVA, VTE

SHOULD PATIENTS ON ANTICOAGULATION BE ON ASA TOO?
Hundreds of thousands of patients in the US are on BOTH ASA plus AC
Commonly agreed upon indications for dual therapy: ACS, recent PCI, CABG

MSS


Adverse Events Associated With the Addition of Aspirin to Direct Oral Anticoagulant Therapy Without a Clear Indication

How often are patients anticoagulated with a DOAC for AFIB or VTE, without a recent MI or heart valve replacement, treated with concomitant aspirin?
How does this impact bleeding outcomes?



Slide 24

MS5 You have this slide on RISK. You really need a slide on BENEFIT of combo therapy - or lack thereof.
Moll, Stephan, 9/16/2021

Case

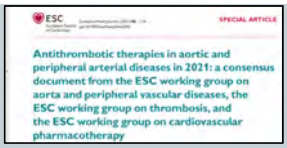
A 75 year old man with HFpEF, DM, HTN is admitted with CHF exacerbation and new AFIB. You are going to start him on a DOAC. He is on ASA for primary CAD prevention. Do you continue this in addition to his full dose DOAC?

1) Yes, he has a lot of risk factors for CAD
2) No, I think the DOAC should cover it
3) I am going to defer this to the PCP

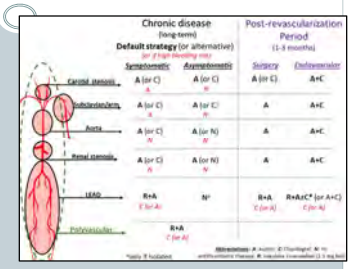
A 75 year old man with **PAD** (iliac bypass 18 months ago),HTN DM is admitted with **new AFIB** with rapid ventricular response. You are going to start him on a **DOAC**. He is on ASA for his PAD. **Do you continue this in addition to his full dose DOAC?**

1) Yes, he needs it for PAD
2) No, I think the DOAC should cover it
3) I am going to defer this to the PCP

European Society of Cardiology 2021 Consensus


ESC SPECIAL ARTICLE

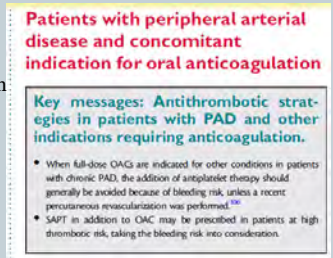
Antithrombotic therapies in aortic and peripheral arterial diseases in 2021: a consensus document from the ESC working group on aorta and peripheral vascular diseases, the ESC working group on thrombosis, and the ESC working group on cardiovascular pharmacotherapy



Eur Heart J. ehab390, https://doi.org/10.1093/eurheartj/ehab390

Peripheral Artery Disease

<u>If peripheral stent</u>
short term clopidogrel in addition to AC (~1 month)
Add ASA (triple therapy) ONLY in select cases at highest risk ie.,
prior stent thrombosis, slow flow


Patients with peripheral arterial disease and concomitant indication for oral anticoagulation

Key messages: Antithrombotic strategies in patients with PAD and other indications requiring anticoagulation.

- When full-dose OACs are indicated for other conditions in patients with chronic PAD, the addition of antiplatelet therapy should generally be avoided because of bleeding risk, unless a recent percutaneous revascularization was performed.
- DAPT in addition to OAC may be prescribed in patients at high thrombotic risk, taking the bleeding risk into consideration.

Eur Heart J. ehab390, https://doi.org/10.1093/eurheartj/ehab390

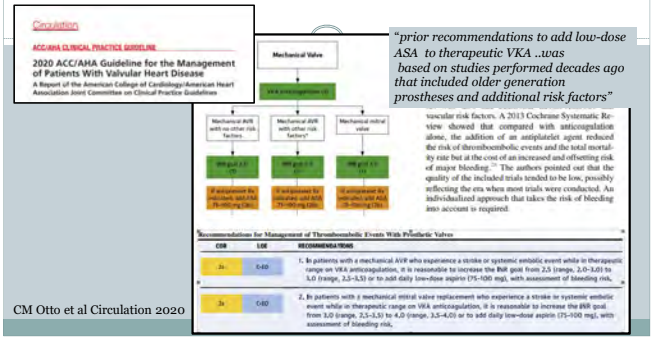
Case

A 75 year old man with PAD (iliac bypass 18 months ago),HTN DM is admitted with new AFIB with rapid ventricular response. You are going to start him on a DOAC. He is on ASA for his PAD. Do you continue this in addition to his full dose DOAC?

1) Yes, he needs it for PAD
2) No, I think the DOAC should cover it
3) I am going to defer this to the PCP

A 60 year old man with HTN and mechanical aortic valve placed 2017 is on **warfarin and ASA.** He is admitted for **GIB**. INR is 2.0 on admission, warfarin is held and he has EGD which shows **gastric ulcer** which is treated endoscopically. His Hgb stabilizes and he resumes his warfarin. **Should he resume his ASA as well?**

1) Yes, he needs it for his mechanical valve
2) No, I think the warfarin should cover it
3) I am going to defer this to the PCP



"prior recommendations to add low-dose ASA to therapeutic VKA ..was based on studies performed decades ago that included older generation prostheses and additional risk factors"

CM Otto et al Circulation 2020

Case

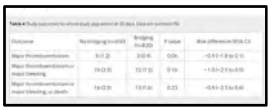
A 60 year old man with HTN and mechanical aortic valve placed 2017 is on warfarin and ASA. He is admitted for GIB. INR is 2.0 on admission, warfarin is held and he has EGD which shows gastric ulcer which is treated endoscopically. His Hgb stabilizes and he resumes his warfarin. Should he resume his ASA as well?

1) Yes, he needs it for his mechanical valve
2) No, I think the warfarin should cover it

It is decided to resume warfarin therapy but to stop the ASA. **Should he be bridged?**

1) Yes, he needs it for his mechanical valve
2) No, I think the warfarin monotherapy should cover it
3) I am going to defer this to his PCP


Postoperative low molecular weight heparin bridging treatment for patients at high risk of arterial thromboembolism (PERIOP2): double blind randomised controlled trial



Kovacs et al BMJ 2021

Case

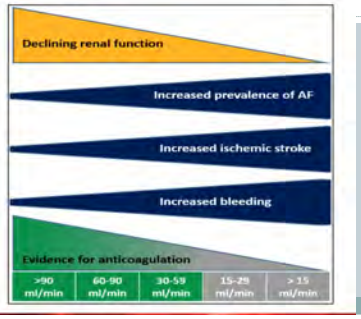
It is decided to resume warfarin therapy but to stop the ASA. Should he be bridged?

1) Yes, he needs it for his mechanical valve
2) No, I think the warfarin monotherapy should cover it
3) I am going to defer this to his PCP

79-year-old female with **DM** and **ESRD** is transferred to the ED from her dialysis center for dizziness, shortness of breath. She is 62 kg, normal BP HR , normal aPTT/PT, CBC, thyroid, liver; SCr 6.3 mg/dL. ECG shows **AFIB**. ECHO without valvular disease. **Should she be started on anticoagulation?**

1) **Yes, would start apixaban**
2) **Yes, would start warfarin**
3) **No, I am going to defer this to the PCP**

ANTICOAGULATION FOR AFIB IN ESRD



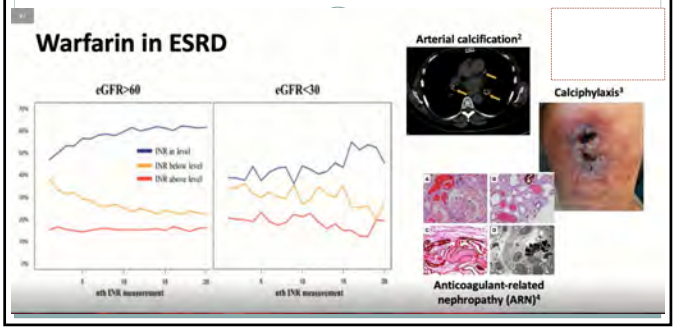
WHAT ABOUT AGE?
Declining benefit:
Age > 87 warfarin
Age > 92 apixaban

WARFARIN FOR AFIB IN ESRD

Warfarin vs. No AC in ESRD

Study	Design	Isch stroke/ systemic embol.	Hemorrhagic stroke	Major bleeding	[illegible]
Warfarin vs. no oral anticoagulation (OAC)					
Randhawa[1]	Metanalysis (n= 47,480)	7.7 vs 7.1% HR 0.96 (0.82-1.13)	**2.4 vs. 1.9% HR 1.46 (1.05-2.04)**	**16.1 vs. 15% HR 1.2 (1.09-1.47)**	43.4 vs. 52 HR 0.95 (0.83-1.09)
Kuno[2]	Metanalysis (n= 71,877)	HR 0.91 (0.72-1.16)	Not reported	**HR 1.31 (1.15-1.5)**	HR 0.94 (0.82-1.09)
Pokorney[3]	Medicare claims (n= 8,140)	HR 1.9 (0.82-1.23)	**HR 1.3 (1.07-1.59)**	**HR 1.26 (1.09-1.46)**	HR 1.02 (0.94-1.1)

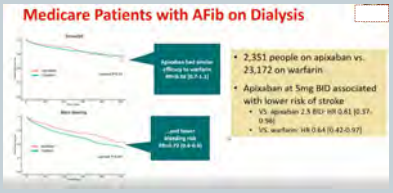
Randawa JAMA 2020 Kuno JACC 2020 Pokorney 2020



DOACS FOR AFIB IN ESRD

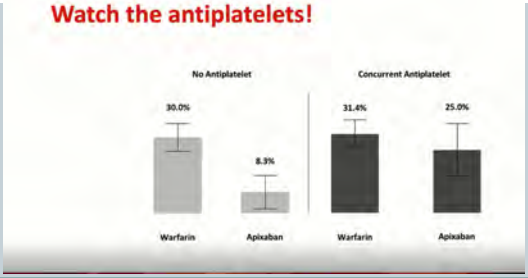
- Apixaban FDA approved for use in ESRD for AFIB (not VTE)
  - Based on SINGLE dose of 5 mg apixaban recommended no dose adjustment-same dosing algorithm as those not on HD BUT subsequent studies showed accumulation of drug at this dose, but not at 2.5 mg BID dosing.

APIXABAN FOR AFIB IN ESRD



Siontis CK Circulation 2018

APIXABAN FOR AFIB IN ESRD

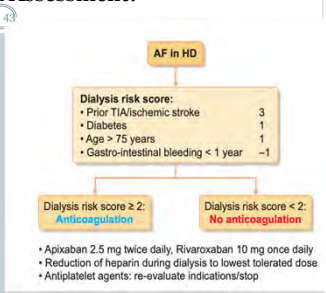


Ionescu et al Eur Journ of Hematology 2021

ESRD-specific Risk Assessment?

43

- 90% ESRD have CHADS2-vasc≥2
- Not validated in ESRD
- Overestimates stroke risk
- Risk may outweigh benefits



De Vriese et al Nephrol Dial Transp 2021

What the AF Guidelines Say

Guideline	Stroke prevention with anticoagulation in ESRD ± dialysis
ACC/AHA/HRS 2019[1]	• May be reasonable to prescribe warfarin or apixaban (IIb)
KDIGO 2021[2]	
• Primary prevention	• Decision to anticoagulate and choice of agent should be discussed with nephrologist
• Secondary prevention	• Refers to ACC/AHA/HRS recommendations • Consider left atrial appendage occlusion if additional bleed risks
CCS/CHRS 2020[3]	• Suggest patients not routinely receive antithrombotic therapy (Weak recommendation) • Individualized on risk vs. benefit and patient preference
ESC/EACTS 2021[4]	• Evidence is limited (no specific recommendation)

1. January et al. 2019, doi: 10.1161/CIR.0000000000000665; Kelly et al. Stroke 2021 https://doi.org/10.1161/STROKEAHA.120.029680
2. Andrade et al. 2020. doi.org/10.1016/j.cjca.2020.09.001 ;Hindricks et al. EHJ 2020. doi:10.1093/eurheartj/ehaa612

CONSIDER ANTICOAGULATION FOR AFIB IN ESRD

IF	Patient amenable through shared-decision making[1] Places higher value on avoiding stroke than bleed[2] Apixaban is an option for the patient
AND	Thorough risk/benefit analysis of thrombosis/bleed/frailty is done No need for DAPT (recent stent, TAVR) Optimization of other parameters to avoid adverse events (BP, etc)
BUT	If these are not possible, consider LAAO with Watchman or Amulet recognizing patient will require brief period of antithrombotic therapy after placement[3]

1. www.cardiosmart.org/SDMAFib?_ga=2.87317343.673555683.1631903462-1257589260.1631903462
2. LaHaye et al. Thromb Haemost 2014. DOI: 10.1160/TH13-05-0424
3. Genovesi et al. J Nephrol 2021. https://doi.org/10.1007/s40620-020-00774-5

Case

79-year-old female with DM and ESRD is transferred to the ED from her dialysis center for dizziness, shortness of breath and "flip-flopping" sensation in her chest, "similar to episodes over the last month but worse…"

She is 62 kg, normal BP HR , normal aPTT/PT, CBC, thyroid, liver SCr 6.3 mg/dL. ECG shows AFIB. ECHO without valvular disease.

Should she be started on anticoagulation?

1) **Yes, would start apixaban**
2) **Yes, would start warfarin**
3) **No, I am going to defer this to the PCP**

Objectives

- Anticoagulation in COVID 19
  - No anticoagulation prior to admission, no compelling evidence ofr anticoagulation after DC in all patients; all patient admitted with COVDI receive at least prophylactic anticoagulation-critically ill PROPHYLAXIS, moderately ill PROPHYLAXIS vs THERAPEUTIC
- ASA + anticoagulation
  - Avoid when possible. Reserve for those in whom benefit outweighs the risk, TALK TO YOUR COLLEAGUES-vascular, cardiology, neurology
- Anticoagulation for AFIB in ESRD
  - NO GOOD DATA; warfarin not benign, DOACs maybe alternative but high level data lacking and dosing still unclear

Questions?

Anticoagulant-associated gastrointestinal bleeding: Framework for decisions about whether, when and how to resume anticoagulants

Yan Xu | Deborah M. Siegal

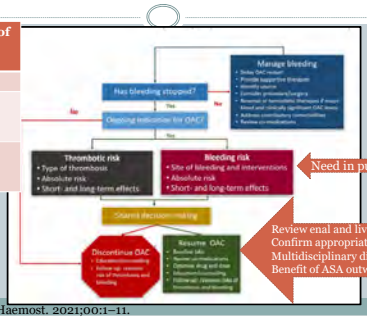
ASA IS A HUGE RISK FACTOR FOR GIB ON AC
40% of AC related bleeds on ASA

We don't know if PPI provide PRIMARY prevention of GIB
COMPASS TRIAL

Siegal et al. J Thromb Haemost. 2021;00:1–11.

RESUMPTION OF AC AFTER GIB

Indication	Mortality of Recurrent event
AFIB	25%
Secondary prevention VTE	4%
Secondary prevention VTE in cancer	15%



Need in put from GI

Review enal and liver & meds
Confirm appropriate dose
Multidisciplinary discussion
Benefit of ASA outweigh risk?

Siegal et al. J Thromb Haemost. 2021;00:1–11.

2021 Update in Diagnosis and Management of Stroke

S. Andrew Josephson MD
Carmen Castro Franceschi and Gladyne K. Mitchell Neurohospitalist Distinguished Professor
Chair, Department of Neurology
Founder, Neurohospitalist Program
University of California, San Francisco

The speaker has no disclosures

Case 1

- A 65 year-old right handed man with a history of HTN presented to the ED in a delayed fashion after the sudden onset of right sided weakness.
- Exam shows an expressive aphasia, R face and arm weakness as well as R visual field cut and L gaze deviation
- He was last seen normal at 1 p.m., and it is now 10:45 pm

UCSF "Stroke Protocol" CT

- Obtained at UCSF in suspected acute stroke and TIA patients hours from onset

1. Non-contrast CT of the head
2. CT Angiography from aortic arch to the top of the head
3. CT Perfusion study
4. Post-contrast CT of the head

What treatment should this patient likely receive?

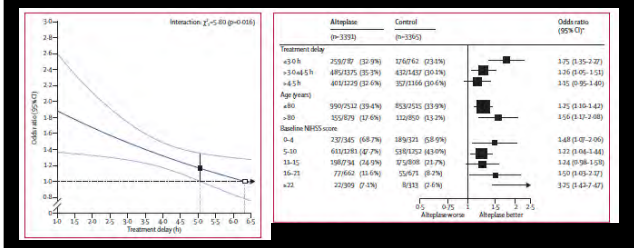
A. IV t-PA alone
B. IV t-PA followed by embolectomy
C. Embolectomy alone
D. IV heparin
E. Antiplatelets

The 2021 Acute Stroke Timeline

- Time of onset= last time seen normal

0-4.5 Hours	IV-tPA
0-6 Hours	Mechanical Embolectomy for all
6-24 Hours	Mechanical Embolectomy for some

Intravenous t-PA: Broad Success



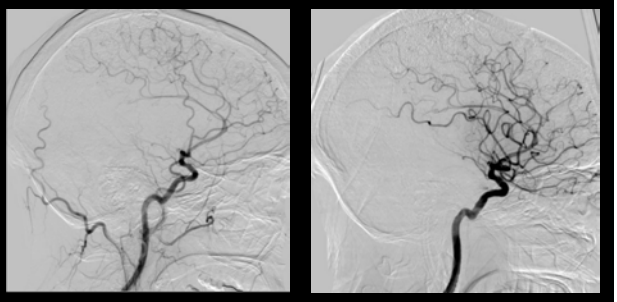
Emberson, J et al: *Lancet* 2014

Speed Matters: Time is Brain

- Examination of the Get With the Guideline Registry in the U.S. over the last decade
  - 1400 hospitals, nearly 59,000 patients
  - Mean time to treatment was 144 minutes
    - Earlier on weekdays, more severe stroke, arrival in ambulance
- For every 15 min earlier administration…
  - Significantly lower in-house mortality
  - Significantly lower rates of ICH
  - Significantly more independent ambulation at d/c
  - Significantly higher rate of d/c to home

Saver J et al: *JAMA* 309:2480, 2013

Embolectomy in NeuroIR Suite



Pre-treatment Post-treatment

The 2015 Endovascular Revolution

- Five major positive trials of endovascular therapy all published in 2015 in NEJM
- Trial design somewhat differed, but common to each:
  - 1. Used newer-generation devices
  - 2. Selected patients who were eligible via CTA
  - 3. IV t-PA in those who were eligible followed by embolectomy
  - 4. Typically a 6 hour time window

The 2018 Second Revolution

- DAWN and DEFUSE3 Trials
- Select patients with LVO treated up to 24 hours based on CT perfusion selection
  - Automated CT software widely available
- Has led to major reexamination of triage and ED/hospital protocols

Nogueira R et al: *N Engl J Med* 378:11, 2018
Albers GW, et al: *N Engl J Med* 378:708, 2018

What do we do given this data?

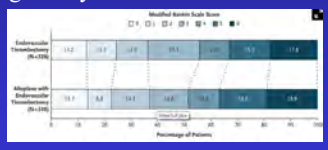
- 1. All patients eligible for IV t-PA should receive it (quickly)
- 2. Patients within 6 hours should receive a CTA to look for a large vessel occlusion (LVO)
- 3. If LVO present, endovascular therapy should occur, even following IV t-PA regardless of perfusion data

What do we do given this data?

- 4. If the patient has a LVO and presents between 6-24 hours, CT perfusion is required and selects patients who should receive endovascular therapy
- 5. Very late endovascular cases may emerge as still possible with favorable perfusion

What is coming up in acute stroke?

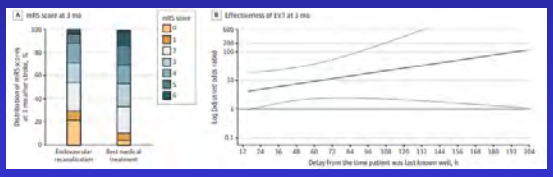
- Tenecteplase as an alternative to t-PA
  - Easier to administer with identical outcomes
- Skip the t-PA before embolectomy?
  - Large study failed to show benefit



Campbell B et al: N Engl J Med 378:1573, 2018
Yang P et al: N Engl J Med 382: 1981, 2020

What is coming up in acute stroke?

- Very late treatment of LVO in patients with favorable perfusion
  - 24 hours was selected for trials on no specific scientific basis



Kim B et al: JAMA Neurol 2020

Case 2

- A 65 year-old man with a history of HTN presents with 3 days of R arm weakness
- Examination shows a R pronator drift and mild weakness in the extensors of the R hand and arm
- The patient takes aspirin 81mg daily as well as HCTZ

Which of the following is not part of the standard embolic stroke workup?

A. Echocardiogram
B. Extended cardiac telemetry
C. Lipid panel
D. B12, TSH, RPR, ESR
E. Carotid evaluation

Standard Large-Vessel Stroke Workup

- Cardioembolic: afib, clot in heart, paradoxical embolus
  - 1. Telemetry
  - 2. TEE with bubble study
- Aortic Arch
  - 2. TEE with bubble study
- Carotids
  - 3. Carotid Imaging (CTA, US, MRA, angio)
- Intracranial Vessels
  - 4. Intracranial Imaging (CTA, MRA, angio)

And evaluate stroke risk factors

TEE vs. TTE

- 231 consecutive TIA and stroke patients of unknown etiology underwent TTE and TEE
- 127 found to have a cardiac cause of emboli, 90 of which (71 percent) only seen on TEE
- TEE superior to TTE for: LA appendage, R to L shunt, examination of aortic arch
- More recently: TEE found additional findings in 52% and changed management in 10%

De Bruijn S et al: *Stroke* 37:2531, 2006
Katsanos AH, et al: *Neurology* 87:988, 2016

Atrial Fibrillation Detection

- EKG
- 48 Hours of Telemetry
- Long-term cardiac event monitor (>21d)
  - 15-20% of patients with cryptogenic stroke otherwise unexplained had afib detected
  - Clearly changes management
  - Probably cost effective

Gladstone D et al: *N Engl J Med* 370:2467, 2014

Really Long Term Monitoring: 2021

- STROKE-AF: randomized trial comparing usual care with ICM for 1 year
  - 492 patients aged 60 (or 50 with 1 stroke risk factor) who had stroke within 10 days
- Afib found in 12.1% vs 1.8%
- Large and small vessel strokes included
- Clinical significance not certain

Bernstein RA et al: *JAMA* 325:2169, 2021

Approach to Stroke Treatment

Acute Stroke Therapy?

No

Anticoagulants?

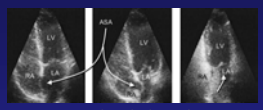
No

Antiplatelets

Shrinking Indications for Anticoagulation in Stroke

1. Atrial Fibrillation
2. Some other cardioembolic sources
   - Thrombus seen in heart
   - ~~?EF<35~~ WARCEF 2012
   - ~~?PFO with associated Atrial Septal Aneurysm~~
3. ~~Vertebral or Carotid dissection~~ CADISS 2015
4. Rare hypercoagulable states: APLS

The "Absolute Mess" of PFO in Stroke



Meier B and Lock JE *Circulation*. 107-5, 2003

- Around 20-25% of all patients have a PFO
- PFO alone is not necessarily associated with higher risk of recurrent stroke
  - Higher risk: Larger PFO, associated atrial septal aneurysm, perhaps younger age
- Three previous *negative* trials of closure devices <u>but</u> cardiologists pre-2017 were still performing these procedures widely

More Actionable Data

	RESPECT	Gore REDUCE	CLOSE
Inclusion Criteria	Cryptogenic stroke within past 270 days + PFO	Cryptogenic stroke within past 180 days + PFO	Stroke attributed to PFO + atrial septal aneurysm OR large PFO
Participants	980 participants	644 participants	663 participants
Intervention Arm	PFO closure	PFO closure + antiplatelet	PFO closure + antiplatelet
Medical Rx Arm	Antiplatelet or anticoagulation	Antiplatelet	Arm 1: antiplatelet Arm 2: anticoagulation
Results	Less recurrent stroke with PFO closure (NNT 42)	Less recurrent clinical and clinical+radiographic stroke with PFO closure (NNT 28)	Less recurrent stroke with PFO closure (NNT 20)

N Engl J Med, 2017

What now?
"Let's close all these PFOs!"

- DO NOT close all these PFOs
- DO screen patients for PFO (?how)
- It is sensible to discuss with your cardiologists some "Rules of the Road"
- At the end of the day, this is an exciting advance for some (young) people with stroke that can make a substantial impact on recurrence rates

Rules of the Road

- Consider PFO closure if:
  - The patient is younger than 60 years old
  - AND you can be sure the PFO is the most likely etiology after a thorough workup
  - AND the qualifying event is a stroke (not TIA) that appears embolic (not lacunar)
  - Likely concentrate on large PFOs or those with an atrial septal defect
    - Cardiologists new task: start counting bubbles

Heparin in Acute Stroke

- Study examined the largest trials of heparin, heparinoids, LMWH in acute stroke
- Could find no benefit even in those patients with highest risk of recurrent ischemia and lowest risk of hemorrhage
- Considering use of heparin for "selected patients" therefore seems unwise

Whiteley WN et al: *Lancet Neurol* 12:539, 2013

Case 3

- A 70 year-old woman with a history of DM, smoking presents 10 hours after the onset of slurred speech and right arm and leg weakness.
- The patient is taking ASA 81mg daily

Stroke workup is unrevealing. your Treatment?

A. Increase ASA to 325mg daily
B. Add Plavix to ASA
C. Stop ASA, start Plavix
D. Stop ASA, start Aggrenox
E. Anticoagulate

Approach to Stroke Treatment

Acute Stroke Therapy?

↓ No

Anticoagulants?

↓ No

Antiplatelets

Antiplatelet Options

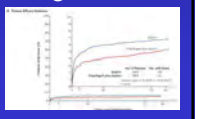
- 1. ASA
  - 50mg to 1.5g equal efficacy long-term
- 2. Aggrenox
  - 25mg ASA/200mg ER Dipyridamole
- 3. Clopidogrel (Plavix)
  - Multiple secondary prevention studies (CHARISMA, SPS3) show no long-term benefit in combination with ASA

Antiplatelet Options

- If on no antiplatelet medication
  - Plavix vs. Aggrenox (or ASA)
- If already on ASA
  - Switch to Plavix vs. Aggrenox
- If already on Plavix or Aggrenox
  - ???

Clopidogrel + ASA: Ever A Winning Combination?

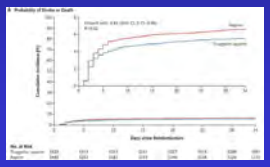
- POINT trial
- Select those with only minor or no deficits (NIHSS 3 or less or ABCD2 of 4 or more)
- Nearly 5000 TIA or Minor Stroke patients assigned to 90d of daily ASA + Placebo versus daily ASA + Clopidogrel following 600mg load
- Modestly improved efficacy (1.5%)
- Minimally (0.5%) more hemorrhage



Johnston SC et al: *N Engl J Med* 379:215, 2018

Ticagrelor: Another Short-term DAPT Option

- THALES trial (like POINT trial)
- Nearly 11000 TIA or Minor Stroke patients assigned to 30d of daily ASA + Placebo versus daily ASA + Ticagrelor following 180mg load
- Modestly improved efficacy (1.1%)
- Severe bleeding in 0.5%
- When to use?



Johnston SC et al: *N Engl J Med* 383:207, 2020

When to use Dual Antiplatelets

- NOT all the time!
- After minor stroke or TIA for only 21* days
- After a fresh carotid or coronary stent
- With severe intracranial atherosclerosis (>70%) and stroke/TIA in that territory for only 90 days

Other Acute Stroke Management

- Statins for (almost) all patients with stroke or TIA
  - 80mg atorvastatin if LDL>100 for at least 5 years
- Tight Glucose and Fever control in acute period
- Enoxaparin for DVT prophylaxis (better than compression stockings or UFH)

Permissive Hypertension

- National Guidelines
  - To at least 220/120
  - After IV tPA: less than 185 systolic for 24 hours
- We typically stop all meds except half-dose β-blockers and (maybe) clonidine

Permissive Hypertension

- When to stop remains controversial
- Situations where more important
  - Large Vessel Occlusion
  - Fluctuating symptoms
- We begin a medicine before discharge (~72h) and aim for normotension over a matter of weeks
  - Choose thiazides and ACEI first

Case 4

- A 73 year-old woman with HTN comes to the ED after a 5 minute episode of right arm weakness that has since resolved.
- Exam is normal except blood pressure is elevated at 176/97

Other than TIA, what is the most common neurologic diagnosis here?

A. Conversion disorder
B. Migraine
C. Focal Seizure
D. UTI
E. Cervical spine lesion

TIA versus Stroke

- Up to 30-50% of TIA have infarct on MRI
- Conceptually the same disorder
  - Same workup, same treatment
- Pendulum swing
  - Pre-2001: Much more aggressive with stroke
  - 2002-2007: TIA and stroke equally aggressive
  - 2008-present: A more aggressive approach with TIA outside of the acute treatment window

Risk of Future Stroke with TIA: ABCD^2 Score

- 7-day risk overall 8.6-10.5 percent
- Age
  - >60 =1 point
- Blood Pressure
  - SBP>140 or DBP>90 =1 point
- Clinical Features
  - Unilateral weakness =2 points
  - Speech disturbance without weakness =1 point
- Duration
  - >60 minutes =2 points
  - 10-59 minutes =1 point
- Diabetes=1 point

Johnston SC et al: *Lancet* 369:283, 2007

Aggressive Therapy for TIA

- 1. SOS-TIA trial
  - 1085 patients with TIA admitted to a 24-hour center
  - All treated with standard therapy
    - 74 percent discharged on same day, stroke risk reduced 80 percent from ABCD^2 prediction
- 2. EXPRESS study
  - 80 percent reduction in risk with urgent TIA clinic visit versus usual primary care visit in 1278 patients

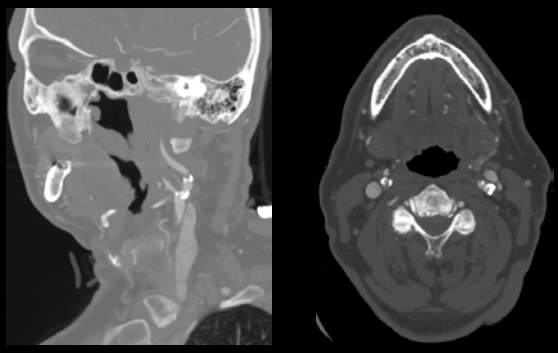
Lavallee PC et al: *Lancet Neurology* 6:953, 2007
Rothwell PM et al: *Lancet* 370:1432, 2007

TIA Aggressive Therapy: A Modern Look

- 2009-2011 TIA registry of nearly 5000 patients
- Population at baseline was high risk as with historical cohorts
- 78% saw a stroke specialist within 24 hours
  - Hospitalists not mentioned in this European study
- 1-year stroke rate was 5.1%
- Rates at 2d, 7d, 30d, 90d, 1y were all less than half of that in historical cohorts

Amarenco P, et al: *N Engl J Med* 374:1533, 2016

CT Angiogram: 95% L ICA stenosis



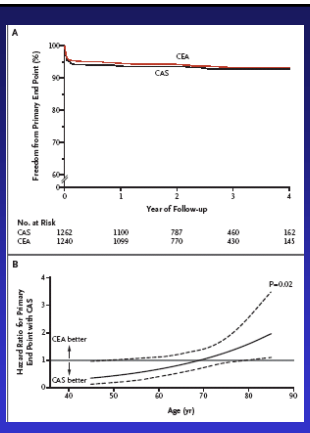
When to Fix the Carotid?

- NASCET in early 1990s
  - Benefit of endarterectomy in patients with symptoms ipsilateral to 70-99% stenosis
    - Comparison: best medical management at the time
  - 50-69% symptomatic stenosis revascularization has limited benefit, especially in women
- In stroke management don't miss carotid disease or atrial fibrillation

How to Fix the Carotid?

- Stenting vs. CEA: CREST Trial
- 4-year study of 1321 symptomatic and 1181 asymptomatic patients randomized to CEA vs. carotid stenting
- Combined endpoint of stroke, MI, death not significantly different
  - More strokes in first 90 days in stenting group, more MIs in surgical group
  - After 90 days, similar endpoints

Brott TG et al: *N Engl J Med* 363:11, 2010



Brott TG et al: *N Engl J Med* 2010

The High-Yield Neurologic Examination

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Carmen Castro Franceschi and Gladyne K. Mitchell Neurohospitalist Distinguished Professor
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The speaker has no disclosures

Examination Approach

- Two types of neurologic examinations
  - 1. Screening Examination
  - 2. Testing Hypotheses
- Select high-yield tests and techniques

Examination Approach

- Organization
  1. Mental Status
  2. Cranial Nerves
  3. Motor
  4. Reflexes
  5. Sensory
  6. Coordination
  7. Gait

The "High-Yield" Neurologic Examination: Top Ten Suggestions for a Better Neurologic Examination

1. If the patient can give a completely coherent history, then the mental status examination is probably normal

Digits Forward

- Outstanding test of attention to screen for delirium
- Given successively long strings of digits 1 second apart
  - 6-8-2-4
  - 5-1-9-3-5
  - 8-6-2-6-3-7
  - 5-4-6-9-7-5-2
- Less than 5 is abnormal and indicates an attentional deficit

Case 1: Mental Status

- A 73 year-old woman comes to the ER with 2 days of feeling fatigued
- General physical examination is normal and there is no weakness on neurological examination
- Language testing is abnormal

The "High-Yield" Neurologic Examination: Top Ten Suggestions for a Better Neurologic Examination

1. If the patient can give a completely coherent history, then the mental status examination is probably normal
2. Speech does not equal language: test three elements of language in each patient

Aphasia Testing

- Fluency: Use Naming and Conversation
- Comprehension: More difficult commands
- Repetition: "Today is a sunny day…"

Aphasia Chart

Name	Fluency	Comp	Rep
Broca's	Bad	Good	Bad
Wernicke's	Good	Bad	Bad
Global	Bad	Bad	Bad
Conduction	Good	Good	Bad
Transcort Motor	Bad	Good	Good
Transcort Sens.	Good	Bad	Good
Transcort Mixed	Bad	Bad	Good

Cranial Nerve Testing

II: Pupils, Acuity, Visual Fields
III, IV, VI: Extraocular Movements
V: Facial Sensation
VII: Facial Strength
VIII: Hearing
IX, X: Palatal Elevation and Gag
XI: SCM and Trapezius Power
XII: Tongue Power

The "High-Yield" Neurologic Examination: Top Ten Suggestions for a Better Neurologic Examination

1. If the patient can give a completely coherent history, then the mental status examination is probably normal
2. Speech does not equal language: test three elements of language in each patient
3. Visual field testing is highly informative and underutilized by the non-neurologist

Screening for Visual Field Deficits

- Cooperative patient: Move examiner finger in the center of each quadrant with patient gaze fixed
  - Test each eye by covering the opposite eye, present stimulus in all 4 quadrants
- Uncooperative patient: Use a single digit to suddenly approach each half of the visual fields; normally elicits a blink
  - Avoid using entire hand: elicits corneal reflex
  - Report as "Does/Does not blink to threat"

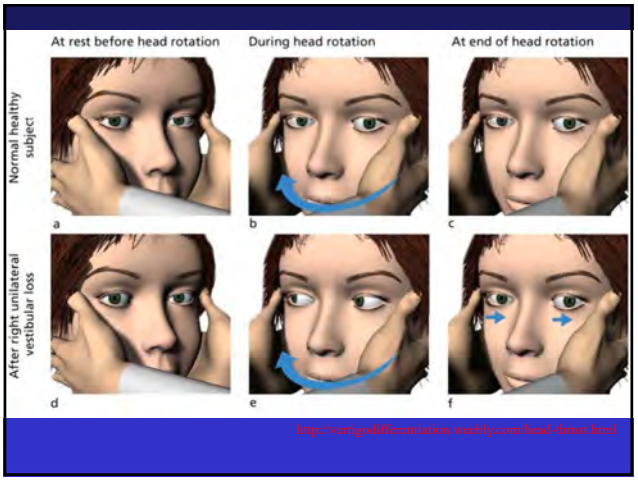
Central vs. Peripheral: Vertigo Exam Findings

- Always central, always needs imaging
  - 1. Any Cranial Nerve Lesion
  - 2. Any Asymmetric Cerebellar Finding
  - 3. Complete Absence of Peripheral Signs

HINTS

- Three step screen
  - 1. Head Impulse (should perform last)
  - 2. Nystagmus
  - 3. Test of Skew

http://content.lib.utah.edu/cdm/singleitem/collection/ehsl-dent/id/6



http://vertigo101presentation.weebly.com/head-thrust.html

Coma

- Definition:
  - Not Awake
  - Not Arousable
  - Not Aware

The "High-Yield" Neurologic Examination: Top Ten Suggestions for a Better Neurologic Examination

4. After establishing new-onset coma, the pupillary examination is the most important initial neurologic examination test

Two Localizations of Coma

- 1. Brainstem
- 2. Bilateral Hemispheres

- Step 1: CN exam to localize to brainstem or hemispheres
- Step 2: Pupils uneven: Structural not metabolic etiology

Case 2: Cranial Nerves

- A 54 year-old man with no PMH presents after being hit in the right temple with a baseball while playing with his son.
- General physical exam is normal. On neurologic examination the patient is lethargic. The right pupil is 7mm and minimally reactive while the left reacts briskly 3 to 2mm. The rest of the neurologic examination is normal.

"Fixed" Pupils and Coma

- Dilated (7-9mm): Early Herniation
- Mid-Position (3-5mm): Late Herniation
- Caveats
  - ? Adequacy of light stimulus
  - ? Drug Effect

Case 2: Cranial Nerves

- Over the next hour, the patient becomes unresponsive and develops extensor posturing on his left side

Cranial Nerve Testing: Coma

II: Pupils, Visual Fields

III, IV, VI: Oculocephalic Maneuver

V, VII: Corneal Reflex

VIII: Cold Calorics

IX, X: Gag, Cough, Spontaneous Respirations

The "High-Yield" Neurologic Examination: Top Ten Suggestions for a Better Neurologic Examination

4. After establishing new-onset coma, the pupillary examination is the most important initial neurologic examination test
5. Use an appropriate screen for Upper Motor Neuron-type weakness

Case 3: Motor

- A 75 yo male with HTN, DM and current tobacco use comes to the ED with mild problems walking and a complaint of "my left arm is not working right."

Case 3: Motor

- The ED physician tells you that he knows the patient has no weakness in his extremities as his own exam shows equal hand grasps, moving all fours, and "stepping on the gas" in the lower extremities.

Upper Motor Neurons of the Pyramidal Tract

Predictable Pattern of Weakness

Distal Extensors of the UEs and Distal (Dorsi)Flexors of the LEs

Quick Screen for Upper Motor Neuron/Pyramidal Weakness

- Pronator Drift
- Fine Finger Movements/Toe Taps
- One muscle in each of four extremities
  - Upper Extremities: 1st DI or finger extensors
  - Lower Extremities: Extensor of big toe
- Common ED screen VERY insensitive!

The "High-Yield" Neurologic Examination: Top Ten Suggestions for a Better Neurologic Examination

4. After establishing new-onset coma, the pupillary examination is the most important initial neurologic examination test
5. Use an appropriate screen for Upper Motor Neuron-type weakness
6. Use the exam to localize the weakness in the nervous system

	UMN	LMN
Pattern of Weakness	Pyramidal	Variable
Function/Dexterity	Slow alternate motion rate	Impairment of function is mostly due to weakness
Tone	Increased	Decreased
Tendon Reflex	Increased	Decreased, absent or normal
Other signs	Babinski sign, other CNS signs (e.g. aphasia, visual field cut)	Atrophy (except with problem of neuromuscular junction)

	Motor Neuron Disease	Neuropathy	NMJ	Myopathy
Weakness Pattern	**Variable**	**Distal**	**Diffuse**	**Proximal**
DTR	**Increased, normal and/or decreased**	**Decreased or absent**	**Normal or decreased**	**Normal or decreased**
Atrophy	**Yes**	**Yes**	**No**	**No**
Fasciculations	**Yes**	**Sometimes**	**No**	**No**
Sensory symptoms/ signs	**No**	**Yes**	**No**	**No**

The "High-Yield" Neurologic Examination: Top Ten Suggestions for a Better Neurologic Examination

4. After establishing new-onset coma, the pupillary examination is the most important initial neurologic examination test
5. Use an appropriate screen for Upper Motor Neuron-type weakness
6. Use the exam to localize the weakness in the nervous system
7. Use the sensory examination sparingly and logically, testing each major pathway

Sensory Testing Modalities

- Vibration (128Hz Tuning Fork)
- Joint Position Sense/Proprioception
- Temperature
- Pinprick
- Light Touch (Not Useful)

Sensory Testing Modalities

- Vibration (128Hz Tuning Fork)
- Joint Position Sense/Proprioception
- Temperature
- Pinprick

Case 4: Sensory

- A 45 yo man presents with 2 days of progressive tingling and weakness of the lower extremities. He now is having trouble walking and rising from a chair.

Case 4: Sensory

- Exam
  - MS, CN normal
  - Motor: normal tone throughout, normal power in upper ext., 4/5 throughout in the lower extremities
  - Sensory: decreased PP/Vib/temp patchy in lower extremities
    - A sensory level is found at T10

The "High-Yield" Neurologic Examination: Top Ten Suggestions for a Better Neurologic Examination

8. Symmetry of reflexes is important, rather than absolute value

Reflex Tips

- Know the cord level of each reflex
  - Biceps: C5-6
  - Triceps: C7-8
  - Patella: L2-4
  - Ankle: L5-S1
- Symmetric positioning is key
- Expose the muscle being tested
- Strike with only moderate force

Case 5: Coordination

- A 54 year-old woman presents with vertigo and gait difficulties
- On finger-nose-finger, she exhibits dysmetria with the right upper extremity, but not with the left

The "High-Yield" Neurologic Examination: Top Ten Suggestions for a Better Neurologic Examination

8. Symmetry of reflexes is important, rather than absolute value
9. In the coordination exam, bilateral abnormalities are often benign

Key Cerebellar Exam Tips

- Bilateral dysfunction is often benign and drug/medication related
- Unilateral dysfunction is a cerebellar lesion until proven otherwise
  - CT insensitive in this region
- Cerebellar tracts run through the brainstem
  - Cerebellar signs with cranial nerve deficits is a brainstem lesion until proven otherwise

The "High-Yield" Neurologic Examination: Top Ten Suggestions for a Better Neurologic Examination

8. Symmetry of reflexes is important, rather than absolute value
9. In the coordination exam, bilateral abnormalities are often benign
10. The single most useful test on the neurologic exam is having the patient ambulate

The (Misunderstood) Romberg

- How to perform
- What systems help us stand?
  - 1. Cerebellum
  - 2. Motor
  - 3. Vestibular
  - 4. Dorsal Columns
  - 5. Vision

Part of the Sensory Exam!

NOT Gait or Coordination Exam

The Quick Screening Exam

1. Mental Status: Digits forward, 3 elements of language
2. Cranial Nerves: Pupils, visual fields, EOMs, facial droop
3. Motor: 3-step screen for UMN weakness
4. Reflexes:
5. Sensory: Test toes w/ 2 modalities (1 from each path); Romberg
6. Coordination: Finger-nose-finger
7. Gait: Walk the patient

Challenging cases of hospitalized patients with cirrhosis

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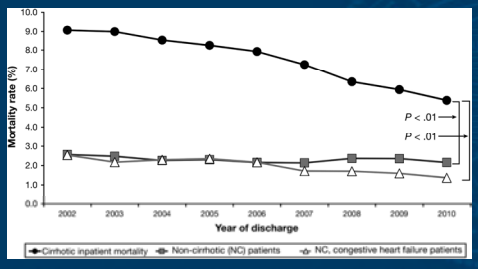
October 21, 2021

Disclosures

- Grant/research support: Gilead, NGM, Genentech

Improving Mortality In Hospitalized Cirrhotic Patients



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Development of Quality Measures in Cirrhosis by the Practice Metrics Committee of the American Association for the Study of Liver Diseases

Fasiha Kanwal,[1-3] Elliot B. Tapper,[4] Chanda Ho,[5] Sumeet K. Asrani,[6]* Nadia Ovchinsky,[7] John Poterucha,[8] Avegail Flores,[9] Victor Ankoma-Sey,[10] Bruce Luxon,[11] and Michael Volk[12]

Tough consult questions

- Beta blockers: what the heck should I do with them?
- My patient is in pain, what do I do?
- My patient has AKI. Is it hepatorenal syndrome?
- Should this patient get a TIPS?
- What can I do for this patient with refractory hydrothorax?
- This patient is admitted with ascites again. Do I really need to tap them?
- Does my patient need a liver transplant?

Case 1

55yo woman with NASH cirrhosis, Child's class B, with moderate ascites previously controlled on diuretics and hepatic encephalopathy. She has no history of prior variceal bleeding. She undergoes screening endoscopy and is noted to have medium varices. She is started on a nonselective beta blocker for primary prevention of variceal hemorrhage.

Case 1

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6 months later, she is hospitalized with tense ascites and acute kidney injury.

Case 1

55yo woman with NASH cirrhosis, Child's class B, with moderate ascites previously controlled on diuretics and hepatic encephalopathy. She has no history of prior variceal bleeding. She undergoes screening endoscopy and is noted to have medium varices. She is started on a nonselective beta blocker for primary prevention of variceal hemorrhage.

6 months later, she is hospitalized with tense ascites and acute kidney injury.

What should be done with her beta blocker?

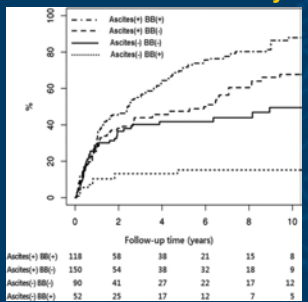
What should happen to a NSBB in a patient with worsening ascites/decompensation?

A. Stop the beta blocker
B. Switch to a selective beta blocker
C. Increase the beta blocker dose
D. It depends
E. I don't know, please tell me, that's why you're here

What should happen to a NSBB in a patient with worsening ascites/decompensation?

A. Stop the beta blocker
B. Switch to a selective beta blocker
C. Increase the beta blocker dose
D. **It depends**
E. I don't know, please tell me, that's why you're here

Beta blockers may be associated with increased risk of AKI in refractory ascites



Kim, *Liver Transpl*, 2017.

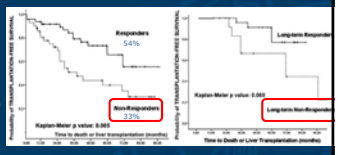
No impact of NSBB on survival in patients with ascites

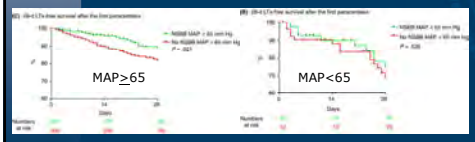
	Impact of NSBB
All cause mortality	None
Refractory ascites	None
Nonrefractory ascites	None
Short-term (6-month) mortality	Trend toward poorer survival

Chirapongsathorn, *Clin Gastro* Hep, 2016. Bhutta, *Alim Pharm Ther*, 2017. Wong, *Liver International*, 2019.

MAP and BB response impact survival

- Patients who respond to beta blockers and maintain response (based on portal pressures) have superior survival than those who never respond or lose response to beta blockers





- Survival benefit of beta blockers may be lost in patients with baseline MAP of <65

Augustin, *Hepatology*, 2012.
Tergast, *Alim Pharm Ther*, 2019.

What is happening?

- Beta blockers can blunt compensatory increases in cardiac output
  - Worsened hypotension in patients with baseline low SVR
  - Decreased renal perfusion

Case 1 (cont'd)

55yo woman with NASH cirrhosis, with recent worsening of ascites, hospitalized with tense ascites, rising MELD score, AKI. She is on a NSBB for primary prevention of variceal bleeding.

Diagnostic paracentesis shows evidence of spontaneous bacterial peritonitis (SBP).

Case 1 (cont'd)

55yo woman with NASH cirrhosis, with recent worsening of ascites, hospitalized with tense ascites, rising MELD score, AKI. She is on a NSBB for primary prevention of variceal bleeding.

Diagnostic paracentesis shows evidence of spontaneous bacterial peritonitis (SBP).

Now what should be done with her beta blocker?

What should you do with a NSBB in a patient with SBP?

A. Stop the beta blocker during hospitalization
B. Switch to a selective beta blocker
C. Increase the beta blocker dose
D. I don't know, please tell me, that's why you're here

What should you do with a NSBB in a patient with SBP?

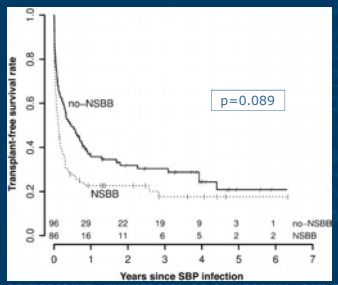
A. **Stop the beta blocker during hospitalization**
B. Switch to a selective beta blocker
C. Increase the beta blocker dose
D. I don't know, please tell me, that's why you're here

Beta blockers reduce risk of developing SBP

	n	Child A/B/C (%)	Ascites (%)	Follow-up (months)	SBP BB vs control (%)
Turnes AJG, 2006	71	83/17/0	35	76	8 vs 15
Gonzales-Suarez Eur J Gastroenterol Hep, 2006	230	22/57/21	64	23	10 vs 15
Abraldes Hepatology 2003	77	42/47/11	31	70	4 vs18
Cholongitas J Gastroenterol Hep 2006	134	9/59/32	100	36	24 vs 33
Hoshino AJG 2000	139	--	100	96	5 vs 28

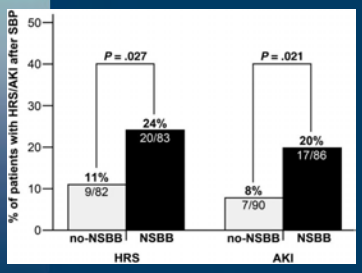
Senzolo, *Liver International*, 2009.

Beta blockers increase risk of death after first episode of SBP



Mandorfer, *Gastro*, 2014.

Beta blockers increase risk of HRS/AKI after first episode of SBP



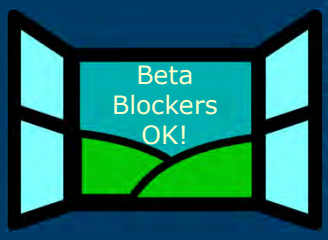
- Patients treated with beta blockers were sicker
  - More often Child's C cirrhosis (67 vs 53%)
  - Higher bilirubin (5 vs 3)

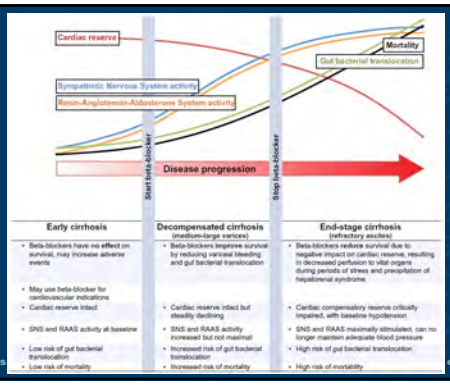
Mandorfer, *Gastro*, 2014.

Summary: NSBB

- Beta blockers may have deleterious effects in cirrhosis
  - Poorer survival in patients with refractory ascites
  - Increased risk of HRS/AKI in SBP
- Some of the effects of beta blockers observed may be due to sicker patients treated with beta blockers
- Beta blocker effect may vary over time
  - Discontinuation or nonadherence due to side effects
  - Loss of response over time
- No RCT level data to help guide decision making in decompensated cirrhosis

Window Hypothesis





Take home points: NSBB

- Consider stopping NSBB in patients with refractory ascites if they have:
  - Systolic blood pressure <90mmHg or MAP <65
  - Na <130 and/or Cr >1.5
  - No history of variceal bleeding or large varices
- Stop NSBB during a hospitalization for SBP
- Consider limiting NSBB dose to:
  - Propranolol <120mg/day
  - Nadolol <80mg/day

Case 1 (cont'd)

55yo woman with NASH cirrhosis, hospitalized with tense ascites, rising MELD score, and AKI, found to have SBP.

She reports problems with abdominal pain that is preventing her from sleeping and ambulating.

Case 1 (cont'd)

55yo woman with NASH cirrhosis, hospitalized with tense ascites, rising MELD score, and AKI, found to have SBP.

She reports problems with abdominal pain that is preventing her from sleeping and ambulating.

How should you manage her pain?

How should you manage pain in a patient with decompensated cirrhosis?

A. Ibuprofen
B. Hydrocodone/acetaminophen
C. Oxycodone
D. Acetaminophen
E. Did you really include acetaminophen as an option? That's crazy talk.

How should you manage pain in a patient with decompensated cirrhosis?

A. Ibuprofen
B. Hydrocodone/acetaminophen
C. Oxycodone
D. **Acetaminophen**
E. Did you really include acetaminophen as an option? That's crazy talk.

Challenges of pain management in cirrhosis

PATIENT
- Metabolic comorbidities
- Substance use disorders
- Psychiatric disease
- Low socioeconomic status / health literacy

DISEASE
- Variable presentations
- Minimal research on cirrhosis-related pain

PHARMACOLOGIC
- Impaired hepatic metabolism
- No biomarkers to measure hepatic function
- Impaired renal excretion
- Risk for adverse effects
  - Renal failure
  - GI bleeding
  - Hepatic encephalopathy
- Potential for abuse

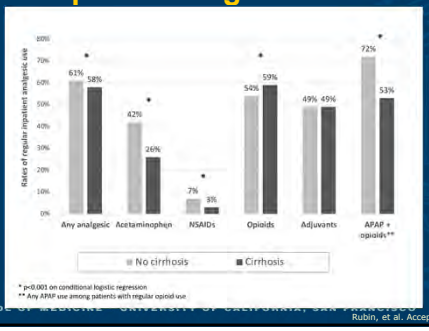
CLINICIAN
- No guidelines
- Discomfort with analgesic options
- Stigma/bias

SYSTEM
- Regulatory issues
- Transplant center requirements
- Fragmentation of care

**Slide used with permission from Jessica Rubin MD*

Adapted from Rakoski M, et al. Clinical Liver Disease. 2018;11(6):135-140.

How is pain managed in cirrhosis?



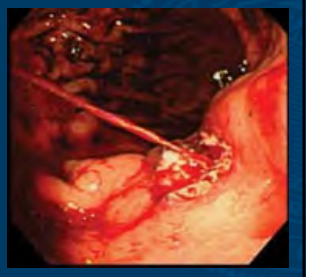
Rubin, et al. Accepted for publication.

Myth: patients with cirrhosis can't take acetaminophen

- Acetaminophen (APAP) is the leading cause of drug-induced liver injury in the US
  - This occurs when APAP is taken above recommended limits (4g/day in patients without liver disease)
- Upper limit of APAP in chronic liver disease = 2 grams/day
  - Potential for decreased metabolism of APAP
  - Chronic alcohol use depletes glutathione stores, thereby lowering the threshold for APAP toxicity
- Combination opioid/APAP formulations may be high risk due to habituation to opioid component leading to escalating use and increased APAP intake

NSAIDs are high risk in cirrhosis

- Acute kidney injury
  - Prostaglandin inhibition reduces renal perfusion
  - Higher risk in patients with ascites on diuretics
- Gastrointestinal bleeding risk
  - Gastric mucosal injury
  - Decreased platelet aggregation due to thromboxane inhibition



Opioid impact on morbidity and mortality

- Mechanisms that impact hepatic encephalopathy (HE)
  - Decreased metabolism and clearance
  - Increased brain sensitivity to opioids in patients with HE
  - Decreased gut motility
- Outcomes
  - Increased risk of (all cause) hospitalization
  - Post-transplant outcomes in pre-transplant opioid users
    - Poorer graft survival
    - Increased hospitalizations

Rogal, *Clin Transplant*, 2016; Randall, *Liver Transpl*, 201; Braun, *Am J Surg*, 2021; Bosilkovsk, *Drugs*, 2012; Acharya, *Alim Pharm Ther*, 2017; Chandok, *Mayo Clin Proc*, 2010.

Take home points: Pain management in cirrhosis

- Acetaminophen is the safest pain reliever in patients with cirrhosis
  - Limit intake to <2g/day
- Avoid NSAIDs, particularly in patients with ascites
- Avoid opioids, particularly in patients with hepatic encephalopathy

Wait, what about the AKI?

55yo woman with NASH cirrhosis, hospitalized with tense ascites, rising MELD score, and **AKI**, found to have SBP.

Labs: Cr 2.87, Na 130, WBC 5, hct 32, plts 83, INR 2.0, tbili 7, albumin 2.7
Baseline Cr 0.5

Wait, what about the AKI?

55yo woman with NASH cirrhosis, hospitalized with tense ascites, rising MELD score, and **AKI**, found to have SBP.

Labs: Cr 2.87, Na 130, WBC 5, hct 32, plts 83, INR 2.0, tbili 7, albumin 2.7
Baseline Cr 0.5

So, does she have hepatorenal syndrome? What do I do about it?

What are the next steps in evaluation of AKI in this patient?

A. This is hepatorenal syndrome. Start midodrine and octreotide.
B. The patient is volume overloaded. Increase diuretics.
C. Hold diuretics, give IV albumin, diagnostic paracentesis
D. Hold diuretics, give IV NS, diagnostic paracentesis
E. Continue diuretics, give IV albumin, diagnostic paracentesis

What are the next steps in evaluation of AKI in this patient?

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AKI in cirrhosis
International Ascites Club criteria

Subject	Definition
Baseline sCr	• sCr obtained within 3 months prior to admission • If >1 value within the previous 3 months, the value closest to the admission • If no previous sCr, the sCr on admission should be used
Definition of AKI	• **Increase in sCr ≥0.3** mg/dl (≥26.5 μmol/L) within **48 hours** or • **Increase sCr ≥50%** within the prior **7 days**

- AKI as defined is associated with ICU transfer, longer hospital stay, and increased in-hospital and 90-day mortality

Angeli, *Gut*, 2015.

Management of AKI

- Investigate non-HRS causes:
  - Review medication history: diuretic dose change or initiation, NSAIDs or other nephrotoxic drugs, iodinated contrast
  - Urinalysis with microscopy
  - Renal ultrasound
- Evaluate for infection
- Administer volume expansion: IV albumin 1g/kg (using 25% albumin) x 2 days

Hepatorenal syndrome (HRS)-AKI
International Ascites Club Criteria

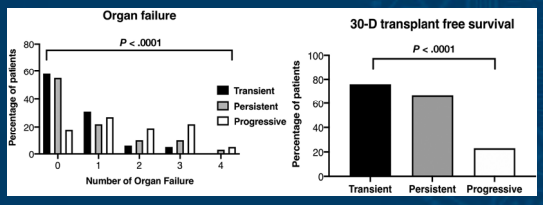
- Cirrhosis with ascites
- AKI as defined by ICA-AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and volume expansion
- Absence of shock
- No nephrotoxins
- No signs of structural kidney injury
  - Urine protein <500mg/day
  - No microscopic hematuria
  - Normal renal ultrasound

Angeli, *Gut*, 2015.
Biggins, *Hepatology*, 2021

Treatment of hepatorenal syndrome

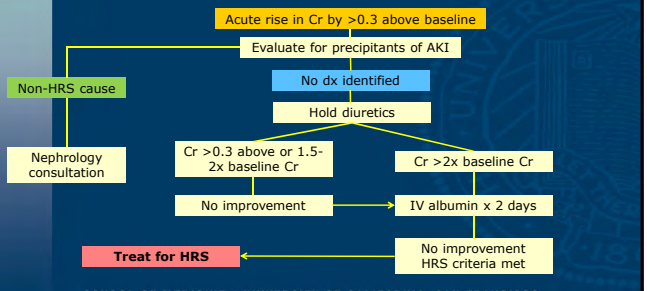
- Vasoconstriction of systemic and splanchnic circulation to improve effective circulating volume and renal perfusion
  - Oral: midodrine
  - IV/SQ
    - Octreotide 100-200mcg SQ TID (with midodrine)
    - Norepinephrine: requires ICU level of care or special floor protocol
    - Terlipressin: not approved for use in the US
- Albumin dose of 40-50g/day

AKI progression is associated with illness severity and survival



Wong, *Clin Gastro Hep*, 2021.

Management of AKI in cirrhosis



Adapted from Biggins et al, *Hepatology*, 2021.

Should my patient get a TIPS?

Which patient(s) is (are) candidates for TIPS?

A. 57F with refractory ascites, MELD 32
B. 57F with refractory ascites, MELD 16
C. 43M with large varices on routine endoscopy, platelet count 43, MELD 15
D. 43M admitted with variceal bleeding, Child's B cirrhosis
E. A&C
F. B&D
G. All of the above

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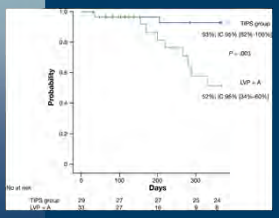
C. 43M with large varices on routine endoscopy, platelet count 43, MELD 15
D. 43M admitted with variceal bleeding, Child's B cirrhosis
E. A&C
F. **B&D**
G. All of the above

Case 3a

- 57F with cirrhosis due to autoimmune hepatitis with refractory ascites.
- She has been getting therapeutic paracentesis for the past 4 months, and the frequency has now increased to every 5 days, with removal of 8-10L each time
- She is hospitalized frequently due to intermittent problems with volume overload, AKI, and/or hyponatremia
- Labs: INR 1.5, Na 136, Cr 1.1, tbili 2.2, MELD-Na 16

TIPS confers survival benefit over serial paracentesis



LT-free Survival

Predictors of mortality

	HR	95% CI
TIPS	0.61	0.41-0.91
Age	1.024	1.001-1.048
Bilirubin	1.22	1.029-1.46
Sodium	0.95	0.92-0.99

Bureau, *Gastro*, 2017. Salerno, *Gastro*, 2007.

TIPS vs. serial paracentesis

- Incidence of hepatic encephalopathy is similar between TIPS vs paracentesis groups, though severe HE may be more common with TIPS

Bureau, *Gastro*, 2017. Salerno, *Gastro*, 2007.

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Most other portal hypertensive complications improve with TIPS

	TIPS	LVP
Total	15%	28%
GI bleeding	8%	13%
SBP	2%	3%
HRS	5%	13%

Bureau, *Gastro*, 2017. Salerno, *Gastro*, 2007.

Contraindications to TIPS

Relative	Absolute
Hepatocellular carcinoma, especially centrally located	Primary prevention of variceal bleeding
Obstruction of all HVs	Congestive heart failure
PV thrombosis	Severe tricuspid regurgitation
Moderate pulmonary hypertension	Severe pulmonary hypertension
Severe coagulopathy (international normalized ration >5)	Multiple hepatic cysts
Thrombocytopenia of <20,000 cells/cm^3	Uncontrolled systemic infection or sepsis
Hepatic encephalopathy	Unrelieved biliary obstruction

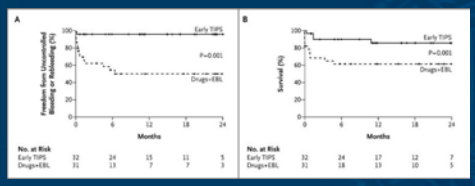
MELD >15-18 and/or total bilirubin >3

Patidar, *Clin Liver Dis*, 2014.

Case 3b

- 43yo man with alcohol related cirrhosis who is hospitalized with hematemesis
- Recent onset ascites and jaundice
- VS: HR 120 BP 95/63 RR 20 SpO2 95%
- Gen: uncomfortable, lethargic, hematemesis in ED
- Abd: distended, bulging flanks, mildly uncomfortable to palpation but no peritoneal signs. +melenic stool
- Labs: WBC 4, Hb 5.7, plts 80, INR 1.6, Na 136, Cr 0.9, total bili 4.3, albumin 2.9, CP C10, MELDNa 18
- Intubated for airway protection, 2 PIVs, transfused 2u pRBCs, protonix gtt, octreotide gtt, ceftriaxone
- Urgent EGD shows actively bleeding EVs

Early TIPS in variceal bleeding



- Greatest benefit in Child's C cirrhosis in this RCT
- Several studies (incl meta-analysis) show similar findings supporting use of pre-emptive TIPS

Garcia-Pagan, *NEJM*, 2010.

Take home points

- TIPS has a survival benefit in patients with refractory ascites and select patients with variceal bleeding
- If you are considering TIPS, you should also be considering referral for liver transplant evaluation
- Pre-TIPS checklist:
  - TTE to rule out heart failure and pulmonary hypertension
  - CT to evaluate hepatic vasculature

Quickfire Challenge

Quickfire Case 1

- 57F with NASH cirrhosis is hospitalized for the 4th time in 2 months with shortness of breath
- She has a history of hepatic hydrothorax that has gotten progressively worse over time
- She undergoes therapeutic thoracentesis now twice weekly, with 1-2L fluid removed each time
- She is frustrated with her frequent hospitalizations and poor quality of life
- Diuretic doses have been increased to the highest tolerable dose, with higher doses associated with AKI, hyponatremia, and/or hyperkalemia in the past

Quickfire Case 1

- VS: T36.4 HR 73 BP 109/53 RR 24 SpO2 95% 2LNC
- Gen: chronically ill
- Resp: Decreased breath sounds throughout all lung fields on the right
- Labs: WBC 6, hct 28, plt 51, INR 1.4, Na 134, Cr 1.02, total bili 2, albumin 2.7, MELD-Na 16

QC1. What is the best treatment option available to this patient with refractory hepatic hydrothorax, MELD-Na 16?

A. Pleurex catheter insertion
B. Serial therapeutic thoracentesis
C. TIPS
D. Pleurodesis

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A. Pleurex catheter insertion
B. Serial therapeutic thoracentesis
C. **TIPS**
D. Pleurodesis

TIPS and hepatic hydrothorax

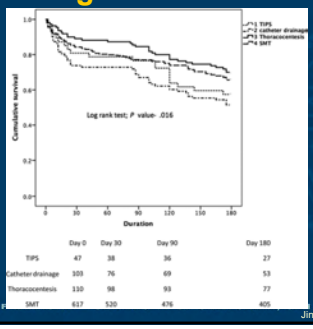
- Response rates: 59-82%
- Mortality
  - 30-day: 5-25%
  - 1-year: 36-52%

Pleural catheter for HH

- Attractive option for patients who need frequent thoracentesis or who are at higher risk of bleeding
- May result in spontaneous pleurodesis in 33%
- Risk of complications: 36%
  - 10-16% SBE
  - Deaths typically due to sepsis
- If used as a bridge to transplant, plan should be made in conjunction with transplant team

Kniese, *Chest*, 2019.
Shojaee, *Chest*, 2019

Patients with HH are at high risk of death regardless of management



Jindal, *Liver Int*, 2019.

Quickfire Case 2

- 47M with alcohol related cirrhosis is brought into the ED with altered mental status
- He had been taking lactulose as prescribed, but his family notes that he has not had a bowel movement in the past 24 hours

Quickfire Case 2

- VS: T36.7 HR 80 BP 117/62 RR 12 SpO2 99%
- Gen: chronically ill, muscle wasting
- Neuro: Unarousable to verbal stimuli, occasionally grunts in response to deep physical stimuli. Oriented x 0. +clonus
- Labs: WBC 5, hct 33, plt 95, INR 1.9, Na 136, Cr 0.97, total bili 4.7, albumin 2.6

QC2. What are your next steps for management of severe HE?

A. Check ammonia. Titrate lactulose dose according to serial ammonia levels
B. Intubate. Place feeding tube for frequent administration of lactulose and rifaximin +/- PEG. Adjust dose according to mental status and stool output
C. Give flumazenil
D. Intubate. Use midazolam for sedation. Administer lactulose PR

QC2. What are your next steps for management of severe HE?

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Management of hepatic encephalopathy (HE)

Overt HE

Triage to appropriate level of care

Evaluate and treat precipitants
- Infection
- GI bleeding
- AKI/hypovolemia
- Sedating meds
- Medication nonadherence

Severe HE

Intubate if needed
Lactulose* and rifaximin per NGT/FT, titrate to mental status
Rifaximin

If no improvement in 24 hrs
Add zinc sulfate
CT head +/- neuro consult
Evaluate for PS shunt

Non-severe HE

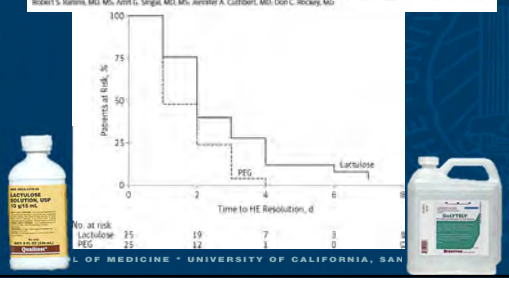
Lactulose PO, titrate to mental status
Add rifaximin if not already taking

Continue maintenance therapy once HE resolves

*or PEG

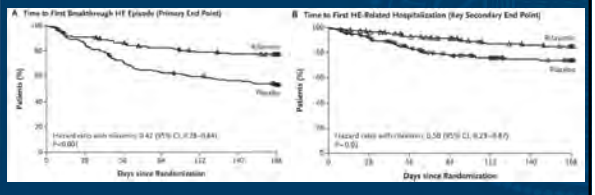
Lactulose vs Polyethylene Glycol 3350-Electrolyte Solution for Treatment of Overt Hepatic Encephalopathy
The HELP Randomized Clinical Trial

JAMA Internal Medicine



Rifaximin reduces hospitalization and its use is cost-effective

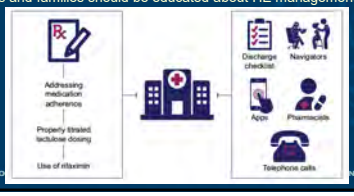
- Rifaximin reduces episodes of breakthrough HE, need for HE-related hospitalization, and length of hospitalization
- Numerous studies have demonstrated cost-effectiveness of rifaximin



Bass, *NEJM*, 2010. Neff, *PharmacoEconomics*, 2018. Orr, *Liver International*, 2016. Rahimi, *Am J Med*, 2021. Vadharya, *Medcine*, 2020.

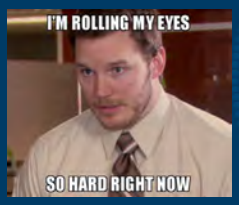
Coordination of care after HE hospitalization

- ~40-50% of patients discharged after a hospitalization for HE may not fill prescriptions for HE meds, in part related to medication cost (rifaximin >>>>> lactulose)
  - Measures should be taken to ensure patients can access rifaximin after hospital discharge
  - Patients and families should be educated about HE management

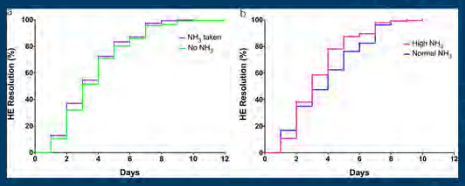


Frenette, *Dig Dis Sci*, 2021.

What about ammonia levels?



Ammonia levels have no impact on HE outcomes



Haj, *Am J Gastro*, 2019.

Quickfire Case 3

- 55F with NASH cirrhosis with a history of ascites on diuretics, presents to the emergency department with complaints of abdominal pain and increasing distension.
- Ascitic fluid analysis from paracentesis in 2018 and 2019 showed high SAAG and low total protein
- VS: T37 HR 65 BP 110/70 RR 20 SpO2 98%
- Gen: chronically ill, slightly uncomfortable due to abdominal distension
- Resp: normal other than decreased BS at bases
- GI: tensely distended abdomen with dullness to percussion, nontender
- Neuro: AAOx3, no asterixis
- Labs: WBC 5, hct 30, plt 55, INR 2.3, Na 130, BUN 53, Cr 1.6, total bili 5, albumin 3.0

QC3a. What are your next steps for evaluating worsening ascites?

A. Diagnostic paracentesis, with fluid sent for culture in blood culture bottles
B. Diagnostic paracentesis, with fluid sent for culture in a sterile tube
C. No need for paracentesis, there is no abdominal tenderness, fever, nor leukocytosis
D. Arrange for urgent TIPS

QC3a. What are your next steps for evaluating worsening ascites?

A. **Diagnostic paracentesis, with fluid sent for culture in blood culture bottles**
B. Diagnostic paracentesis, with fluid sent for culture in a sterile tube
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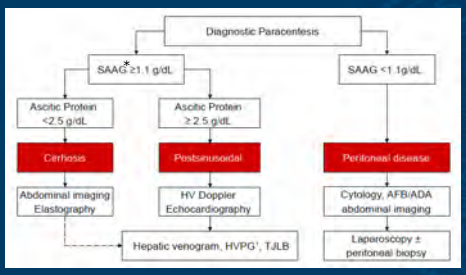
Evaluation of ascites



*Serum:ascites albumin gradient (SAAG) = serum ascites – albumin ascites

Biggins et al, *Hepatology*, 2021.

Diagnostic paracentesis

Diagnostic paracentesis

Diagnostic paracentesis

	1st paracentesis	Subsequent paracentesis
SAAG	Yes	No
Cell count w/ diff	Yes	Yes
Culture	Yes	Yes
Protein	Yes	Maybe*
Glucose	Only as driven by clinical suspicion (e.g., no cirrhosis, secondary peritonitis, malignancy, pancreatitis)	
Cytology		
Amylase		

*If needed to determine primary SBP prophylaxis and/or concerned about secondary peritonitis

Biggins et al, *Hepatology*, 2021.

QC3b. When should I do paracentesis on this patient?

A. Within 4 hours of admission
B. Within 1 day of admission
C. I told you I'm not doing paracentesis, there is no abdominal tenderness, fever, nor leukocytosis
D. Whenever IR can do the procedure

QC3b. When should I do paracentesis on this patient?

A. Within 4 hours of admission
B. **Within 1 day of admission**
C. I told you I'm not doing paracentesis, there is no abdominal tenderness, fever, nor leukocytosis
D. Whenever IR can do the procedure

Rosenblatt et al, *Am J Gastro*, 2019.
Orman et al, *Clin Gastro Hep*, 2014.
Kim et al, *Am J Gastro*, 2014.

Spontaneous bacterial peritonitis (SBP)

- ~30% of patients with SBP may lack typical signs/symptoms of fever, abdominal pain, and/or leukocytosis
- Diagnosis: 250 PMNs/mm^3
- Prognosis
  - In-hospital death: 10-20%
  - Median survival: 9 months
  - Recurrent SBP: 40-70% at 1 year

Garcia-Tsao, *Sherlock's Dis of the Liver and Biliary System*, 2011.

Quickfire Case 3 (cont'd)

- 55F with NASH cirrhosis presents to the emergency department with complaints of abdominal pain and distension
- US: Coarse, nodular liver without focal mass. Splenomegaly. Patent portal and hepatic veins. Large ascites
- Paracentesis with removal of 5L amber fluid
  - WBC 893 (75% PMNs), RBC 100
  - Albumin 1.0, total protein 1.2
  - Cultures pending

QC3b. What are your next steps in management?

A. Supportive care. Wait to start antibiotics until culture results return
B. Treat for SBP with vancomycin.
C. Arrange for urgent TIPS
D. Treat for SBP with ceftriaxone. Give 1.5g/kg IV albumin on day 1, 1g/kg IV albumin on day 3

QC3b. What are your next steps in management?

A. Supportive care. Wait to start antibiotics until culture results return
B. Treat for SBP with vancomycin.
C. Arrange for urgent TIPS
D. **Treat for SBP with ceftriaxone. Give 1.5g/kg IV albumin on day 1, 1g/kg IV albumin on day 3**

Prevention of HRS in SBP

- RCT of 126 patients with SBP treated with cefotaxime, albumin vs no albumin
  - 1.5g/kg on day 1, 1g/kg on day 3

	Albumin	Control	p value
Renal impairment	10%	33%	0.002
Death			
In hospital	10%	29%	0.01
3 months	22%	41%	0.03

- Impact may be greatest in patients with Cr>1, BUN>30, and/or tbili >4

Sort P et al, *NEJM*, 1999.
Sigal et al. *Gut*, 2007.

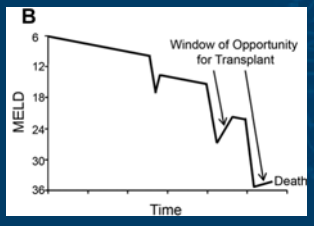
QC4. Which patient(s) should you refer for liver transplant evaluation urgently?

A. 35M with alcohol associated cirrhosis with 3 months sobriety, refractory ascites, AKI/HRS, MELD 32
B. 53F with NASH cirrhosis, BMI 41, DM, frequent admissions for AKI and/or HE, MELD 32
C. 71M with cirrhosis due to HBV + NASH, acute decompensation from HBV flare, MELD 37. Working full time and exercising regularly right before hospitalization
D. 65F with cirrhosis due to autoimmune hepatitis, CKD stage 3, worsening liver failure and AKI on CKD after variceal bleeding, MELD 31
E. All of the above

QC4. Which patient(s) should you refer for liver transplant evaluation urgently?

A. 35M with alcohol associated cirrhosis with 3 months sobriety, refractory ascites, AKI/HRS, MELD 32
B. 53F with NASH cirrhosis, BMI 41, DM, frequent admissions for AKI and/or HE, MELD 32
C. 71M with cirrhosis due to HBV + NASH, acute decompensation from HBV flare, MELD 37. Working full time and exercising regularly right before hospitalization
D. 65F with cirrhosis due to autoimmune hepatitis, CKD stage 3, worsening liver failure and AKI on CKD after variceal bleeding, MELD 31
E. **All of the above**

Narrow window for LT in acute on chronic liver failure (ACLF)



Asrani, *Clin Liver Dis*, 2014.

Cases or questions from the audience

Thank you!

Danielle.Brandman@ucsf.edu

SCHOOL OF MEDICINE • UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

THROMBOEMBOLISM Q & A 2021

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Objectives

- Lingering questions from this mornings presentations
- Duration of anticoagulation for VTE
- Approach to subsegmental PE, calf vein DVT and superficial vein thrombosis
- Role of thrombophilia work up
- Resuming anticoagulation after a bleed

Resources

- AC Forum clinical guidance-VTE, splancnic vein, reversal etc. https://acforum.org/web/education-guidance.php
- University of Washington Anticoagulation http://depts.washington.edu/anticoag/home

Case

51 year old man with no PMHX presents with acute CP and SOB, BP stable, HR 120s O2 sat 92%, d-dimer 1500, CT PE with bilateral PE in all lobes with RV/LV ratio > 1.0. BNP 370, trop 1.5. He is started on rivaroxaban. He has no identifiable provoking factors. How long should he remain on anticoagulation?

1) At least 3 months
2) One year
3) Forever

ESC PE Guidelines-Duration of Therapy

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[c]	DURATION OF AC
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures	≥ 3 months
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight	ESC: Suggest indefinite CHEST 2021 Recommend AGAINST indefinite Weak rec/mod evid
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease	
	No identifiable risk factor		
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome	Recommend indefinite

Konstantinedes et al. Eur Heart J. 2019;

Table 4 Estimated risk of venous thromboembolic disease recurrence after anticoagulants discontinuation in proximal deep vein thrombosis

Estimated risk of recurrence	Risk factor category for index DVT	Examples
Low (<3%/year)	Major transient/ reversible risk factors	• Surgery with general anaesthesia for longer than 30 min • Confined to bed in hospital (only "bathroom privileges") for at least 3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8%/year)	Minor transient/ reversible risk factors	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Obesity (high body mass index) • Ongoing oestrogen therapy • Pregnancy or puerperium • Confined to bed out of hospital for at least 3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for at least 3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel and active autoimmune diseases (risk may change depending on activity and treatment)[a]
High (>8%/year)	Major persistent risk factors	• One or more previous episodes of VTE in absence of a major transient or reversible factor • Active cancer • Antiphospholipid antibody syndrome • Major hereditary thrombophilia[b] • Strong family history[c]
Variable	First episode with no identifiable risk factors	Higher recurrency risk: men, proximal DVT, concomitant PE, high D-dimers at anticoagulation discontinuation, age

Mazzolai et al European Journal of Preventative Cardiology

Duration of Anticoagulation for VTE: 2016 CHEST and AC Forum Guidelines/Guidance

Indication	CHEST 2021[1]	AC Forum 2016[2]
1st provoked VTE	3 mo	3 mo (surgical)[a] ≥3 mo (medical)
1st unprovoked VTE	Extended[b]	Extended
2nd unprovoked VTE	Extended[b]	Extended
VTE + cancer	Extended[b]	Extended

[a]Unless risk factors for recurrence persist
[b]No scheduled stop date, unless high bleeding risk.
Kearon C et al. *Chest*. 2016;149(2):315-352. Streiff MB et al. *J Thromb Thrombolysis*. 2016;41:32-67

VTE and Bleeding Risk: 2016 CHEST Guideline

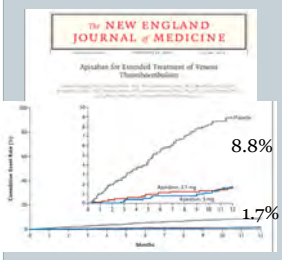
Risk of Major Bleeding After 3 Mo of Anticoagulation, %/y	Low (*0 risk factors*)	Moderate (*1 risk factor*)	High (*≥2 risk factors*)
Baseline risk	0.3	0.6	≥2.5
Increased risk	0.5	1.0	≥4.0
Total risk	0.8	1.6	≥6.5

Risk Factors for Bleeding with Anticoagulation

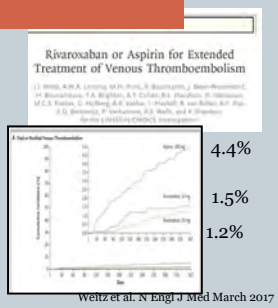
- **Age >65 y**
- **Age >75 y**
- **Previous bleeding**
- **Cancer**
- **Renal or hepatic failure**
- **Thrombocytopenia**
- **Previous stroke**
- **Diabetes**
- **Anemia**
- **Antiplatelet therapy**
- **Poor anticoagulation control**
- **Recent surgery**
- **Frequent falls**
- **Alcohol abuse**
- **NSAID use**

Reprinted from Ch.F. Dunn et al, Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report, 315-352, with permission from the American College of Chest Physicians.

CHEST 2021-suggest reduced dose DOAC over full dose for extended phase anticoagulation



Agnelli etal NEJM 2013



Weitz et al. N Engl J Med March 2017

UNPROVOKED VTE

- All - 3-6 months of FULL intensity anticoagulation
  - At 3-6 months determine candidacy for secondary prevention
- ~50% will develop recurrent VTE in 10 years off anticoagulation; Case fatality rate of VTE is ~4% in all comers but closer to 9% in PE
- Case fatality rate of bleeding is ~10%
- Case by case decision…consider continuation if not high bleeding risk. Most compelling in low bleed risk patients and in those with PE

Secondary Prevention Options
Low dose DOAC***
Full dose anticoagulation
ASA

Do not use dose reduced DOAC:
Cancer
Recurrent VTE on AC
Obesity

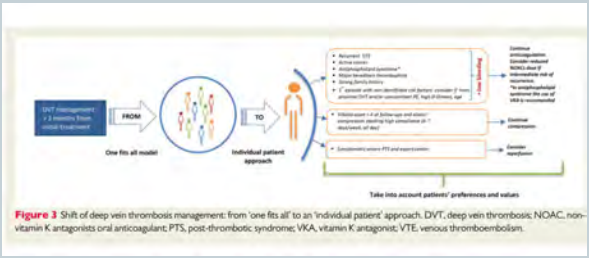


Figure 3 Shift of deep vein thrombosis management: from 'one fits all' to an 'individual patient' approach. DVT, deep vein thrombosis; NOAC, non-vitamin K antagonists oral anticoagulant; PTS, post-thrombotic syndrome; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Mazzolai et al European Journal of Preventative Cardiology

Case

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1) At least 3 months
2) One year
3) Forever

After 6 months you:
1. Continue full dose rivaroxaban
2. Reduce dose of rivaroxaban to prophylactic intensity
3. Transition to ASA

Subsegmental PE

A 77 yo man had undergoes colectomy for recurrent bleeding from diverticulosis. On POD # 3 he becomes tachycardic to the 110s. WBC is elevated.The surgical team orders an abdominal CT which shows a fluid collection concerning for early abscess. It also shows an isolated RLL subsegmental PE. A dedicated CTa shows a single isolated RLL subsegmenral PE. Do you anticoagulate this patient?

a) Sure, it is a PE.
b) No this is incidental. Let's pretend we don't know it is there

Isolated Subsegmental PE

Definition: PE shown on CT angiography that occurred in a subsegmental branch but no larger order of vessels. The subsegmental PE may involve one or more than one subsegmental branch

Identification of ISSPE has tripled over past decade

Isolated Subsegmental PE

Anticoagulant treatment for subsegmental pulmonary embolism

Hugo HB Yoo[1], Thaís HAT Queluz[2], Regina El Dib[2]

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Contact address: Hugo HB Yoo, Department of Internal Medicine, Botucatu Medical School, UNESP - Univ Estadual Paulista, Distrito de Rubiao Junior, s/n, Campus de Botucatu, Botucatu, Sao Paulo, 18618-970, Brazil. hugo@ibnb.unesp.br.

Editorial group: Cochrane Vascular Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2016.
Review content assessed as up-to-date: 15 December 2015.

Citation: Yoo HHB, Queluz THAT, El Dib R. Anticoagulant treatment for subsegmental pulmonary embolism. *Cochrane Database of Systematic Reviews* 2016, Issue 1. Art. No.: CD010222. DOI: 10.1002/14651858.CD010222.pub3.

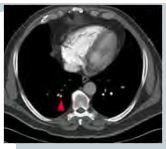
Summary of main results

There is currently no evidence from randomised controlled trials to assess the effectiveness and safety of anticoagulation therapy versus no intervention in patients with isolated subsegmental pulmonary embolism (SSPE) or incidental SSPE.

Isolated Subsegmental PE

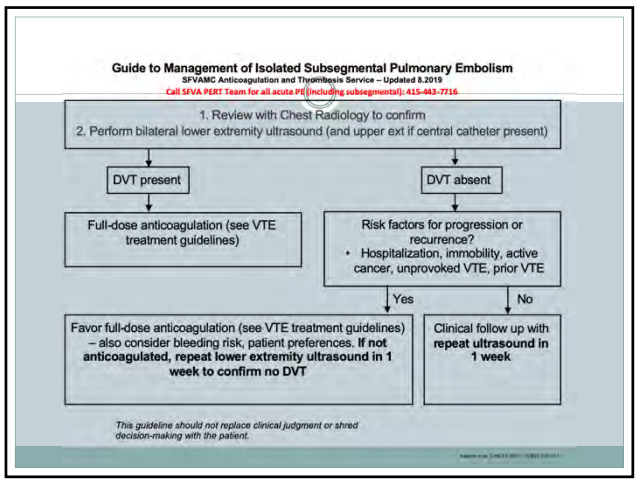
Whether to Anticoagulate Subsegmental PE

***19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation** (Grade 2C) **or (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C).



IS IT REAL?
ISSPE is more likely to be TRUE if....good quality scan, mult defects, centrally located, d-dimer elevated, seen on mult cuts, patient symptomatic vs incidental;high pretest prob of PE
Get u/s of bilateral lower extrem (upper if CVC)
Consider risk of recurrence-higher if not post op; immobile; active cancer
IF high bleed risk –don't AC: get serial u/s

Kearon et al. Chest. 2016;149(2):315-352.



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a) Sure, it is a PE.
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Superficial Vein Thrombosis

A 67 year old man with cirrhosis, new diagnosis of HCC is admitted with diarrhea, lowish BP and AKI. On exam he has bilateral lower extremity swelling, R> L. In the ED he has an ultrasound which shows thrombosis of the greater saphenous vein extending from the calf proximally and terminating 6 cm from the deep femoral vein. What do you recommend?

a. Prophylactic fondaparinux
b. Prophylactic rivaroxaban
c. Full dose DOAC or warfarin
d. Full dose LMWH
e. Warm compresses, no anticoagulation

Superficial Vein Thrombosis –CHEST Guidelines

- Factors that favor the use of AC : extensive SVT; above the knee, close to saphenofemoral junction; severe symptoms; involvement of the greater saphenous vein; history of VTE or SVT; active cancer; recent surgery
- In patients with superficial vein thrombosis of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B).

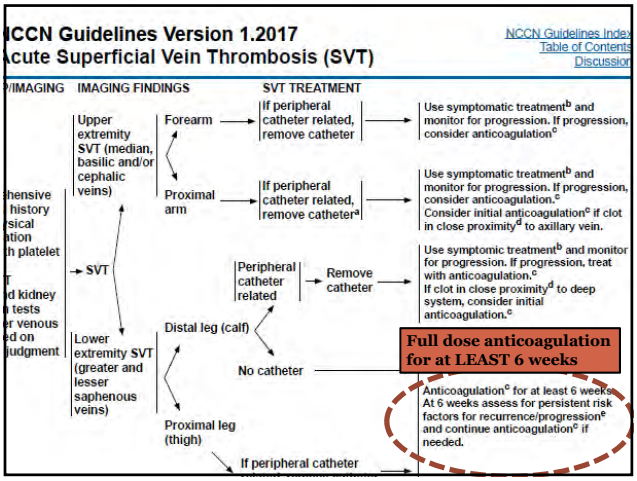
CALISTO TRIAL- fonda vs placebo
Primary outcome 1% vs 6%

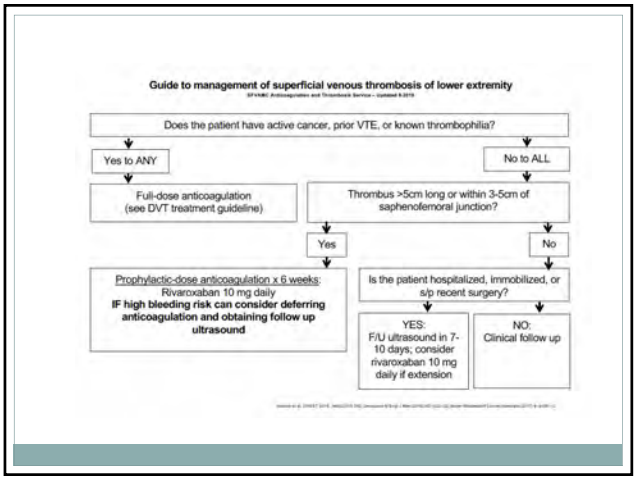
Kearon C et al. *Chest*. 2012

Superficial Vein Thrombosis

Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 2b trial

- >400 pts symptomatic SVT riva 10 mg v fonda 2.5mg
- Symptomatic above the knee SVT of at least ≥ 5 cm length + other risk factor (>65 , male,hx VTE , cancer, autoimmune disease, non-varicose veins)
- No difference in primary efficacy outcome
- After 6 weeks 7% recurrence risk in high risk patients (v 1.2% in CALISTO)





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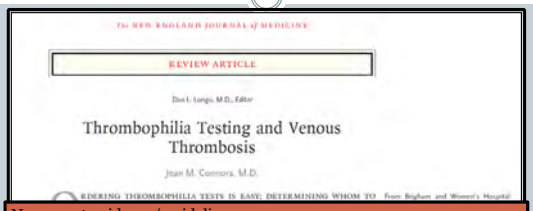
a. Prophylactic fondaparinux
b. Prophylactic rivaroxaban
c. Full dose DOAC or warfarin
d. Warm compresses, no anticoagulation

Thrombophilia Testing

50 year old man presents with unprovoked PE. He is hemodynamically stable but CT PE shows elevated RV/LV ratio. ECHO is ordered. He is admitted and started on rivaroxaban. Should you send a work up for thrombophilia?

- Yes-why not, he is here.
- No-then I am going to have interpret it and who needs that

Thrombophilia Testing


REVIEW ARTICLE

Thrombophilia Testing and Venous Thrombosis

Jean M. Connors, M.D.

No current guidance/.guidelines
EXCEPT ASH Choosing Wisely Campaign-"do not test in provoked VTE"
Results of thrombophilia testing should RARELY affect clinical decisions about VTE treatment-no strong influence on recurrence risk beyond stratification based on clinical presentation
Can help explain "why"
Can be of interest to family members
Current tests are insufficient for identifying inherited VTE risk

Who should we suspect harbors thrombophilia?

Table 1. Clinical Characteristics Suggestive of Inherited Thrombophilia in Patients with Venous Thromboembolism (VTE).

Thrombosis at a young age (<50 yr), especially in association with weak provoking factors (minor surgery, combination oral contraceptives, or immobility) or unprovoked VTE
Strong family history of VTE (first-degree family members affected at a young age)
Recurrent VTE events, especially at a young age*
VTE in unusual sites such as splanchnic or cerebral veins†

* The antiphospholipid syndrome must also be considered, but it is not inherited.
† Patients with splanchnic-vein VTE should be assessed for myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria.

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UNPROVOKED THROMBOSIS IN YOUNG PATIENT THINK ABOUT:

- PROTEIN C, S, ANTITHROMBIN DEFICIENCY→OFTEN POSITIVE FAMILY HISTORY
- FACTORV LEIDEN MUTATION AND PROTHROMBIN GENE MUTATION -Northern European descent
- APLS-PRIMARY OR SECONDARY (lupus)
- MAY THURNERS SYNDROME- ILIAC VEIN COMPRESSIOJN SYNDROME…LEFT LOWER EXTREM VENOUS COMPRESSION-LEFT ILIAC VEIN COMPRESSED BY RIGHT ILIAC ARTERY
- UPPER EXTREMITY DVT-PAGET SCHROEDERS SYNDROME-THORACIC OUTLET SYNDROME WITH VENOUS COMPRESSION
- NEPHROTIC SYNDROME/IBD/PNH
- PREGNANCY, IVF
- CANCER (less likely < 50 yo)

VENOUS AND ARTERIAL THROMBOSIS

- APLS
- PFO-with paradoxical embolism
- HYPERHOMOCYSTIENEMIA
- SICKLE CELL
- P VERA
- PNH
- HIT
- CANCER
- DIC
- Beurgers disease
- Hyperviscosity-MGUS, MM

Thrombophilia Tests

Table 1. Thrombophilia Tests and Prevalence of Risk Factors.*

Thrombophilia Type	Assay	Prevalence
Inherited		
Increased procoagulant activity (common)		
Factor V Leiden	APCR and PCR	White, 5.0% Hispanic, 2.2% Black, 1.2% Native American, 1.2% Asian, 0.4%
Prothrombin gene mutation	PCR	White, 3%
Decreased anticoagulant activity (uncommon)		
Protein C	Activity assay	<0.5%
Protein S	Activity assay	<0.5%
Antithrombin	Activity assay	<0.5%
Acquired		
Lupus anticoagulants†	In vitro clotting assay: PTT-LA, dRVVT, silica clotting time ELISA: ACL IgG and IgM, beta-2 glycoprotein I IgG and IgM	Overall, 0–5% Patients with VTE, 10–12% Patients with SLE, 35%

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Summary of Recommendations Regarding Testing for Thrombophilia.

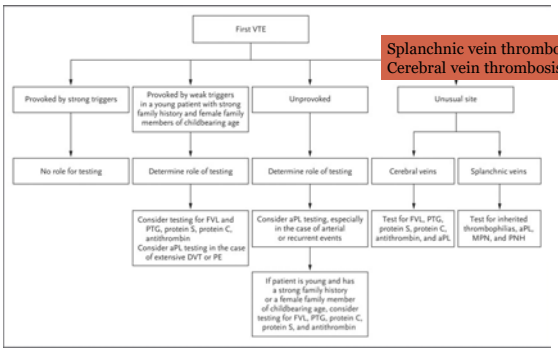
Table 2. Summary of Recommendations Regarding Testing for Thrombophilia.*

Recommendation	Explanation
Do not test at time of VTE event	Test at completion of anticoagulant therapy for provoked VTE; for unprovoked VTE, test after treatment for acute event if cessation of anticoagulant therapy is contemplated and test results might change management strategy
Do not test while patient is receiving anticoagulant therapy	Test when VKA has been stopped for at least 2 wk, DOAC has been stopped for at least 2 days (preferably longer), and UFH or LMWH for antithrombin levels has been stopped for more than 24 hr
Do not test if VTE is provoked by strong risk factors	Strong risk factors are major trauma, major surgery, immobility, major illness
Consider testing	Consider testing in patients in whom VTE occurs at a young age in association with weak provoking factors or a strong family history of VTE or in patients who have recurrent VTE
Identify goals of testing	Identify goals in order to aid decision-making regarding future VTE prophylaxis, to guide testing of family members (especially regarding risk associated with COC or pregnancy in female family members), and to determine cause (especially for severe VTE, fatal VTE in family members, or VTE in an unusual location); test results alone should not be used for decision making regarding duration of anticoagulant therapy

* COC denotes combination oral contraceptives, DOAC direct oral anticoagulant, LMWH low-molecular-weight heparin, UFH unfractionated heparin, and VKA vitamin K antagonist.

The NEW ENGLAND JOURNAL of MEDICINE

Algorithm for Selecting Patients with a First Venous Thromboembolism (VTE) for Thrombophilia Testing.



Splanchnic vein thrombosis
Cerebral vein thrombosis

The NEW ENGLAND JOURNAL of MEDICINE

IMPACT OF ANTICOAGULATION & THROMBOSIS ON THROMBOPHILIA LABS

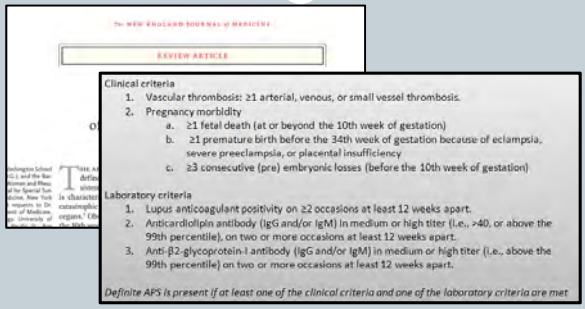
	ACUTE THROMBOSIS	WARFARIN	HEPARIN	DOAC
PROTEIN C,PROTEIN S	↓ (FALSE POSITIVE)	↓(FALSE POSITIVE)	NO EFFECT	FALSE NORAML
ANTITHROMBIN	↓ (FALSE POSITIVE)	↑(FASLE NEGATIVE)	↓(FALSE POSITIVE)	FALSE NORMAL
LUPUS ANTICOAGULANT	NO EFFECT	FALSE POSITVE	FALSE POSITIVE	FASLE POSITIVE
B2GP1, Acl ABS	NO EFFECT	NO EFFECT	NO EFFECT	NO EFFECT
FACTOR V LEIDEN	NO EFFECT	NO EFFECT	NO EFFECT	NO EFFECT
PROTHROMBIN GENE MUTATION	NO EFFECT	NO EFFECT	NO EFFECT	NO EFFECT

DEFER TESTING (3-6 MOS)

RARELY WE SEND APLS ACUTELYIF STRONG SUSPICION

CAN SEND FLV/PTG BUT IN HETEROZYGOUS FORM NOT IMPORTANT

Antiphospholipid Antibody Syndrome



Antiphospholipid Antibody Syndrome

- WHY- risk of recurrence off AC much higher; at risk for arterial disease, bridge therapy; DOACs generally avoided
- WHO- arterial and venous events, unexpected arterial events, recurrent thrombosis ON anticoagulation, underlying autoimmune d/o, prolonged aPTT
- WHAT-send Lupus anticoagulant, Beta 2 glycoprotein antibodies and anticardiolipin antibodies (IgG & Ig M)
- WHEN-LAC-don't do it on anticoagulation; antibodies you can send anytime
- IF POSITIVE-
  - must repeat in 12 weeks-high rate of transient positivity
  - LAC most predicative of 1st and recurrent VTE, triple positives at highest risk

Thrombophilia Testing

50 year old man presents with unprovoked PE. He is hemodynamically stable but CT PE shows elevated RV/LV ratio. ECHO is ordered. He is admitted and started on rivaroxaban. Should you send a work up for thrombophilia?

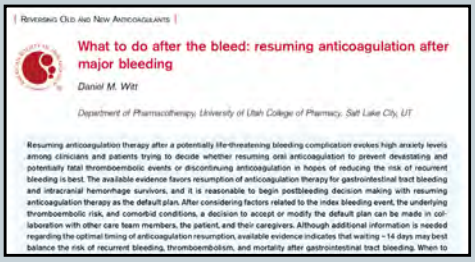
- Yes-why not, he is here.
- No-then I am going to have interpret it and who needs that

What To Do After the Bleed

76 y/o man with CAD (NSTEMI 2006), AFIB CHADS-Vasc=4 on warfarin and ASA is admitted with UGIB. INR is 3.0. He requires 3u PRBCs, vit K and FFP. EGD shows peptic ulcer disease. He is started on high dose PPI therapy, bx for H Pylori done. When should his anticoagulation be restarted?

a) Never
b) In two weeks
c) In three months
d) Let the primary provider deal with this one

What To Do After the Bleed



Reversing Old and New Anticoagulants

What to do after the bleed: resuming anticoagulation after major bleeding

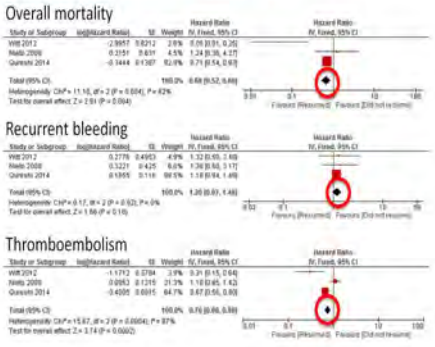
Daniel M. Witt

Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, UT

Resuming anticoagulation therapy after a potentially life-threatening bleeding complication evokes high anxiety levels among clinicians and patients trying to decide whether resuming oral anticoagulation to prevent devastating and potentially fatal thromboembolic events or discontinuing anticoagulation in hopes of reducing the risk of recurrent bleeding is best. The available evidence favors resumption of anticoagulation therapy for gastrointestinal tract bleeding and intracranial hemorrhage survivors, and it is reasonable to begin postbleeding decision making with resuming anticoagulation therapy as the default plan. After considering factors related to the index bleeding event, the underlying thromboembolic risk, and comorbid conditions, a decision to accept or modify the default plan can be made in collaboration with other care team members, the patient, and their caregivers. Although additional information is needed regarding the optimal timing of anticoagulation resumption, available evidence indicates that waiting ~14 days may best balance the risk of recurrent bleeding, thromboembolism, and mortality after gastrointestinal tract bleeding. When to

Witt Hematology 2016

Gastrointestinal Tract Bleeding

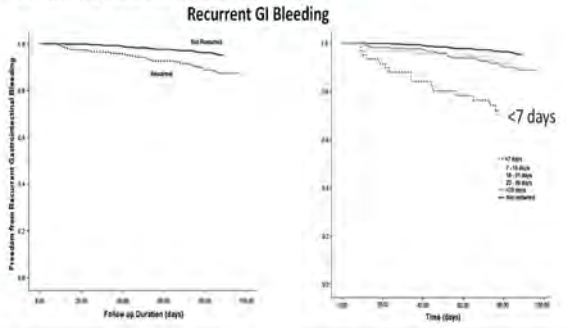


American Society of Hematology

Thromb Haemost 114:819

Gastrointestinal Tract Bleeding

Time-to-event adjusted analyses performed to find an association of restarting warfarin and recurrent GIB, arterial thromboembolism, and mortality.



American Society of Hematology

Am J Card 113:662

AC FORUM Clinical Guidance Antithrombotic Therapy for VTE

"IN THE EVENT OF GI BLEED WE SUGGEST WAITING AT LEAST 7 DAYS WITHOUT EVIDENCE OF ACTIVE BLEEDING AND AFTER ENDOSCOPIC TX BEFORE REINITIATING AC"

GIBs: DOACs vs Warfarin

Table 2
GIBs in studies on patients with AF : DOACs vs warfarin.
Data from: Connolly et al. N Engl J Med 2009;361:1139–1151; Patel et al. N Engl J Med 2011;365:883–891; Granger et al. N Engl J Med 2011;365:981–992; Giugliano et al. N Engl J Med 2013;369(22):2093–104.

	DOAC			Warfarin			DOAC/W (years-pts %)	RR (95% CI) GIB DOAC/W
	GI events (n)	Life-threatening GI events (n)	Total pts. (n)	GI events (n)	Life-threatening GI events (n)	Total pts. (n)		
Dabigatran 110 mg twice daily arm	133	67	6015	120	57	6022	1.12/1.02	1.10 (0.86–1.41) p: 0.43
Dabigatran 150 mg twice daily arm	182	94	6076	120	57	6022	1.51/1.02	1.50 (1.19–1.89) p < 0.001
Rivaroxaban 20 mg once daily arm	224	52 (1 fatal event)	7111	154	47 (5 fatal events)	7125	2.00/1.24	1.46 (1.117–1.902) p < 0.001
Apixaban 5 mg twice daily arm	105	ND	9088	119	ND	9052	0.76/0.86	0.879 (0.624–1.238) p = 0.33
Edoxaban 30 mg once daily arm	129	ND	7002	190	ND	7012	0.82/1.23	0.67 (0.53–0.83) p < 0.001
Edoxaban 60 mg once daily arm	232	ND	7012	190	ND	7012	1.23/1.51	1.23 (1.02–1.50) p = 0.03

ND: not determined.

Di Minno et al. Blood Reviews 2015.

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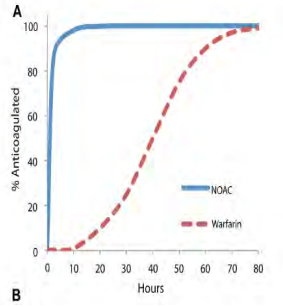
ND: not determined.

Di Minno et al. Blood Reviews 2015.

Resumption of DOACs



Anticoagulation **FULLY** therapeutic within *1-2 hours*

Only dabigatran has a reversal agent

Considerations After GIB on AC

- Reassess risk benefit of anticoagulation
  secondary prevention of VTE therapy, low CHADS-vasc
- Assess risk of rebleeding from source
  identifiable source, treatable lesion?
- Take steps to decrease risk of bleeding related to AC regimen
- Reconsider need for antiplatelet therapy
  if warfarin-was INR in range, is control good?
  spurious elevation in INR or poor TTR →DOAC
  increase INR monitoring->home POC INR?
- If ongoing strong indication for AC determine best time to restart therapy in multidisciplinary meeting with proceduralist -
  Remember DOAC immediately active

What To Do After the Bleed

76 y/o man with CAD (NSTEMI 2006), AFIB CHADS-Vasc=4 on warfarin and ASA is admitted with UGIB. INR is 3.0. He requires 3u PRBC[illegible] peptic ulcer disease. He[illegible] therapy, bx for H P[illegible] anticoagulation be r[illegible]

"Two weeks may provide the best balance among GI bleed recurrence , thromboembolism and mortality""

a) Never
b) In two weeks
c) In three months
d) Let the primary provider deal with this one

Questions?

Tough Problems in Inpatient Pulmonary Disease

LEKSHMI SANTHOSH, M.D., M.A.ED.

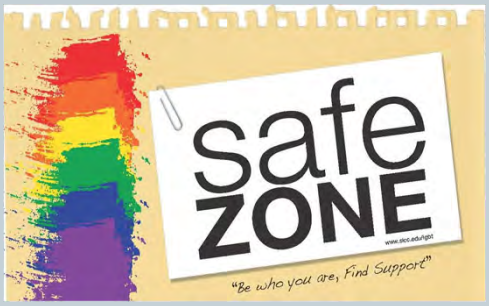
10/21/2021
MANAGEMENT OF THE HOSPITALIZED PATIENT

SMALL GROUP WORKSHOP

Disclosures

None.

Introductions & Ground Rules



Zoom Ground Rules

- I want to create a fun, casual, engaging environment –both in-person & over Zoom! I will try to engage the audience in this hybrid era.
- Please introduce yourself when you are engaging w/ the speaker so that we can all get to know each other
- If you are virtual, we are mindful of barriers to turning video on, however, if you have the capacity to do so, we encourage you to 'show your face' so we can see each other – not required
- Feel free to use the chatbox which I will keep an eye on or the Raise Hand function of Zoom.
- Please mute yourself ☺
- We're all here to learn & have fun so please enjoy our cases!

Choose Your Own Adventure! Top 6 Cases

Could this be VAPI?	It's Not Easy Being Wheezy	Effusion Confusion
A Tickle In the Throat	An International Enigma	Potatoes, Pot-ah-toes

Choose Your Own Adventure! Top 6 Cases

And of Course the COVID-19 Case!

Choose Your Own Adventure: Let's Vote!

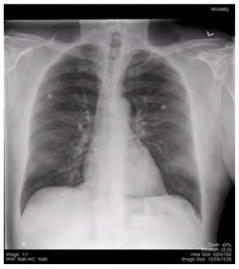
A. Could this be VAPI?
B. It's not Easy Being Wheezy
C. Effusion Confusion
D. A Tickle to the Throat
E. An International Enigma
F. Potatoes, Pot-ah-toes
G. And of course the COVID-19 Case!

Choose Your Own Adventure! Top 6 Cases

Could this be VAPI?	It's Not Easy Being Wheezy	Effusion Confusion
A Tickle In the Throat	An International Enigma	Potatoes, Pot-ah-toes

Case: Mrs. S

- **Patient:** 57 year old woman with suspected COVID-19 pneumonia presents to the hospital with shortness of breath and fever
- **Review of Systems**: + loss of smell/taste, headaches, decreased appetite for 1 week, previously healthy, no sick contacts
- **Exam:** SpO2 84% on RA, bilateral rhonchi, HR 100, RR 25, BP 133/90
- **Diagnostics:** CXR with mild infiltrates



Q1: What PPE should you wear for patient exam?

1 2 3

Audience Response Q: Click 1, 2, or 3!

1 2 3

Choice A is correct

Contact and droplet precautions by health workers caring for suspected and confirmed COVID-19 patients. Surgical facemask at minimum, N95 or higher respirators are preferred if available.

Case: Mrs. S

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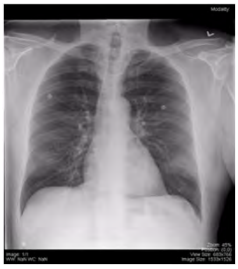
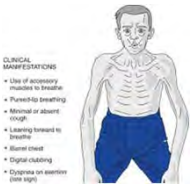


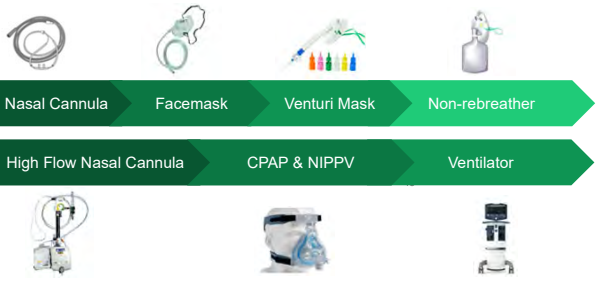
Quick Q

You start her on 2 L NC but she quickly desaturates and requires 6 L NC to keep O2 saturation up. You closely monitor her work of breathing and Sa02 and note that she continues to desaturate, but appears comfortable without tachypnea.



From Copstead LC, Banasik, JL: Pathophysiology, ed 4, Saunders, 2009

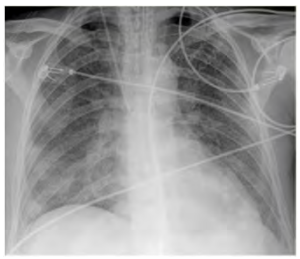
Quick Q: Which oxygen delivery device?



Audience Response Q

1. NC
2. Face Mask
3. Venturi Mask
4. Non-Rebreather
5. HFNC
6. CPAP & NIPPV
7. Ventilator

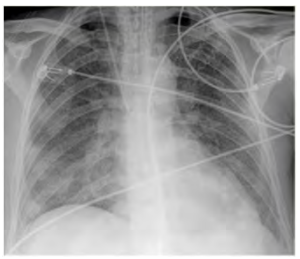
Case (Continued)



- Your patient is started on **NRB mask at 15 LPM for decreasing saturations**
- WIth this SpO2 increases to 94%
- RR 27 BPM, patient feels comfortable
- Chest X-Ray worse bilateral infiltrates

- Over next 24 hours SpO2 decreases to 88%
- Patient remains awake and comfortable

Audience Response Q



- **Which of the following is the most appropriate next step?**

a. **Proning**
b. **Intubation**
c. **Paralysis**
d. **BiPAP**

5

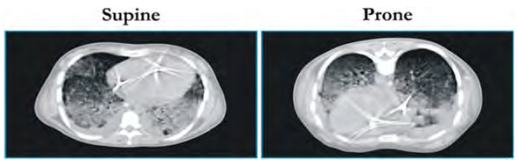
Case (Continued)

- A trial of awake prone positioning is performed
- SpO2 increases to 95% when patient lies prone
- She stays proned at least 16 hours of every 24 hours, when she can tolerate it.

6

Why does proning work in ARDS?

- Prone positioning redistributes opacities from dorsal to ventral zones
- If the patient can tolerate, we may see a marked improvement in oxygenation and ventilation
- If no improvement, need to consider more invasive support



Published in: Luciano Gattinoni; Paolo Taccone; Eleonora Carlesso; John J. Marini; *Am J Respir Crit Care Med* 1881286-1293.

Slide 19

3 are there any from NEJM or others anyone has come across?
Michael Lipnick, 9/28/2020

2 There is the NEJM original proning video. We are working on making a video for proning in COVID times :) If USAID wants to throw some $$$
Lekshmi Santhosh, 10/2/2020

4 what resources do you need?
what are limitations in existing videos?
Michael Lipnick, 10/2/2020

1 Here can have picture of proning - just threw this one in with reference:
https://emcrit.org/pulmcrit/awake-prone-covid/
Lekshmi Santhosh, 10/2/2020

5 https://www.youtube.com/watch?v=cCkHPYpwg2g
Michael Lipnick, 10/2/2020

6 Source = https://www.embeds.co.uk/2020/04/08/

Better if drawn
Michael Lipnick, 10/2/2020

Proning non-intubated COVID-19 patients may improve oxygenation

JAMA Intern Med. Published online June 17, 2020. doi:10.1001/jamainternmed.2020.3030

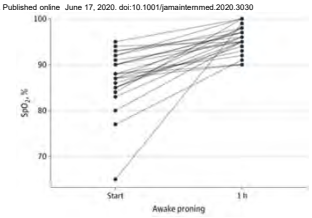


Figure Legend:

Oxyhemoglobin Saturation (Spo_2) 1 Hour After Initiation of the Prone Position in Awake, Nonintubated Patients With COVID-19Spo_2 before and 1 h after initiation of the prone position in awake, nonintubated patients with COVID-19 severe hypoxemic respiratory failure (n = 25).

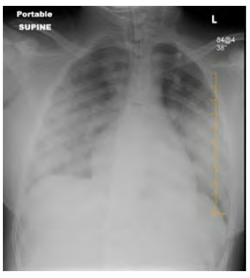
Prone positioning in non-intubated COVID-19 patients

- Proning *ventilated* patients with ARDS leads to lower mortality.
- Evidence is *limited but promising in non-intubated ("awake") patients.*
- A trial of proning in the setting of escalating oxygen requirements in "awake" patients is *low-risk and may be beneficial*, but requires close monitoring in case of deterioration.

Case: Key learning points

- COVID-19 pneumonia cases with **mild to moderate hypoxemia can be managed with 1-10 L/min**
  - 1-6 LPM via NC and 6-10 LPM via facemask (or use both!)
  - Humidification should be included for any flow > 6 LPM.
  - A **non-rebreather face mask** (with bag and reservoir) can increase oxygen delivery to **15 L/min**
- **Be aware of your facilities oxygen delivery capacity and resources**
- **Prone positioning may help both oxygenation and ventilation** by preventing compression of the lungs and redistributing ventilation and blood flow
- **Prone positioning of awake, non-intubated patients** may be helpful, is generally quite safe, but requires close monitoring and patient participation
  - but it is unclear if it is specifically helpful in patients with COVID-19

Case #2 (Continued)



- Despite proning and NRB at 15LPM, over the next 12 hours she worsens. SpO2 remains at 88%. Repeat CXR is shown here.
- Pt is tachypneic though appears comfortable without significant accessory muscle use.
- The term 'happy hypoxemic' has commonly been used to describe patients with COVID19. While frequently observed, the phenomenon of profound hypoxemia and relative absence of symptoms or increased work of breathing is not a new phenomenon, nor specific to COVID.

Quick Q: Which oxygen delivery device would you select?




Nasal Cannula | Facemask | Venturi Mask | Non-rebreather

High Flow Nasal Cannula | CPAP & NIPPV | Ventilator



Audience Response Q

1. NC
2. Face Mask
3. Venturi Mask
4. Non-Rebreather
5. HFNC
6. CPAP & NIPPV
7. Ventilator

High pressure high flow delivery devices

High Flow Nasal Cannula | CPAP & NIPPV | Ventilators

- Nasally delivered
- Can deliver 100% oxygen but uses a lot of flow (**up to 60 liters per minute**)
- Requires active heat and humidification to keep airways from drying out
- Tolerated well and may help avoid mechanical ventilation for a number of COVID patients

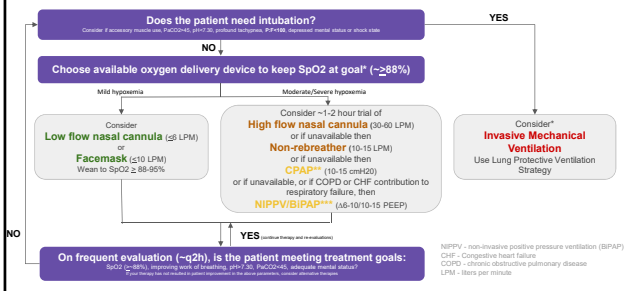
- Delivered by face mask, nasal mask, or helmet
- 100% oxygen delivery if device accepts high pressure O2
- Wide range of flow needs (**~10-60 liters per minute** depending on seal)
- Delivers pressure in addition to oxygen = more support
- Limited long-term tolerance (e.g. skin ulcerations)
- Requires adequate mental status
- Impact on COVID outcomes uncertain

- Delivered via a breathing (endotracheal) tube in sedated patients, but also can be used to deliver BiPAP or CPAP with a mask
- Can deliver 100% oxygen provides higher pressure delivery than CPAP/BiPAP
- Wide range of flow needs (**~10-30 liters per minute** depending on patient settings and vent type
- Standard of care for patients with severe respiratory failure

Case: Key Learning Points

- **Stepwise approach** to increasing oxygen therapy
  - Unless the patient requires immediate intubation
- **HFNC may be effective** in COVID-19 for treatment of hypoxemia
  - It can use a lot of oxygen
  - May increase aerosolization - N95 for provider, surgical mask for patient!
- **NIPPV is controversial** in COVID-19
  - Unclear if helpful in hypoxemia due to COVID-19
  - May increase aerosolization and HCW risk
- **HFNC and NIPPV require close monitoring** for deterioration
  - ***Don't delay intubation if the patient needs intubation!***

Initial management of the hypoxic COVID-19 patient



Choose Your Own Adventure! Top 6 Cases

Could this be VAPI?	It's Not Easy Being Wheezy	Effusion Confusion
A Tickle In the Throat	An International Enigma	Potatoes, Pot-ah-toes

Choose Your Own Adventure: Let's Vote!

A. Could this be VAPI?
B. It's not Easy Being Wheezy
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F. Potatoes, Pot-ah-toes
G. And of course the COVID-19 Case!

The Case

- CC: Shortness of breath, diarrhea

HPI

- 32 year old man with no real PMHx comes to ED for 1 week of diarrhea, abdominal pain, cough and shortness of breath
- PMHx & PSHx: None
- SHx: Never-smoker, rare alcohol, +MJ *
- FHx: None

Physical Exam

VS: T 37, HR 110, BP 100/63, RR 28, O2 83% RA

General: Ill-appearing, diaphoretic, tachypneic

HEENT: Mucus membranes moist, OP clear

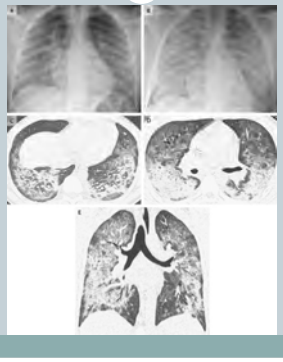
CV: RRR, no murmurs/rubs/gallops

Lungs: Bilateral coarse crackles, tachypnea

Abdomen: Benign, +BS, no rebound/guarding

Ext: No clubbing, cyanosis

Imaging



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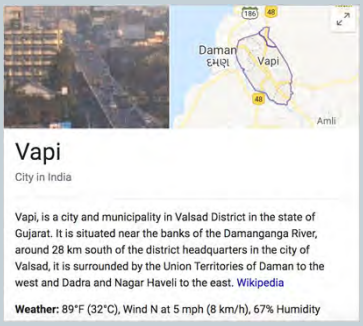

Could this be VAPI?

American Thoracic Society

PUBLIC HEALTH | *INFORMATION SERIES*

Vaping Associated Pulmonary Illness (VAPI)

As of September 2019, the Centers for Disease Control (CDC) has reported over 350 cases of vaping-associated pulmonary illness (VAPI) across 36 states. The observed patterns of disease are variable but all have been associated with recent electronic cigarette use or "vaping." Vaping is a word used to describe the use of an electronic system to deliver inhaled drugs, most commonly nicotine and cannabinoids (natural or synthetic forms of marijuana)[1]. Juuling is another term that is used to describe the use of a specific vape device.

Your Differential Diagnosis? BESIDES VAPI?

- Type in the ChatBox!

Your Differential Diagnosis? BESIDES VAPI?

Rapidly Progressive Respiratory Failure

- ARDS (Acute Respiratory Distress Syndrome)
- Acute infection – viral +/- bacterial pneumonia
- Massive aspiration
- Acute eosinophilic pneumonia
- Lipoid pneumonia
- (Pulmonary embolism)

Clinical Course

- His hypoxemia worsens and he develops worsened hypoxemic respiratory failure requiring intubation
- Now how do you manage him?

Management Pearls for VAPI

- Supportive care
- Limited role for steroids
- Bronchoscopy to rule-out infection
- Lung-protective ventilation strategy
- Fluid-conservative strategy
- Report to CDC, SFDPH, and local research teams

Pulmonary Advocacy re: VAPI

Rx Action Steps

- ✔ Report all suspected cases to CDC.
- ✔ Screen all patients for the use of tobacco and vaping devices.
- ✔ Offer smoking and vaping cessation counseling to all patients who report use.
- ✔ Support legislation to prevent the sale of vaping and tobacco products to anyone under the age of 21.
- ✔ Support stronger penalties for retailers who illegally sell tobacco, nicotine, and vaping devices to minors.
- ✔ Encourage the FDA and Congress to ban flavors in tobacco products.
- ✔ Support research on prevention and cessation strategies for smoking and vaping.

Summary: Key Learning Points

1. Think of VAPI in people who have vaped within 90 ds who have respiratory failure
2. GI sx are common & often people don't disclose immediately
3. Treat with supportive care & report to CDC and SFDPH & local research teams

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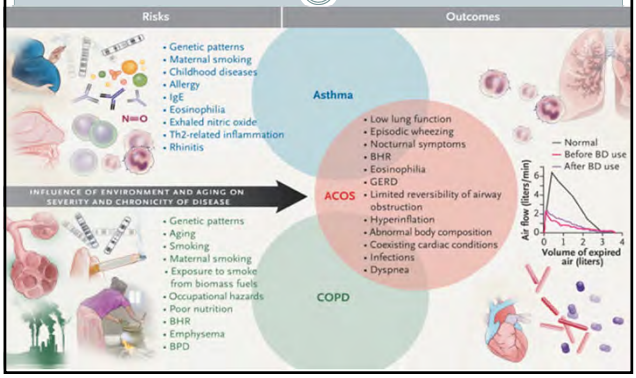
It's Not Easy Being Wheezy

- A 55 year old man who has a history of COPD, OSA, CAD, CKD, jaundice, & childhood asthma admitted for dyspnea. He is still wheezing & hypoxemic despite 5 d steroids & antibiotics.

What is your differential diagnosis for his wheezing? Type in the chat box!

ACOS (Asthma-COPD Overlap Syndrome)



All that Wheezes is not Asthma or COPD

- ❑ Vocal cord dysfunction
- ❑ Allergic bronchopulmonary aspergillosis
- ❑ Vasculitides such as Eosinophilic Granulomatosis with Polyangiitis
- ❑ Infections such as Strongyloides
- ❑ Malignancy (lung or mets)
- × Pulmonary embolism
- × Decompensated CHF
- × Obesity
- × Bronchiectasis
- × Occupational lung diseases
- × Interstitial lung diseases

What About Reactive Airways Disease?

Pulmonary Perspective

"Reactive Airways Disease"

A Lazy Term of Uncertain Meaning That Should Be Abandoned

JOHN V. FAHY and PAUL M. O'BYRNE

Department of Medicine and the Cardiovascular Research Institute, University of California, San Francisco, California; and the Department of Medicine, McMaster University, Hamilton, Ontario, Canada

- Different from Reactive Airways Dysfunction Syndrome -
- Acute wheezing in response to inhaled irritant

Diagnostically, When to C/S Pulm?

- Basic diagnostics are not helpful (PFTs, Chest CT)
- You need advanced testing (e.g. methacholine/bronchoprovocation testing, exercise testing, bronchoscopy, etc.)
- You suspect an asthma/COPD mimic
- You just need extra diagnostic help!

Therapeutically, When to C/S Pulm?

- Severe asthma requiring ICU stay - ICU Admission for asthma and intubation are strong predictors for fatal or near-fatal asthma!
- Uncontrolled asthma despite step-up therapy
- You are considering omalizumab or other IgE-mediated tx

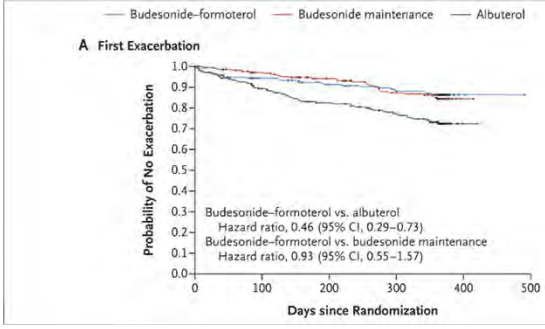
Audience Response Q

- What is the BIGGEST change in asthma guidelines?

A. Start with PRN albuterol for all mild asthma
B. Start with ATC albuterol for all mild asthma
C. Start with PRN LABA/ICS for all mild asthma
D. Start with ATC LABA/ICS for all mild asthma
E. No big changes, I didn't hear anything!

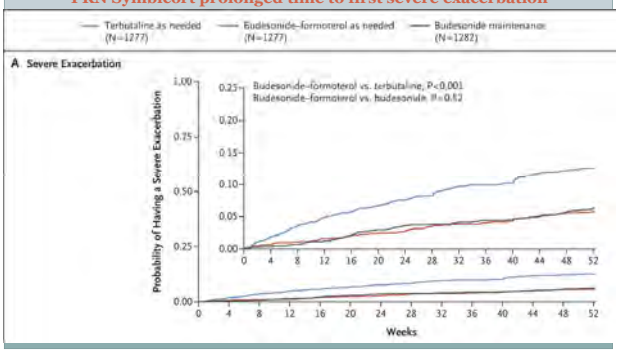
New Data from 2019: START Trial

PRN Symbicort is superior to PRN Albuterol for Prevention of Asthma Exacerbations!



New Data from 2019: SYGMA Trials

PRN Symbicort prolonged time to first severe exacerbation



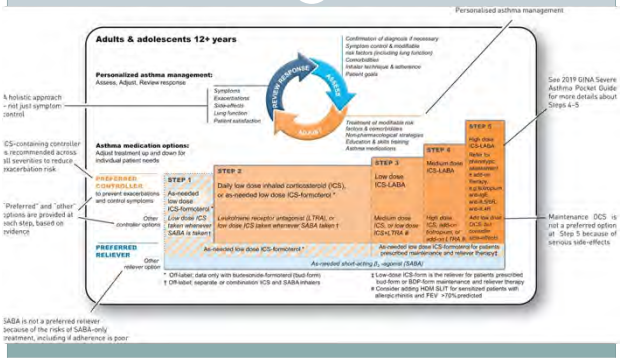
BIG Change in 2019 GINA Guidelines

"The 2019 GINA strategy report represents **the most important change in asthma management in 30 years**.

For safety, GINA no longer recommends treatment with SABA alone…

GINA now recommends that all adults with asthma should receive either symptom-driven or daily low-dose ICS-containing controller treatment."

The Changes in Asthma Management



Summary: Key Learning Points

1. All that wheezes is not asthma/COPD
2. Remember ICU admission for asthma is a predictor for fatal asthma in future
3. BIG change in guidelines this year – no more Albuterol PRN only – consider Symbicort PRN
4. Remember non-pharmacologic management & when to consult Pulmonary

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Effusion Confusion: Audience Response Q!

A 65 year old woman is readmitted for pleural effusion of unknown etiology. Last thoracentesis had negative cytology & cx. You:

a. Repeat the thoracentesis
b. Refer for pleurodesis
c. Refer for pleural biopsy
d. Place a PleurX catheter

Never Forget Your Light's

1. Fluid/serum **p**rotein ≥ 0.**5** **[pentagon]**

2. Fluid/serum LD**H** ≥ 0.**6** **[hexagon]**

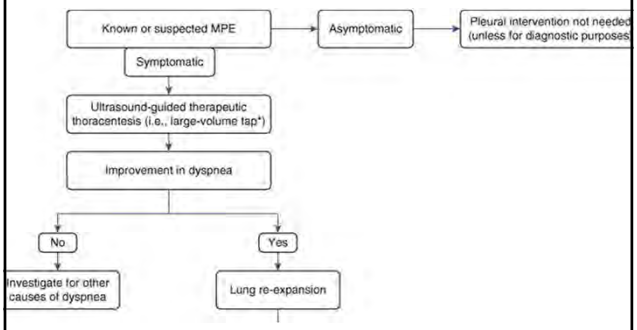
3. LDH ≥ 2/3 normal serum LDH

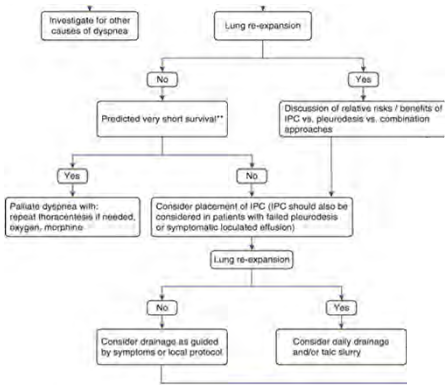
Chest Tube/Effusion Troubleshooting

- **Never** place a chest tube to drain hepatohydrothorax.
- Consider serial drainage + diuretics for recurrent **transudates**
- If drainage **slows** but effusion persists:
  - Consider reimaging: loculation? tube position?
  - Consider TPA and DNAase
- If chest **pain** with chest tube beyond expected:
  - Consider: tube dysfunction/malpositioning?
  - Consider complications like infxn, lung lac, diaphragm injury, reexpansion pulm edema

Effusion Size	Bacteriology	Chemistry	Treatment
Minimal, free-flowing (<10mm)	Neg cx/Gram stain		Antibiotics
Small-to-moderate free-flowing (>10 mm, but < ½ hemithorax)	Neg cx/Gram stain	pH ≥ 7.2	Antibiotics
Large, free-flowing, >1/2 hemithorax, loculated, effusion w/ thickened parietal pleura	Pos cx/Gram stain or frank pus	pH < 7.2	Chest tube drainage

2018 ATS Guidelines on MPEs





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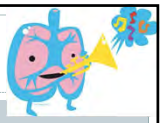

1. Tap, tap & **retap** to increase cyto yield
2. Avoid tapping a hepatic **hydrothorax**
3. For MPE, let **prognosis** be your guide for next step in management
4. Remember your chest tube **troubleshooting** tips

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A Tickle in the Throat

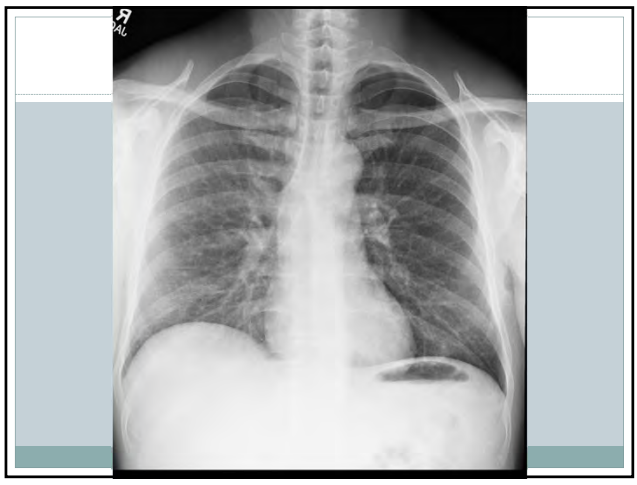
The Consult Question

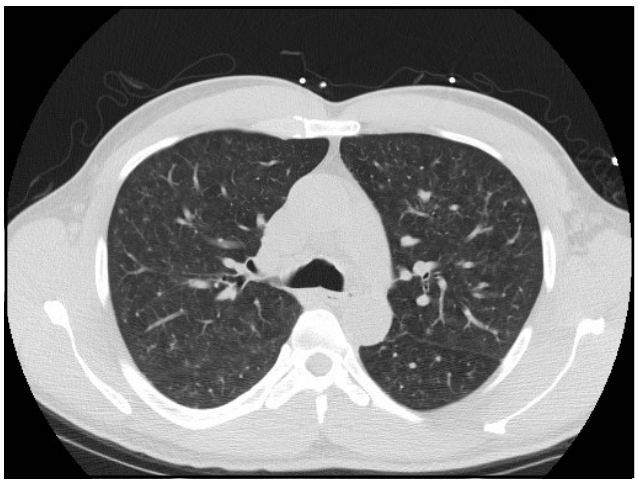
History of Present Illness

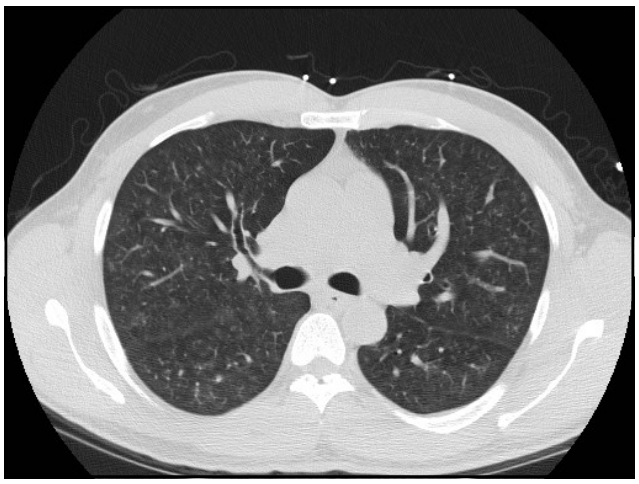
- 55yoM w/ HIV on and off HAART w/ dyspnea
- Dyspnea began on July 4th while walking around
- Presented to ED & given albuterol nebs → sx resolved → D/Ced from ED w/ albuterol inhaler
- Had been using inhaler once/day → q5 minutes
- +Wheezing & sensation of tickle in throat

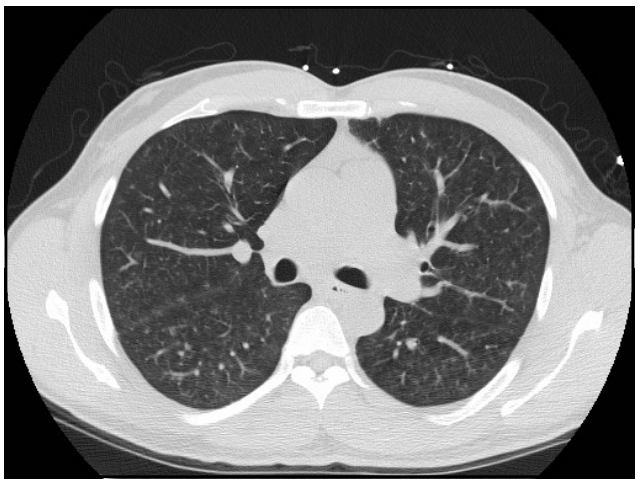
History of Present Illness

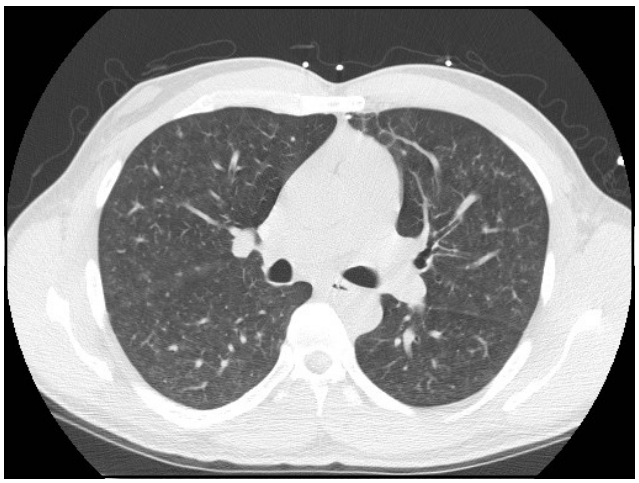
- Reports no cough, hemoptysis, fevers/chills/sweats
- No myalgias and no sick contacts
- No chest pain/palpitations/PND/orthopnea/lower extremity edema
- No recent travel
- …Except to his home country of Fiji 2 months ago

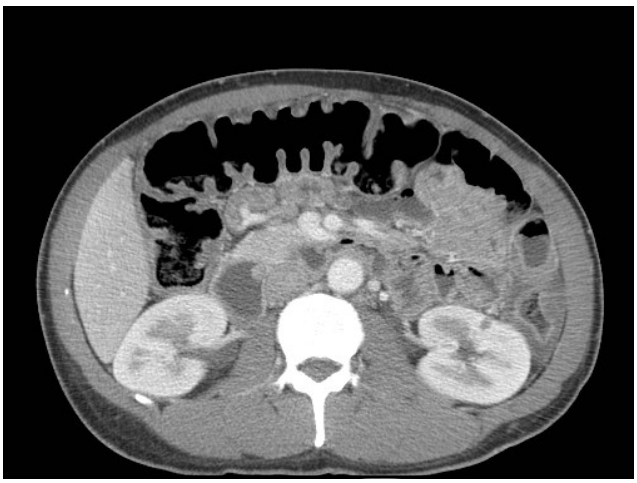




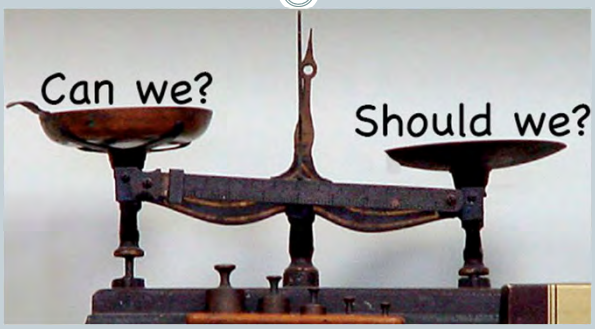






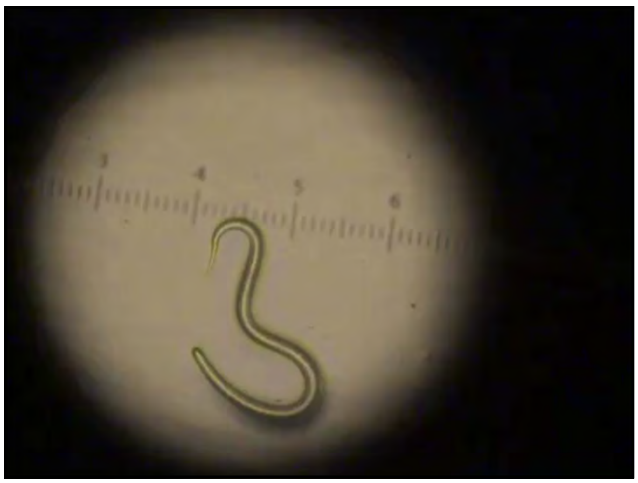


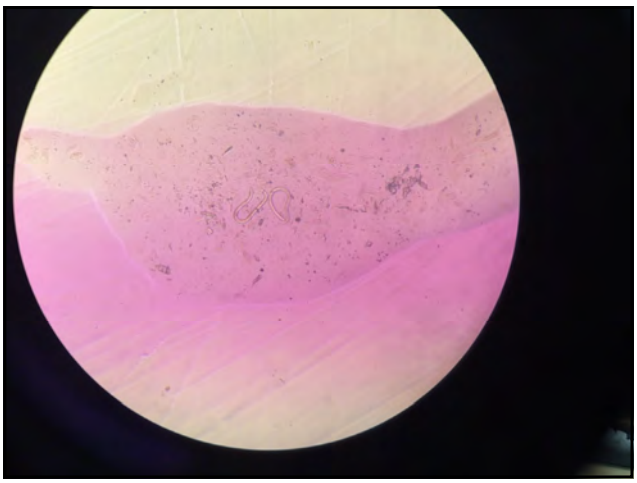
To Bronch or Not to Bronch?

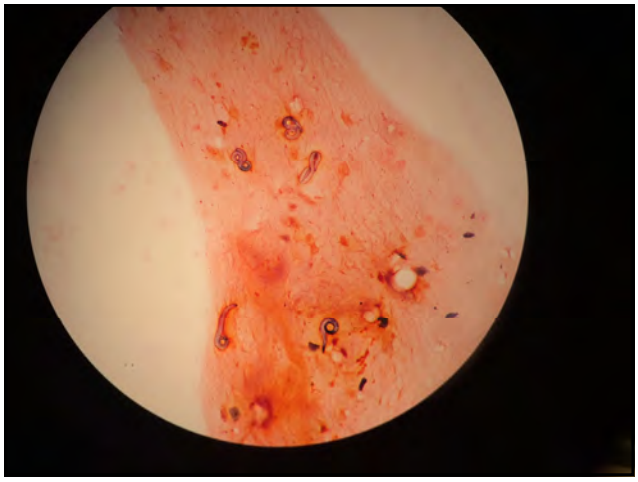


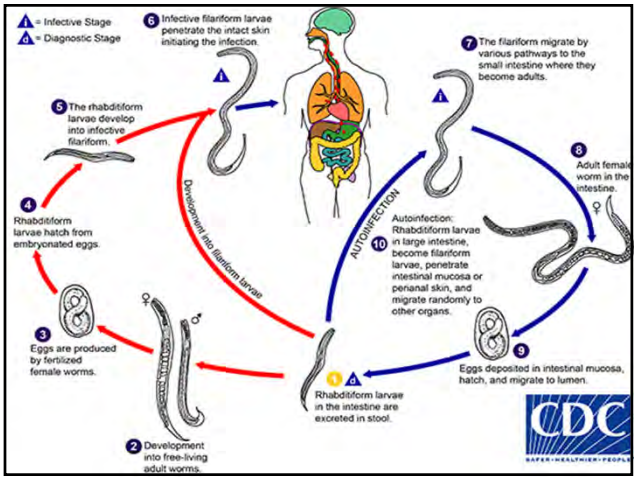
A Diagnostic Test Returns….

Type your thoughts in the chat box!








= Infective Stage
= Diagnostic Stage
6 Infective filariform larvae penetrate the intact skin initiating the infection.
7 The filariform migrate by various pathways to the small intestine where they become adults.
8 Adult female worm in the intestine.
5 The rhabditiform larvae develop into infective filariform.
4 Rhabditiform larvae hatch from embryonated eggs.
Development into filariform larvae
AUTOINFECTION
10 Autoinfection: Rhabditiform larvae in large intestine, become filariform larvae, penetrate intestinal mucosa or perianal skin, and migrate randomly to other organs.
3 Eggs are produced by fertilized female worms.
9 Eggs deposited in intestinal mucosa, hatch, and migrate to lumen.
1 Rhabditiform larvae in the intestine are excreted in stool.
2 Development into free-living adult worms.
CDC

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

Viewpoints

Is Human Immunodeficiency Virus Infection a Risk Factor for *Strongyloides stercoralis* Hyperinfection and Dissemination?

Marc O. Siegel, Gary L. Simon*

Division of Infectious Diseases, George Washington University Medical Center, Washington, DC, United States of America

- NOT a traditional risk factor
- Biggest risk factors are corticosteroid use & HTLV-1
- Only 40 cases of disseminated Strongy in HIV pts – many were also receiving steroids

Diagnosis

- Classic sx: GI symptoms (diarrhea), respiratory symptoms (dry cough, throat irritation), skin (itchy red rash when worm enters skin and can get recurrent red rash along thighs & buttocks)
- Diagnosis usually depends on visualization of the larvae in stool or respiratory culture
- Stool specimens are very insensitive (<50%)
- Serology (ELISA) is 83-89% sensitive, 97% specific

Management

- Treatment is usually ivermectin (200mcg/kg) as first-line treatment, use up to 14 days in case of disseminated strongyloides
- Can combine with albendazole therapy
- Monitor w/ repeat stool studies, CBC w/ diff, anti-Strongyloides antibodies
- Prognosis is good unless you develop bacteremia/sepsis

Summary: Key Learning Points

1. In HIV patients, travel history is key
2. Bronchoscopy is the gold standard for diagnosis of PCP ~ 99% yield!
3. Think of Strongyloides with the triad of eosinophilia, respiratory sx & GI sx
4. Absence of GGOs on HRCT makes PCP unlikely

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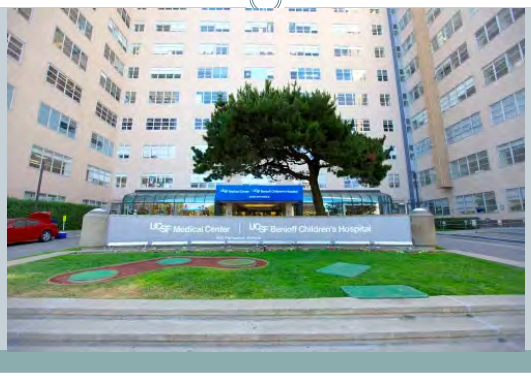
An International Enigma



Chief Complaint

- Abdominal Pain

History of Present Illness

- 42yo woman visiting SF from Canada
- H/o unilateral lung transplant 16 months ago
- For the last 10 days, has been going to multiple OSH ERs with nausea, vomiting, crampy abdominal pain
- Numerous negative CT Scans

Past Medical History

- s/p single lung transplant for NSIP
- GERD
- Obesity

Medications

- CellCept
- Tacrolimus (Prograf)
- PPI
- Septra ppx
- Calcium/Vitamin D

- VS: 37.2, HR 79, 132/86, RR 18, 93% RA
- General: Cushingoid appearing woman lying down, appearing fatigued, no acute distress
- Lungs: Fine crackles throughout R lung field, L lung with basilar crackles, no wheezes
- Abdomen: Hypoactive bowel sounds, tender to palpation in mid-epigastrium and RUQ but no rebound/guarding/peritoneal signs, no CVA tenderness, no suprapubic tenderness, no Murphy's signs

OSH Results

- Normal CBC
- Normal CHEM
- Normal LFTs
- Normal CT Abdomen/Pelvis

A Diagnostic Test Returned….

- Type your thoughts in the chat box!

A Diagnostic Test Returned….

- Tacrolimus level of 21.2!

Tacrolimus Toxicity

- Common sx: fatigue, anorexia, malaise, abdominal pain
- Labs: AKI, hyperkalemia, metabolic acidosis
- Beware of interactions with other drugs!
- Chronic >> acute, especially in renal patients

Summary: Key Learning Points

1. When in doubt, call Transplant team!

1. In any transplant patient, think of:
   a. Infection
   b. Rejection
   c. Recurrence of underlying disease
   d. Medication effect
   e. Post-transplant lymphoproliferative dz

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E. An International Enigma
F. Potatoes, Pot-ah-toes
G. And of course the COVID-19 Case!

Potatoes, Pot-ah-toes

Chief Complaint

- Shortness of breath

History of Present Illness

- 73yoM with multiple myeloma s/p chemo (cyclophosphamide, bortezomib, dexamethasone)
- Was admitted with pneumonia a week ago but since discharge still feeling poorly and requiring 6 L NC on readmission
- +Dry cough, no fevers/chills/LEE/orthopnea/PND

Past Medical History

- Multiple myeloma s/p chemo & radiation to ribs
- Meds: Amlodipine, Lexapro, PPI
- Never-smoker, no alcohol, drugs
- No family history

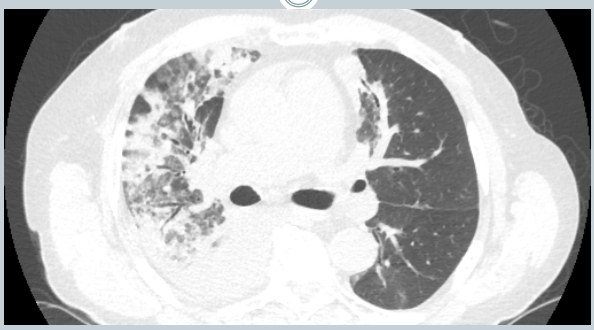
Physical Exam

- VS 37, HR 83, BP 119/69, RR 20, 93% 6 L NC
- Gen: Lying in bed in NAD
- Lungs: RLL and RML crackles, no wheezes, no increased work of breathing
- CV: RRR no murmurs, no JVD
- Ext: No edema

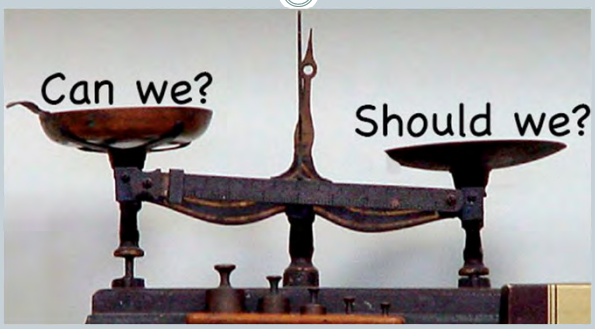
Labs

- Normal CBC & CHEM
- Lower Extremity DVT U/S: No DVT
- Blood cultures negative, Rapid flu negative
- Sputum culture negative

Chest CT Scan



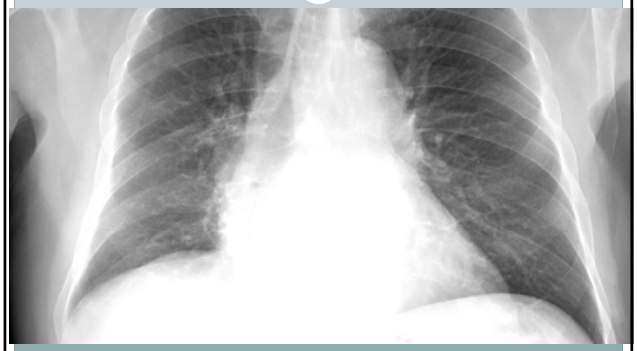
To Bronch or Not to Bronch?



Bronchoscopy

- Bronchoscopy showed no e/o bacterial, fungal, viral infection and cytology showed no PCP
- So we decided to treat and this happened …

Latest CXR – Cured!



What was the Diagnosis?

Radiation Pneumonitis!

Radiation Pneumonitis/OP 2/2 XRT

- Acute phase usually 4-12 weeks after XRT
- Sx: cough, dyspnea, low-grade fever, chest pain
- Immune-mediated change in capillary permeability
- Classically you see well-demarcated imaging findings
- Treatment is high-dose steroids (1mg/kg) for loooong

Summary: Key Learning Points

1. Always ask re: timing of XRT
2. Check drugs on www.pneumotox.com – ESPECIALLY PD1-inhibitors
3. Have to r/o infection before high-dose steroids (& don't forget PJP prophylaxis!)

Choose Your Own Adventure! Top 6 Cases

Could this be VAPI?	It's Not Easy Being Wheezy	Effusion Confusion
A Tickle In the Throat	An International Enigma	Potatoes, Pot-ah-toes

Thank You!

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Common Inpatient ID Consults

Management of the Hospitalized Patient
October 21, 2021

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Disclosures

- I have no disclosures.

Learning Objectives

At the end of this talk, you will be able to:

- Describe the situations in which formal in-person consultation is preferred over curbside consultation
- Outline an approach to common ID questions that arise in the inpatient setting

Outline

- Curbsides vs Formal Consults
- Top ID Consults
  - Staph aureus bacteremia
  - Blood culture contaminant vs real
  - GNR bacteremia treatment
  - Asymptomatic bacteriuria vs UTI
  - Indeterminate Quantiferon

Outline

- **Curbsides vs Formal Consults**
- Top ID Consults
  - Staph aureus bacteremia
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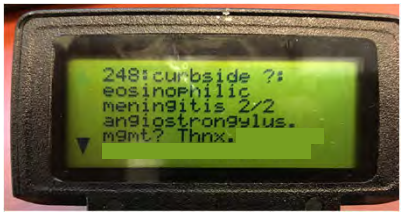
Curbside #1

What is the dose of ertapenem when the CrCl is <30?

Is This An Appropriate Curbside?

1. Yes
2. No

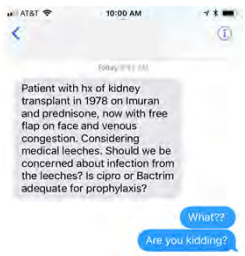
Curbside #2



Is This An Appropriate Curbside?

1. Yes
2. No

Curbside #3



Is This An Appropriate Curbside?

1. Yes
2. No

Curbside #4

I have a theoretical patient with mild cystitis due to VRE that is only sensitive to doxycycline. Does doxycycline penetrate into the urine?

Is This An Appropriate Curbside?

1. Yes
2. No

Curbsides vs Formal Consults

Study of 47 curbsides vs. formal consults

- Medicine consult
- Curbside → formal consult by a colleague
- Curbsided providers could not look in chart

Curbsides

- Information inaccurate or incomplete in 51%

Formal Consults

- Changed Rx in 60% (36% "major changes")
- If info was inaccurate, then it changed Rx in 92% (45% "major changes")

Burden et al, J Hosp Med 2013, 8:31.

Are Curbsides Okay?

- Formal consult is preferred in general, but need to balance patient safety, provider workload, education
- Curbside volume in ID is high
- Use e-consults when possible
- Impossible in many practices to convert all inpatient curbsides into formal consults

Grace et al, Clin Infect Dis 2010, 51:651. Wachter, B. "The Dangers of Curbside Consults… and Why We Need Them."Wachter's World. 29 Apr. 2013.

What is an Appropriate Curbside?

- The Goldilocks of Curbside Consultation
  - Not too simple: can be easily looked up
  - Not too complicated: requires nuanced clinical judgment, data interpretation, reading the literature
  - Just right: Hypothetical, factual question

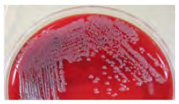
- We also tell our ID fellows it should be a consult if:
  - You need to look up the answer
  - It's early in the year
  - The team calls you back several times
  - The patient's history is complicated
  - Calls from the ED

Outline

- Curbsides vs Formal Consults
- **Top ID Consults**
  - **Staph aureus bacteremia**
  - **Blood culture contaminant vs real**
  - **GNR bacteremia treatment**
  - **Asymptomatic bacteriuria vs UTI**
  - **Indeterminate Quantiferon**

Case #1

60 year old man with lung cancer undergoing chemo admitted with a PICC line infection due to MRSA c/b bacteremia and psoas abscess. PICC line is removed. Cultures only clear after the psoas abscess is drained (positive for 4 days). TEE is negative.



How Long Should He Be Treated With Vancomycin?

1. 2 weeks
2. 3 weeks
3. 4 weeks
4. 6 weeks

ID Consults and *Staph aureus* Bacteremia

- Benefits of ID consultation (vs no consult):
  - ⇧ detection of metastatic foci of infection, endocarditis
  - ⇧ removal of prosthetic devices
  - Improved antibiotic choice and duration
  - ↓ risk of relapse
  - ↓ mortality (by ~20-30%)
- All patients with SAB should have an ID Consult if possible

Saunderson et al, Clin Micro Infect 2015, 21:779. Pragman et al, Infect Dis Clin Pract 2012, 20: 261. Tisot et al, J Infect 2014, 69:226. Forsblom et al, Clin Infect Dis 2013, 56:527.

Curbsides for *Staph aureus* Bacteremia?

- Curbside consult is associated with:
  - Less identification of deep infectious foci (and fewer radiologic tests ordered)
  - Longer duration of fever
  - Less likely to receive the proper duration of therapy
  - ⇧ mortality by > 2-fold compared to bedside consult
- No curbsides for Staph bacteremia!

Forsblom et al, Clin Infect Dis 2013, 56:527.

My Approach to *Staph aureus* Bacteremia

1. Look for metastatic foci of infection → source control
   - Exam: Brain, lungs, spleen/liver/kidneys, spine, skin, MSK
   - Low threshold for imaging
2. Get surveillance blood cultures
3. Evaluate for endocarditis (TTE vs TEE)
4. Decide appropriate ABx choice
   - Always IV
   - Beta-lactam for MSSA
5. Decide appropriate ABx duration (complicated vs uncomplicated bacteremia)

Antibiotic Choice

- MSSA
  - Cefazolin
  - Nafcillin (if need CNS penetration)
  - "Inocolum effect" of cefazolin likely not clinically signficicant
- MRSA
  - Vancomycin
  - Daptomycin
  - If need CNS penetration consider adding rifampin or adding/switching to linezolid

Antibiotic Duration

Uncomplicated Bacteremia	Complicated Bacteremia
1. No endocarditis 2. No metastatic foci of infection 3. Repeat blood cx neg at 2-4 days 4. Defervesce in <3 days of ABx 5. No prostheses (e.g., prosthetic valves, cardiac devices, joints) 6. No immunocompromise? Duration = minimum 2 weeks (this will be uncommon!)	Does not meet criteria for uncomplicated disease Duration = 4-6 weeks

Liu et al, Clin Infect Dis 2011; 52:1.

Implanted Prostheses and Antibiotic Duration

- Presence of prosthetic implants in SAB → poor outcomes/complications
  - 2-4 fold ⇧risk death, stroke, recurrent infection, metastatic foci
  - This is true *even if prosthetic material is not the primary infection/source of bacteremia*
- Implanted prostheses have high rates of being seeded hematogenously during unrelated SAB
  - 20-50% risk of seeding prosthetic heart valves/valve rings
  - 30% risk of seeding of prosthetic joints, cardiac devices

Fowler et al, Arch Intern Med 2003; 163:2066. Fowler et al, Clin Infect Dis 2005; 40:695. Murdoch et al, Clin Infect Dis 2001; 32:647. Chamis et al, Circulation 2001; 104:1029. Chang et al, Medicine 2003; 82:322). El-Ahdab et al, Am J Med 2005; 118:225.

Echocardiography in SAB

- Purpose of echo:
  - At least 5-15% of patients with SAB have endocarditis
  - Echo serves to rule out endocarditis as an *etiology for* or *subsequent complication* of SAB
- Needed for all?
  - Although there is some debate, most experts agree that all patients with *Staph aureus* bacteremia should undergo echocardiography (start with TTE)

Liu et al, Clin Infect Dis 2011; 52:1. Holland et al, JAMA 2014; 312:1330.

Transesophageal Echocardiography (TEE)

- Important points about TEE:
  - More sensitive for vegetations (85-90% vs 75% for TTE)
  - Better to evaluate prosthetic valves, device leads
  - Better to evaluate for myocardial abscess
  - May be less sensitive for tricuspid lesions
  - Increased cost and risk compared to TTE

- IDSA: TEE is "preferred" because of higher sensitivity
- In practice, TEE is performed in only 15-80% of patients with SAB

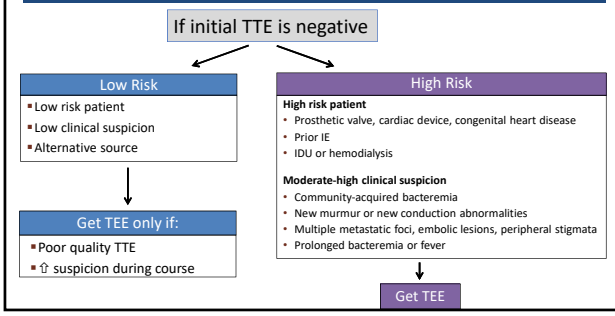
Kaasch and Jung, Clin Infect Dis 2015; 61:29. Liu et al, Clin Infect Dis 2011; 52:1. Kaasch and Michels, JACC Cardiovasc Imaging 2015; 8:932.

What about TTE in "Low Risk" SAB?

- TTE may have good NPV in a subset of patients with low risk for endocarditis (low quality evidence, somewhat controversial)
- Some experts define low risk as meeting <u>all</u> of the following:
  - Nosocomial-acquired bacteremia
  - Negative blood cultures within 4 days after initial set
  - Absence of prosthetic valve or cardiac device
  - No hemodialysis
  - No clinical signs of IE or secondary foci of infection

Holland et al, JAMA 2014; 312:1330.

A Real World Approach to Echo in SAB



Other TEE Considerations

- May consider deferring TEE in:
  - Patients with significant co-morbidities
  - Patients whose GOC are to avoid invasive procedures
  - Patients getting 6 wks of Abx for another reason (eg osteomyelitis) where:
    - There is no concern for intra-cardiac complications (eg conduction abnormalities)
    - ABx regimen would not change if the patient had endocarditis
- Important to use clinical judgment
- If defer TEE and give a short course of ABx, consider getting surveillance cultures after stopping

Take Home Points: Approach to Staph Bacteremia

1. Look for metastatic foci of infection → source control
2. Get surveillance cultures
3. Evaluate for endocarditis
   - TTE in all patients
   - TEE if low quality TTE, high risk patient, moderate to high clinical suspicion
4. Decide appropriate Abx (always IV, beta lactam for MSSA)
5. Decide appropriate ABx duration (define bacteremia as complicated or uncomplicated)

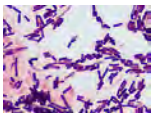
My SAB Checklist

SAB checklist:

[ ] Surveillance blood cultures: ***
[ ] Echo: ***
[ ] Original source: ***
[ ] Possible sites of metastatic infection: ***
[ ] Antibiotic choice: ***
[ ] Antibiotic duration: ***

Case #2

Do I need to worry about Bacillus if it grew in the blood? The patient is totally fine and this grew out at 3 days, right after discharge.



Do you need to worry about the Bacillus?

1. Yes
2. No
3. Not sure

How to Determine a Contaminant vs True Infection

What is the clinical situation?

What is the organism? Most common contaminants:
- Coagulase-negative *Staph* (82%)
- *Corynebacterium* (not *jeikieum*) (>88%)
- *Bacillus* spp. (not *anthracis*) (>92%)
- *Propionibacterium acnes* (>94%)
- Viridans group streptococci (50-55%)

How many blood culture sets are positive?
- More likely real if 2 out of 2 sets
- Caveat: 2/2 common for coag-neg *Staph.* Check species or antibiograms (100% sensitive for same strain, 84% specific)

When did it turn positive?
Growth at ≥3-5d → more likely contaminant

 # blood culture bottles positive in a set does NOT correlate

Hall and Lyman, Clin Micro Rev 2006, 19:788. Pien et al, Am J Med 2010, 123:819.

Case #3

55 year old woman with MS and h/o neurogenic bladder is admitted with sepsis.

Her urine and blood cultures are growing pan-sensitive *Klebsiella pneumoniae*.

She is currently on ceftriaxone and doing well.

How Long Should She Be Treated?

1. 5 days
2. 7 days
3. 10 days
4. 14 days

What Would You Send Her Home On?

1. PO TMP-SMX
2. PO Ciprofloxacin
3. PO Cephalexin
4. IV Ceftriaxone

GNR Bacteremia: Major Questions

How long to treat?

2 major RCTs on duration of Rx in GNR bacteremia

Are oral Abx ok? Which ones?

1 large retrospective study and 1 meta-analysis

GNR Bacteremia: Major Questions

How long to treat?

2 major RCTs on duration of Rx in GNR bacteremia

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In General, Shorter is Usually Better!

Table 1. Diseases for Which Short-course Antibiotic Therapy Has Been Found to Be Equally Effective to Longer Traditional Courses of Therapy (With References)

Diagnosis	Short (d)	Long (d)	Result
Community-acquired pneumonia [6–14]	3 or 5	7, 8, or 10	Equal
Hospital-acquired/ventilator-associated pneumonia [15, 16]	7–8	14–15	Equal
Complicated urinary tract infections/pyelonephritis [17–22]	5 or 7	10 or 14	Equal
Complicated/postoperative intraabdominal infections [23, 24]	4 or 8	10 or 15	Equal
Gram-negative bacteremia [25]	7	14	Equal
Acute exacerbation of chronic bronchitis/chronic obstructive pulmonary disease (meta-analysis of 21 trials [26])	≤5	≥7	Equal
Acute bacterial skin and skin structure infections (cellulitis/major abscess) [27–29]	5–6	10	Equal
Chronic osteomyelitis [30]	42	84	Equal
Empiric neutropenic fever [31]	Afebrile and stable × 72 h	Afebrile and stable × 72 h and with absolute neutrophil count > 500 cells/μL	Equal

Wald-Dickler and Spellberg, CID 2019.

RCT #1 on Duration for GNR Bacteremia

Study #1	Inclusion	Exclusion	Patient Characteristics	Results
Yahav et al, CID 2019 RCT of 7 vs 14 days Abx (n=604)	• Afebrile • Stable by day 5 • Source control	• **Immunocompromise**: HIV, HSCT, neutropenia (note in the study 25% were ICH and 8% SOT) • **Complicated infection**: Endocarditis, NSTI, Osteo, CNS, empyema • **Persistent bacteremia** • **Polymicrobial infection**	Microbiology: • 90% Enterobacteriaceae (63% Ecoli,13% Kleb, 19% ESBL) • 8% Pseudomonas Source: • Urinary 68% • Intra-abdominal 12% • Unknown 8%, CVC 6%, resp 4% PO antibiotics • Given for part of the course in 64% of 7d group, 81% of 14d group • 74% Fluoroquinolones • 18% beta-lactams • 8% TMP-SMX	No difference in composite outcome of all-cause mortality, clinical failure, re-admission, LOS>14d (at 90 days)

Yahav et al, CID 2019.

RCT #2 on Duration for GNR Bacteremia

Study #2	Inclusion	Exclusion	Patient Characteristics	Results
Von Dach et al, JAMA 2020 RCT of CRP guided transition (got 7d) vs 7d vs 14d (n=504)	• Afebrile x 24h • Stable by day 5	• **Severe immunocompromise**: HIV CD4<500, HSCT <1 mo, neutropenia in last 48h, high dose steroids (>40mg pred) for >2 wks in last 2 wks • **Complicated infection or abscess** • **Persistent bacteremia** • **Polymicrobial infection** • **Nonfermenters**	Microbiology: • Ecoli 74%, Kleb 17%, ESBL 8% Source: • Urinary 73% • Intra-abdominal 18% • Unknown source 5%, Resp 4%, Endovasc 1% PO antibiotics • IV to PO switch not standardized (percentages not reported)	No difference in clinical failure at day 30

Von Dach et al, JAMA 2020.

GNR Bacteremia: Back to Our Questions

How long to treat?

RCT data supports 7 day course of antibiotics for:

- Enterobacteriaceae bacteremia
- Urinary, GI source
- Have source control
- Clinically stable by day 5

Unanswered questions:

- Non-urinary/GI source? (yes)
- ESBL? (yes)
- Immunosuppression? (yes, if not severe)
- When can you switch to orals? Can you use an oral beta-lactam?

GNR Bacteremia: Major Questions

How long to treat?

2 major RCTs on duration of Rx in GNR bacteremia

Are oral Abx ok? Which ones?

1 large retrospective study and 1 meta-analysis

Studies of Oral Step Down Rx for GNR Bacteremia

Tamma et al, JAMA IM 2019

- Retrospective (n=1478)
- Inclusion:
  - Enterobacteriaceae bacteremia
  - Stable, could take PO, had source control
- Exclusion: complicated infections (e.g. osteo)
- Compared oral step down (got 3d IV then PO) vs all IV for total 14 days
- Source: GU 40%, GI/biliary 34%, line 18%

Results

- No diff in mortality, oral group had ↓ LOS
- Oral group: 70% FQ, 13% TMP-SMX, 17% oral BL
- No diff between FQ/TMP-SMX vs oral BL

Punjabi et al, OFID 2019

- Meta-analysis (8 studies, n=2289)
- Compared FQ/TMP-SMX vs oral BL for stepdown after 3-5 days of IV therapy (total 14-16 days)
- 65% FQ, 8% TMP-SMX, 27% oral BL

Results

- No difference in mortality between oral beta-lactams vs FQ/TMP-SMX
- Recurrence of infection was more common (OR 2.05) in the oral BL group

What about for ESBL?

- 10-20% of patients in the 7 vs 14 day RCTs had ESBL
- Two additional (small) retrospective studies show that FQ or TMP-SMX are effective as step-down therapy for ESBL bacteremia
- IDSA Guidelines on Treatment of Antimicrobial Resistant Gram Negative Infections: oral therapy with FQ or TMP-SMX is a viable option if otherwise meet clinical milestones for oral therapy

Lo et al, JMII 2017. Meije et al, IJAA 2019. Tamma et al, IDSA 2020.

GNR Bacteremia: Back to Our Questions

How long to treat?

RCT data supports 7 day course of antibiotics for:

- Enterobacteriaceae bacteremia
- Urinary, GI source
- Have source control
- Clinically stable by day 5

Are oral Abx ok?

Oral step-down therapy (by day 3) is safe and effective in:

- Enterobacteriaceae bacteremia
- From urinary, GI, lines
- Source control and clinically stable
- Especially with FQ or TMP-SMX but likely also oral beta-lactams

GNR Bacteremia Summary

Step-down to Oral Antibiotics to Complete 7d

Inclusion:
- Controlled source of infection
- Active IV therapy for at least 48 hours
- Clinically stable, no pressors x 48h
- AF x 48h without anti-pyretics
- Able to tolerate/absorb oral meds
- Organism is susceptible
- Enterobacteriaciae

Exclusion:
- Severe immunocompromise
  - SOT in last 3 mo or augmented IS
  - Neutropenia, HSCT <12 mo, active GVHD
- Complicated infections
  - Endocarditis, CNS infection, empyema
  - Nec fasc, osteo, septic arthritis
  - Undrainable abscess or infected prosthesis
  - Complex urinary anatomy or prostatitis
- Polymicrobial infection
- Persistent bacteremia

Draft UCSF IDMP Guideline 2021: Enterobacterales Bloodstream Infection Adult IV to PO Step-Down Guideline.

An Approach to Oral Options

1st tier: FQ	• Ciprofloxacin or levofloxacin (750mg dosing)
2nd tier: TMP-SMX	• TMP-SMX 8-10mg/kg/day in 2-3 divided doses
3rd tier: oral BL (avoid use in ESBL or ampC)	• Cefuroxime 500mg PO bid • Amoxicillin 1gm PO tid • Cephalexin 500mg PO qid • Amox-clav 875/125 bid

Notes
- Assuming normal renal fxn
- Cefuroxime > cefpodoxime > cefdinir for GU penetration
- Consider renal function, side effects (eg QTc), DDIs, #days of IV, clinical situation, immunosuppression
- AmpC = Enterobacter, Citrobacter, Providencia, Morganella, Serratia, Hafnia

Draft UCSF IDMP Guideline 2021: Enterobacterales Bloodstream Infection Adult IV to PO Step-Down Guideline.

Case #4

An 89 year old woman with mild cognitive impairment is admitted after a fall with mild mental status changes and inability to care for herself at home. She has no clear localizing symptoms except pain at the site of her fall.

Afebrile, vitals stable.
WBC 10.0
UA 25-50 WBC/hpf

Does She Need Antibiotics?

1. Yes
2. No
3. Not sure

Case Continued

She was started on ceftriaxone and improved overnight. PT/OT eval for discharge recs is pending.

Urine culture grows >100K E coli ESBL (sensitive to amp/sulbactam, cipro, ertapenem)

What Would You Do with Her Antibiotics?

1. Amox/clav
2. Ciprofloxacin
3. Ertapenem
4. No antibiotics

New IDSA GUIDELINES for ASB (2019)

Clinical Infectious Diseases

IDSA FEATURES

IDSA Infectious Diseases Society of America hivma hiv medicine association

Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America[a]

Nicolle et al, Clin Infect Dis 2019:68:e83.

Asymptomatic Bacteriuria: Definition

ASB = positive urine culture
AND no signs/symptoms of UTI
irrespective of the presence of pyuria

Caveats:

- Voided specimen or indwelling catheter: $\geq 10^5$ cfu/mL, straight cath specimen: $\geq 10^2$ cfu/mL
- For women: need 2 consecutive specimens (since often repeat is negative)

Nicolle et al, Clin Infect Dis 2019, 68:e83.

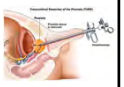
Asymptomatic Bacteriuria is COMMON!

- Seen in up to:
  - 20% of elderly, diabetic, HD patients
  - 50% of patients in long term care facilities
  - 70% of patients with spinal cord injury
  - Acquired at 3-5% per day in patients with short-term catheters
  - ~100% of patients with long-term catheters
- Of positive urine cultures obtained on the wards after hospital admission → ~90% are ASB

Nicolle et al, Clin Infect Dis 2005, 40:643. Leis et al, Clin Infect Dis 2014, 58:980. Nicolle et al, Clin Infect Dis 2019, 68:e83.

Exceptions: Who With ASB Should Be Treated?

- Pregnancy
  - ↓ risk pyelo, premature delivery



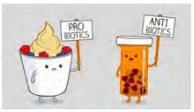
- GU procedures w/mucosal bleeding
  - ↓ post-procedure bacteremia/sepsis
  - 2019 guidelines: Give 1-2 doses, start 30-60 min before the procedure

- Immunosuppressed patients (2019 guidelines)
  - Renal transplant in the first month
  - High risk neutropenia? (IDSA makes no formal rec for or against, but state GU tract is an infrequent source for bacteremia)

Nicolle et al, Clin Infect Dis 2005, 40:643. Nicolle et al, Clin Infect Dis 2019, 68:e83.

Hazards of ASB Treatment

- Side effects of antibiotics
- ⇧ risk of Cdiff
- ⇧ risk of resistance



- May increase risk of recurrent UTI by getting rid of "good" interfering bacteria
- Increased LOS

Cai et al, Clin Infect Dis 2012;55(6):771. Cai et al, Clin Infect Dis 2015;61(11):1655. Petty et al, JAMA IM 2019 epub.

The Heart of the Problem

- It's Hard to Ignore a Positive Culture

- Proof of concept study:
  - At Mount Sinai, 90% of their inpatient urine cultures were ASB, and 50% were treated with ABx
  - They stopped reporting these (+) urine cultures in the EMR
  - Results:
    - The % of ASB that was treated dropped by 80%
    - No untreated UTIs and no sepsis

Leis et al, Clin Infect Dis 2014, 58:980.

How To Distinguish ASB vs. UTI?

- Does the UA help? → Yes, but only if negative
  - Pyuria is seen in >50% of catheterized patients with ASB
  - But the absence of pyuria suggests an alternative dx
- Does the organism help? → NO
  - The same organisms cause ASB and UTI
- Use clinical context – does the patient have signs/symptoms of UTI?

Nicolle et al, Clin Infect Dis 2005, 40:643. Tambyah et al, Arch Intern Med 2000, 160:678. Lin et al, Arch Int Med 2012, 172:33.

What if I Can't Assess Symptoms?

How to define UTI in patients with a catheter?

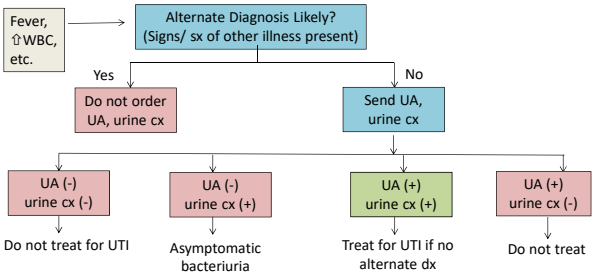
Surrogate signs/symptoms of UTI
- Fever, rigors, malaise
- Flank pain, CVAT, pelvic pain
- Acute hematuria
- Spinal cord injury: ⇧spasticity, autonomic dysreflexia, unease

AND

No other source of infection (i.e., diagnosis of exclusion)

Hooton et al, Clin Infect Dis 2010, 50:625.

Interpreting Urine Studies in a Patient With a Foley



Slide courtesy of Catherine Liu.

What About Older Patients with Confusion?

An elderly patient with functional/cognitive impairment presents with bacteriuria and either AMS or fall

IDSA Guidelines 2019

If no local GU symptoms or other systemic signs of infection → look for other causes; careful observation without antibiotics (*strong rec, low quality evidence)*

Why?
- Current data does now show causality between bacteriuria and MS changes, and treatment does not improve clinical outcomes
- Places high value on avoiding adverse effects of Abx (Cdiff, resistance)

Nicolle et al, Clin Infect Dis 2019:68:e83.

ASB vs UTI: Take-Home Points

- For elderly patients admitted with bacteriuria and AMS, look for other causes and closely observe without antibiotics
- ASB is very common and rarely needs treatment
- Pyuria ≠ UTI, but its absence suggests an alternative dx
- UTI diagnosis in a patient with a catheter requires surrogate signs/symptoms of UTI and no other source of infection

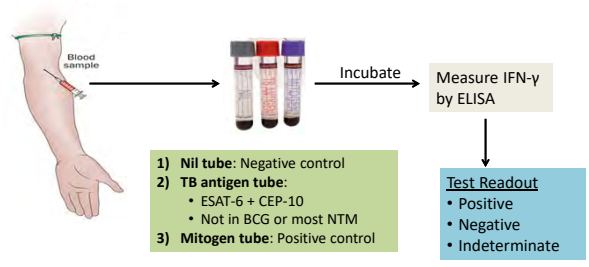
Case #5

23 y/o woman with Takayasu arteritis on prednisone who needs escalation of immunosuppression to infliximab. She has had an indeterminate QuantiFERON (QFT) x 2, negative PPD, and no lung pathology on chest CT. She was born in California and has no known TB exposures or other risk factors. Should she be treated for latent TB infection (LTBI)?

An Indeterminate QFT Means:

1. Intermediate probability of LTBI
2. Borderline/equivocal result
3. Low level positive result
4. The test didn't work

QuantiFERON Interferon Gamma Release Assay (IGRA)



Definition of an Indeterminate Assay

Indeterminate = TEST FAILURE

- Positive control (mitogen) didn't work (>85% of indeterminate results)
- Negative control (nil) had too much background IFN-γ

Reasons for an Indeterminate QFT

Test Factors

- Volume of blood drawn
- Suboptimal handling
- Delays from blood draw to incubation step

Patient Factors

- Immunocompromise impairs ability of T cells to produce IFN-γ in response to mitogen

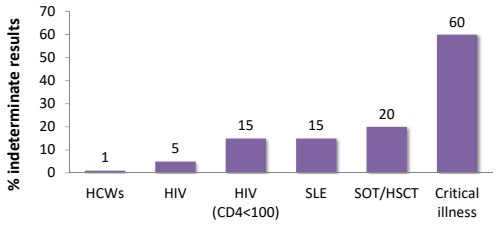
Pai et al, Clin Micro Rev 2014, 27:3.

How Common is an Indeterminate QFT?

- HCWs and TB Screening Programs: 1%
- Tertiary care inpatient settings: 20%
- Immunocompromise: 5-60%

Fabre, Open Forum Infect Dis 2014. Lucet al al, Infect Contrl Hosp Epi 2015, 36:569. Simpson et al, J Immigrant Minority Health 2013, 15:686.

Indeterminate QFT and Immunocompromise

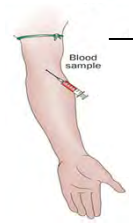


Cho et al, Lupus 2016; 0:1. Huang et al, Sci Rep 2016; 6:19972. Sester et al, Am J Respir Crit Care Med 2014, 190:1168. Leutkemeyer et al, Am J Respir Crit Care Med 2007, 175:737.

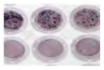
How to Manage Indeterminate QFT?

- If high risk patient → repeat and/or perform a PPD
- Repeat QFT
  - May eliminate possibility of lab-related factors
  - Many will still be indeterminate (40-70%)
  - Consider waiting until CD4 is higher or immunosuppression is decreased
- In a high risk patient, use epidemiologic risk factors, clinical history, chest imaging

T-SPOT TB Test: This DOES Have a Borderline Result



Mix blood PBMC and TB antigens
Check for IFN-γ production by ELISPOT
Also uses a positive and negative control



Test Readout
- Positive (>8 spots)
- Negative (<4 spots)
- Borderline (5-7 spots)
- Invalid (failure of positive or negative control)

Indeterminate QFT: Take-Home Point

- **Indeterminate QFT = test failure** due to failure of either the positive (most likely) or negative control

Thanks For Your Attention!

- Questions?

Fallen Leaf Lake, August 2020

Caring for the Hospitalized Patient with Addictions

Marlene Martín
Director, Addiction Care Team, Division of Hospital Medicine, SFGH
Associate Professor of Clinical Medicine, UCSF

25th Annual Management of the Hospitalized Patient CME Course
October 21, 2021

ACT

I have nothing to disclose

35 Y man admitted with right upper extremity erythema, pain, and swelling

- Started on empiric treatment for cellulitis
- You are receiving sign out from your overnight colleague when you get paged that he is complaining of diarrhea, abdominal pain, headache, and nausea.
- You evaluate the patient and note he is yawning and that his pupils are dilated. He endorses last using heroin right before admission.

Objectives

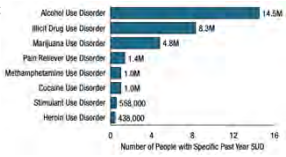
- Diagnose substance use disorders (SUD) most commonly encountered by hospitalists
- Initiate evidence-based medication for alcohol and opioid use disorder treatment
- Identify how to link hospitalized patients with SUD to addiction treatment on discharge

Outline

- **National Landscape of SUD**
- Hospitalized patients with SUD
- Diagnosing SUD
- Medication for opioid and alcohol use disorder treatment
- Care Transitions

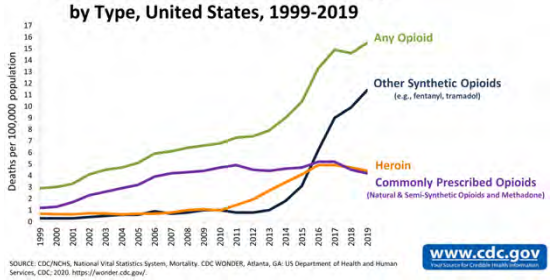
Tobacco, Alcohol, and Drugs

- 20.4 million (7.4%) had an alcohol or drug use disorder in the last year
- 26.8 million (8.2% of population) smoke cigarettes daily



Substance Abuse and Mental Health Services Administration. (2020). Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health (HHS Publication No. PEP20-07-01-001, NSDUH Series H-55). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

Overdose Death Rates Involving Opioids, by Type, United States, 1999-2019

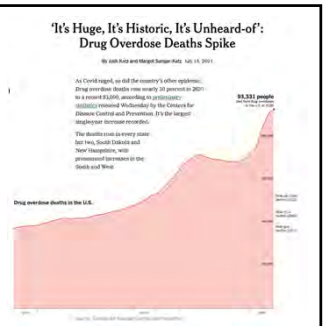


SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/.

www.cdc.gov
Your Source for Credible Health Information

COVID-19 and SUD

- Magnifying the drivers of use
  - Psychosocial and economic impacts
- Riskier use
  - Group programs halted/only accessible via technology
  - Limited hours of Syringe Access Services
  - Using alone
  - Suppliers disrupted
  - Shelters closed/unappealing



SUD Crisis

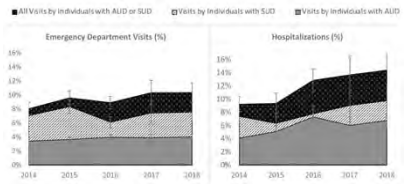
- More than 480,000 tobacco-, 95,000 alcohol-, and 93,000 drug-related deaths yearly
- Stimulant related deaths are increasing
  - Cocaine-related deaths doubled and methamphetamine deaths tripled between 2011-2016
  - Methamphetamine-related deaths are occurring independent of opioids
- Alcohol-related deaths also rising
  - Increasing unhealthy alcohol use among women, older adults, racial/ethnic minorities
  - More rapid acceleration in last few years most prominently among younger age groups and women

Alcohol and Public Health: Alcohol-Related Disease Impact (ARDI). Average for United States 2006–2010 Alcohol-Attributable Deaths Due to Excessive Alcohol Use. Centers for Disease Control and Prevention (CDC).
Kariisa M, Scholl L, Wilson N, Seth P, Hoots B. Drug Overdose Deaths Involving Cocaine and Psychostimulants with Abuse Potential — United States, 2003–2017. MMWR Morb Mortal Wkly Rep 2019;68:388–395.
Spillane S, Shiels MS, Best AF, Haozous EA, Withrow DR, Chen Y, Berrington de González A, Freedman ND. Trends in Alcohol-Induced Deaths in the United States, 2000-2016. JAMA Netw Open. 2020;3(4):e1921451.
Grant BF, Chou SP, Saha TD, Pickering RP, Kerridge BT, Ruan WJ, Huang B, Jung J, Zhang H, Fan A, Hasin DS. Prevalence of 12-Month Alcohol Use, High-Risk Drinking, and DSM-IV Alcohol Use Disorder in the United States, 2001-2002 to 2012-2013: Results From the National Epidemiologic Survey on Alcohol and Related Conditions. JAMA Psychiatry. 2017 Sep 1;74(9):911-923.

Outline

- ❑ National Landscape of SUD
- ❑ **Hospitalized patients with SUD**
- ❑ Diagnosing SUD
- ❑ Medication treatment for OUD and AUD

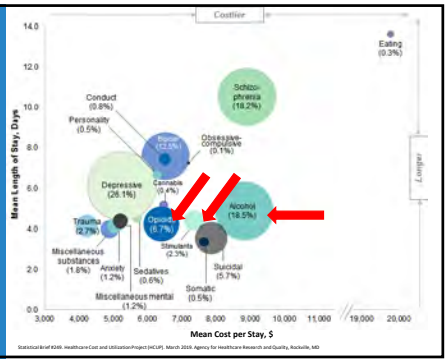
SUD is prevalent among hospitalizations



SUD-related emergency department visits and hospitalizations account for $13.2 billion of healthcare spending/year

Suen LW, Makam AN, Snyder HR, Repplinger D, Kushel MB, Martin M, Nguyen OK. National Prevalence of Alcohol and Other Substance Use Disorders Among Emergency Department Visits and Hospitalizations: NHAMCS 2014-2018. J Gen Intern Med. 2021 Sep 13:1–8. doi: 10.1007/s11606-021-07059-w.
Peterson C, Li M, Xu L, Mikosz CA, Luo F. Assessment of Annual Cost of Substance Use Disorder in US Hospitals. JAMA Network Open. 2021;4(3):e210242.

Percentage, cost, and length of stay for primary mental and substance use disorder diagnoses



Statistical Brief #249. Healthcare Cost and Utilization Project (HCUP). March 2019. Agency for Healthcare Research and Quality, Rockville, MD.

SUD among hospitalized patients

- More likely to be admitted from the emergency department
- Longer lengths of stay, costlier, higher readmission
- High self discharge rates
- Lowest quartile of income
- Unconnected to care

Statistical Brief #249. Healthcare Cost and Utilization Project (HCUP). March 2019. Agency for Healthcare Research and Quality, Rockville, MD.
Brown RL, Leonard T, Saunders LA et al. The prevalence and detection of substance use disorders among inpatients ages 18 to 49: an opportunity for prevention. Prev Med 1998; 27 (1): 101-10).
Englander H, Weimer M, Solotaroff R et al. Planning and Designing the Improving Addiction Care Team (IMPACT) for Hospitalized Adults with Substance Use Disorder. J Hosp Med. 2017 May;12(5):339-342.
Spooner, K.K., Salemi, J.L., Salihu, H.M., Zoorob, R.J., 2017. Discharge against medical advice in the United States, 2002-2011. Mayo Clin. Proc. 92, 525–535.
Walley AY, Paasche-Orlow M, Lee EC, et al. Acute care hospital utilization among medical inpatients discharged with a substance use disorder diagnosis. J Addict Med. 2012 Mar;6(1):50-6.
Roman MV and Herzig SJ. Hospitalizations Related To Opioid Abuse/Dependence And Associated Serious Infections Increased Sharply, 2002-12. Health Aff (Millwood). 2016 May 1;35(5):812-7.

Why treat SUD in the hospital?

2/3 Patients are Motivated to Reduce Use
Pivotal Touch Point

Velez CM, Nicolaidis C, Korthuis PT, Englander H. "It's been an Experience, a Life-Learning Experience": A Qualitative Study of Hospitalized Patients with Substance Use Disorders. J Gen Intern Med. 2017 Mar;32(3):296-303.
Wei L, DeFries T, Lozada M, Young N, Huen W, Tuldy J. An inpatient treatment and discharge planning protocol for alcohol dependence: efficacy in reducing 30-day readmissions and emergency department visits. J Gen Intern Med. 2015 Mar;30(3):365-70.
Englander H, Collins D, Perry SP et al. "We've Learned It's a Medical Illness, Not a Moral Choice": Qualitative Study of the Effects of a Multicomponent Addiction Intervention on Hospital Providers' Attitudes and Experiences. J Hosp Med. 2018 Nov 1;13(11):752-758.
Englander H, Weimer M, Solotaroff R et al. Planning and Designing the Improving Addiction Care Team (IMPACT) for Hospitalized Adults with Substance Use Disorder. J Hosp Med. 2017 May; 12(5):339-342.

Outline

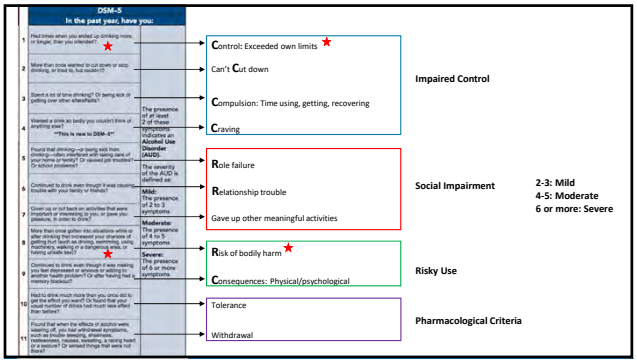
- National Landscape of SUD
- Hospitalized patients with SUD
- **Diagnosing SUD**
- Medication for opioid and alcohol use disorder treatment
- Care Transitions

Diagnosing SUD

Symptoms
- Withdrawal
- Intoxication

Diagnoses
- Skin and soft tissue infections
- Endocarditis, osteomyelitis
- Trauma
- Alcohol withdrawal
- Overdose
- Heart failure exacerbation

Not all who use substances have SUD



35 Y man with cellulitis. He uses heroin 3-4 times daily and has been unable to cut back. He lost his job due to missing work and has distanced himself from his parents due to his use. Does he have OUD?

A) Yes
B) No
C) Need more information

Control: Exceeded own limits
Can't **C**ut down
Compulsion: Time using, getting, recovering
Craving
Role failure
Relationship trouble
Gave up other meaningful activities
Risk of bodily harm
Consequences: Physical/psychological
Tolerance
Withdrawal

Outline

- ❑ National Landscape of SUD
- ❑ Prevalence, demographics, and characteristics of hospitalized patients with SUD
- ❑ Diagnosing SUD
- ❑ **Medication treatment for OUD and AUD**
- ❑ Care Transitions

35 Y man with cellulitis and OUD. What treatments would you offer?

A) Buprenorphine
B) Methadone
C) Clonidine, diphenhydramine, loperamide, Tylenol
D) Extended-release Naltrexone
E) Need more information

Medications for OUD

Mu receptor →

Opioids: full mu agonist
heroin, oxycodone, fentanyl

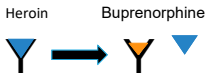
Methadone: full mu agonist

Buprenorphine: partial mu agonist
High affinity, ceiling effect

Extended-release naltrexone:
Full antagonist, high affinity

Initiating Buprenorphine

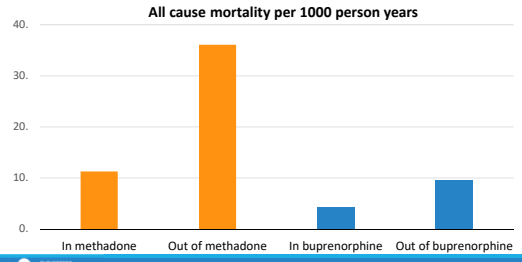
- Withdrawal prior to initiation OR
- Gradual uptitration/microdosing



Medications for OUD

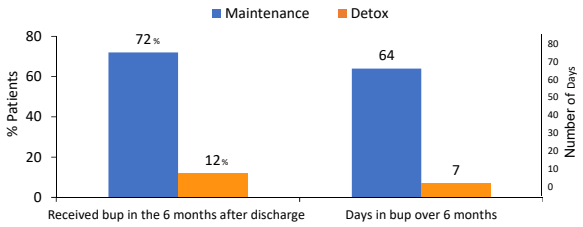
	Methadone	Buprenorphine
Treatment retention	Higher than buprenorphine	Increased retention at doses >16mg
Office visits	Daily visits to Opiate Treatment Program (OTP – methadone clinic)	Daily-monthly; can also provide as DOT in OTPs
Who can prescribe in acute care?	**Any inpatient clinician during hospitalization.** Any provider in ED: up to 72 hours dosing	**Any inpatient clinician during hospitalization.** Any provider in ED: up to 72 hours dosing
Who can prescribe at discharge?	**OTP**	**Any provider with DATA2000 X waiver**
Sedation	Yes at high doses, non-tolerant patients or slow metabolizers	Ceiling effect for respiratory depression
Withdrawal when starting	Takes time to reach comfortable dose	**Withdrawal or gradual uptitration/microdose**

Decreased Mortality



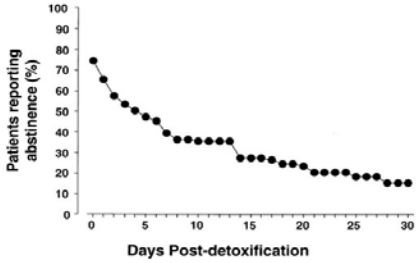
Source: Sordo *et al, BMJ, 2017*

Hospital Initiation of Buprenorphine



Source: Liebschutz *et al, JAMA Internal Medicine*, 2014

Detox Doesn't Last



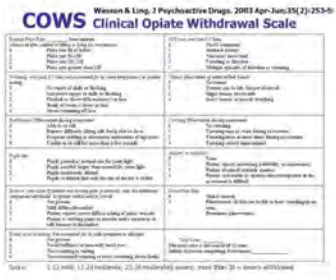
Source: Chutuape M *et al, The American Journal of Drug and Alcohol Abuse*, 2001.

Back to our patient. He wants to start buprenorphine. How would you start it?

A) Low-dose or gradual initiation, "microdosing"
B) 2mg buprenorphine
C) 4mg buprenorphine
D) 8mg buprenorphine
E) Need more information

He wants to start buprenorphine. How would you start it?

- Traditionally
  - At least mild withdrawal prior to initiation (COWS 8-11)
- Recent opioids
  - Wait for mild–moderate withdrawal
  - ~8-12h after short acting and 24-48h after long acting
- Transitioning from methadone or fentanyl or no opioid free period
  - Ask for help!
  - Low-dose buprenorphine/microdose



Withdrawal Assessment

COWS shortcut: Subjective symptoms AND at least 1 objective withdrawal sign

- Subjective: Nausea, abdominal pain, myalgias, chills
- Objective (at least 1): Restlessness, sweating, rhinorrhea, dilated pupils, watery eyes, tachycardia, yawning, goose bumps, vomiting, diarrhea, tremor

Traditional Buprenorphine Initiation

When COWS ≥8, give 2-8 mg

Reassess in 1 hour, then q4-6 hours thereafter.

- Max day 1: 16 mg
- Max day 2: 24 mg

Therapeutic dose 16-24mg/day

Increase dose: craving, withdrawal, pain

Decrease dose: insomnia/mania, sedation

Precipitated withdrawal: more buprenorphine OR short acting full opioid agonist

Works well with pill-based OUD and heroin use disorder

On full opioid agonists or using fentanyl: low-dose, microdosing method

- Depends on buprenorphine formulations available in hour hospital
  - **Sublingual films or tabs** (cut 2mg films or tabs into quarters)
  - Buprenorphine patches (patch protocols on next 2 slides)
  - Buccal buprenorphine
  - Intravenous buprenorphine
- Example protocol using films or tabs:
  - Day 1: 0.5mg q6h = 2mg total
  - Day 2: 1.0mg q6h = 4mg total
  - Day 3: 2.0mg q6h = 8mg total and start decreasing/stopping full agonists (except if acute pain)
  - Day 4: 12-32 mg

As you are ordering buprenorphine via a traditional initiation (since he is in moderate withdrawal after last using heroin yesterday) he asks about methadone. What methadone dose would you start?

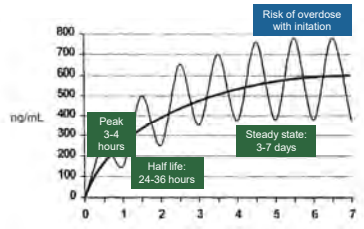
A) 5mg
B) 20mg
C) 100mg
D) None, we cannot start methadone in the hospital
E) Need more information

Yes, we can start methadone in the hospital

(c) This section is **not intended to impose *any* limitations on a physician or authorized hospital staff to administer or dispense narcotic drugs in a hospital to maintain or detoxify a person *as an incidental adjunct to medical or surgical treatment of conditions other than addiction***, or to administer or dispense narcotic drugs to persons with intractable pain in which no relief or cure is possible or none has been found after reasonable efforts.

https://www.deadiversion.usdoj.gov

Methadone



Days at steady dose

Methadone

Day 1

Start with 10-30 mg, reassess in 3-4 hrs, add 10mg PRN withdrawal or cravings, max 40 mg

Check for sedation at 3-4 hours. Ok to give additional short acting opioids throughout.

Day 2

Total Day 1 + 5-10 mg in 3-4 hrs PRN, max 50 mg

Day 3

Today Day 2+ 5-10 mg in 3-4 hrs PRN, max 60 mg

Monitor on 60mg daily for 5 days before increasing again by 5-10mg, then hold that dose for 5 days, etc

Target daily dose 80-120mg

Our patient ultimately chooses buprenorphine and is doing well on 16mg daily. However, he has an abscess and goes to the OR for debridement. How would you treat his pain post procedure?

A) Regional block
B) Morphine
C) Tylenol
D) Adjust buprenorphine dosing/frequency
E) Stop buprenorphine
F) All of the above

Medication for OUD management in the perioperative period

	Verify dose	Before procedure	After procedure
Methadone	Call OTP	Continue full dose	Continue full dose, consider splitting dose in the hospital
Buprenorphine	Records, PDMP, pharmacy	Continue full dose	Continue/increase dose, consider splitting

Kohan L, Potru S, Barreveld AM, Spiritz M, Lane O, Aryal A, Emerick T, Dopp A, Chhay S, Viscusi E. Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel. Reg Anesth Pain Med. 2021 Oct;46(10):840-859. doi: 10.1136/rapm-2021-102807.

Managing acute pain in the setting of medications for OUD treatment

	Interventions to consider
Mild pain	• Split buprenorphine/methadone TID
Moderate pain	• Ibuprofen, acetaminophen, topicals • Neuropathic: gabapentin, TCAs, SNRIs
Severe pain	• Regional and local anesthesia • Give opioids → remember that you will need higher doses due to tolerance • Ketamine

Haber LA, DeFries T, Martin M. Things We Do for No Reason™: Discontinuing Buprenorphine When Treating Acute Pain. J Hosp Med. 2019 Oct 1;14(10):633-635. doi: 10.12788/jhm.3265. Epub 2019 Aug 14.

A week later, you admit a 46-year-old woman with depression for alcohol withdrawal and mild alcohol-related hepatitis. She has no primary care clinician, and this is her first presentation. You diagnose her with AUD using the DSM-5 criteria. What options does she have for alcohol use disorder treatment?

A) Naltrexone
B) Extended-release naltrexone
C) Acamprosate
D) Psychosocial treatment (e.g., residential, mutual help group)
E) All of the above

AUD Treatment

Psychosocial Treatment

OR
AND

Medication Treatment

7.3% receive any treatment
Only 1.6% receive medication for AUD

Key substance use and mental health indicators in the United States. SAMHSA 2019.
Han B, Jones CM, Einstein EB, Powell PA, Compton WM. Use of Medications for Alcohol Use Disorder in the US: Results From the 2019 National Survey on Drug Use and Health. JAMA Psychiatry. 2021 Jun 16;78(8):922–4. doi: 10.1001/jamapsychiatry.2021.1271.

1st Line AUD Medications

Medication	Dose	Mechanism	Adverse Effects	Contraindications	Liver disease	Renal disease	Evidence
Naltrexone or Extended-Release Naltrexone	50mg daily or 380mg/ month	• Mu-opioid antagonist • Reduces cravings, blocks pleasurable effects of EtOH, reduces binges	GI upset, transaminitis,	• LFTs>5 ULN • Decompensated cirrhosis • Childs class C • Opioids on board	Not in Child Pugh C	OK to use unless severe CKD	• NNT=12 to prevent return to heavy drinking • NNT=20 for abstinence • High cravings, early AUD, fam history
Acamprosate	666mg TID	• Modulates glutamate hyperactivity • Improves dysphoria, promotes abstinence • Best if already s/p detox and aims abstinence	Diarrhea fatigue	• Dose reduce CKD	Yes	Dose reduce to 333 TID	• NNT=12 to prevent return to any drinking • Not useful in heavy drinking • 6 pills per day
Disulfiram	250-500 daily	• Aldehyde dehydrogenase inhibitor • Causes negative physical effects if EtOH intake	Diarrhea, headache, dermatitis, rare hepatitis	• LFTs> 5 ULN • Alcohol use in past 24 hrs • Severe CV disease	No	Yes as long as not severe	• Only effective in RCT of directly observed treatment (DOT)

Rosner et al 2010 Cochrane, Jonas et al 2014 JAMA, Anton et al 2006 JAMA, Anton et al 2011 Am J Psychiatry

2nd Line AUD Medications

Medication	Dose	Mechanism	Adverse Effects	Contraindications	Liver disease	Renal disease	Evidence
Gabapentin	600 TID	• Facilitates GABA • Improves anxiety, dysphoria, sleep	Somnolence, dizziness	Dose reduce CKD	Yes	Dose reduce	• Reduces binges and improves abstinence • NNT 8 for abstinence • NNT 5 for reduced binge drinking • Can combine with naltrexone
Topiramate	25 BID → 150 BID	Facilitates GABA, decreases glutamate. Improves dysphoria, cravings, impulsivity	• Cognitive slowing • Paresthesias • Somnolence • Rare metabolic acidosis • Kidney stones • Glaucoma	H/o kidney stones, narrow-angle glaucoma	Yes	Dose reduce	• Reduces heavy drinking days, drinks/day in meta-analysis. • NNT for return to heavy drinking 7.5, adjust for adverse events • Use even with ESLD • Useful in PTSD, seizures, weight loss • Can combined with naltrexone

Jonas et al 2014 JAMA, Mason et al 2014 JAMA IM.

AUD Medications

MAINTAIN ABSTINENCE	DECREASE USE
Naltrexone / extended-release naltrexone	**Naltrexone / extended-release naltrexone**
Acamprosate	Gabapentin*
Gabapentin*	Topiramate*
Disulfiram	~~Baclofen*~~
	Prazosin*
* Not FDA approved	Ondansetron*
	Varenicline*

Chaignot C et al. Pharmacoepidemiol Drug Saf 2018.

Back to our case

46-year-old woman with depression and moderate AUD. Alcohol withdrawal resolves. Her AST/ALT are both <200 and she does not have cirrhosis. She is not receiving opioids. You discuss medications for AUD and psychosocial treatment options with her. She chooses to start naltrexone because of her strong cravings for alcohol and you initiate before discharge.

Increasing Rates of AUD

	2001-2002	2012-2013	% Change
Alcohol use	65.4%	72.7%	11.2%
Risky Drinking	9.7%	12.5%	29.9%, most pronounced in women, racial/ethnic minorities, older adults, low SES
AUD	8.5%	12.7%	49.4% most pronounced in women, low SES, older adults

National Epidemiologic Survey on Alcohol and Related Conditions
Grant BF et al. JAMA Psychiatry 2017.

Increasing Alcohol-related deaths

Table. Age-Standardized Rates of Alcohol-Induced Deaths and APCs, 2000 to 2016

Racial/Ethnic Group	Men	No. of Deaths per 100 000 Residents*			Women	No. of Deaths per 100 000 Residents*		
	Period	Start	End	APC (95% CI), %	Period	Start	End	APC (95% CI), %
All	2000-2005	14.4	13.9	-0.6 (-1.5 to 0.3)	2000-2006	4.1	4.4	0.9 (0.1 to 1.8)
	2005-2012	13.9	15.3	1.3 (0.6 to 1.9)	2006-2013	4.4	5.4	3.4 (2.6 to 4.1)
	2012-2016	15.3	17.8	4.2 (3.1 to 5.3)	2013-2016	5.4	6.6	7.1 (5.1 to 9.1)
Non-Latino white	2000-2011	12.9	14.8	1.4 (1.0 to 1.7)	2000-2006	3.9	4.6	2.4 (1.5 to 3.2)
	2011-2016	14.8	18.2	4.4 (3.3 to 5.4)	2006-2013	4.6	6.0	4.1 (3.3 to 4.9)
					2013-2016	6.0	7.6	7.8 (5.7 to 9.9)
Latino/Latina	2000-2003	24.4	21.0	-5.1 (-9.8 to -0.1)	2000-2012	3.1	3.8	1.0 (0.1 to 1.9)
	2003-2011	21.0	19.6	-0.6 (-1.4 to 0.2)	2012-2016	3.8	4.7	5.6 (2.0 to 9.4)
	2013-2016	19.6	21.9	4.1 (0.3 to 8.1)				
Non-Latino black	2000-2006	19.6	13.0	-6.2 (-7.5 to -4.9)	2000-2007	5.6	3.5	-5.9 (-8.2 to -3.6)
	2006-2012	13.0	12.2	-1.7 (-3.6 to 0.2)	2007-2016	3.5	4.6	3.1 (1.5 to 4.8)
	2012-2016	12.2	13.8	2.7 (0.2 to 5.4)				
API	2000-2016	3.5	4.4	1.2 (0.3 to 2.1)	2000-2016	0.9	1.0	2.2 (0.5 to 4.0)
AIAN	2000-2016	66.9	113.2	3.3 (2.6 to 4.0)	2000-2016	10.7	58.8	4.2 (3.8 to 4.6)

Abbreviations: AIAN, American Indian and Alaska Native; APC, annual percentage change; API, Asian and Pacific Islander.
* Rates are for single years at time interval boundaries.

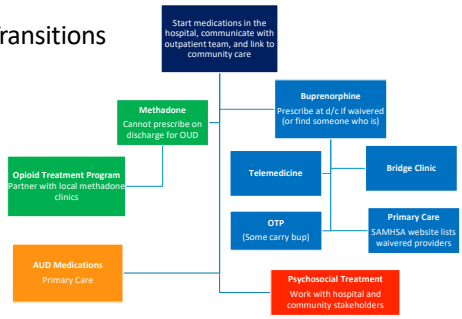
Spillane S et al. JAMA Netw Open 2020.

As clinicians, we see patients with AUD for…

Outline

- National Landscape of SUD
- Prevalence, demographics, and characteristics of hospitalized patients with SUD
- Diagnosing SUD
- Medication treatment for OUD and AUD
- **Care Transitions**

Care Transitions



Objectives

- Diagnose substance use disorders (SUD) most commonly encountered by hospitalists
- Initiate evidence-based medication for alcohol and opioid use treatment
- Identify how to link hospitalized patients with SUD to addiction treatment on discharge

Opportunities for you to improve SUD care

DIAGNOSE SUD | TREAT SUD | LINK TO CARE

How you can help today

1	2	3	4
Get your X waiver now!	Prescribe naloxone for overdose prevention including stimulants	Assess your patients for SUD and their SUD goals	Continue SUD medications during admission

Get your X-Waiver Now!

1. Go to: https://buprenorphine.samhsa.gov/forms/select-practitioner-type.php
2. To complete the application:
   - Under training you received, click other and mark: "practice guidelines"
   - Date: today
   - City: type "Practice Guidelines"
   - State: Type in your state
   - Select 30 patients

Lead systems change

Offer	medications for addiction treatment to patients with SUD
Create	hospital order set or guideline for new starts
Partner	with stakeholders to link patients to community care
Disseminate	knowledge with colleagues
Become	a SUD champion in your hospital

Reflections

Take 1 minute to write down (or tweet):

One concept or tool that you commit to incorporating to improve your care of patients with SUD now

Harm Reduction

MAT = treatment & HR	Needle exchange programs	Review injection practices	Supervised injection facilities
Buddy system	HCV and HIV education, screening, and treatment	HAV, HBV, & TDaP vaccines	Naloxone

ICU Management Pearls for the Hospitalist

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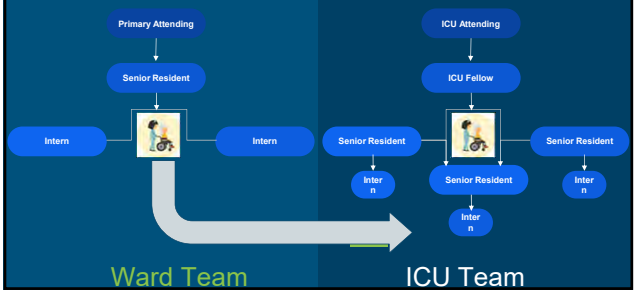
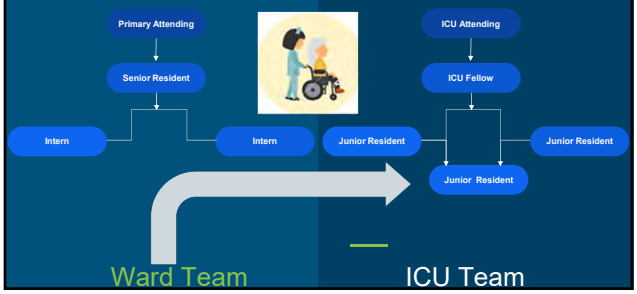
Disclosures

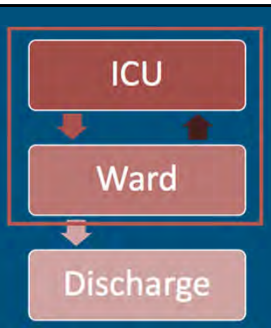
I have no conflicts of interest to disclose.

Organizational Structure of Closed ICUs

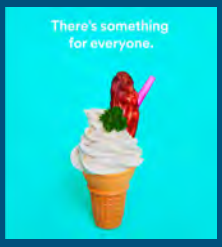


Organizational Structure of Open ICUs





Wherever you Practice, Ward, ICU, Or Neither…



ICU Management Pearls for the Hospitalist

1. Volume, Pressors & Shock
2. Blood, Sweat & Tears
3. Non-Invasive Ventilation
4. Demystifying Tracheostomy

ICU Management Pearls for the Hospitalist

1. **Volume, Pressors & Shock**
2. Blood, Sweat & Tears
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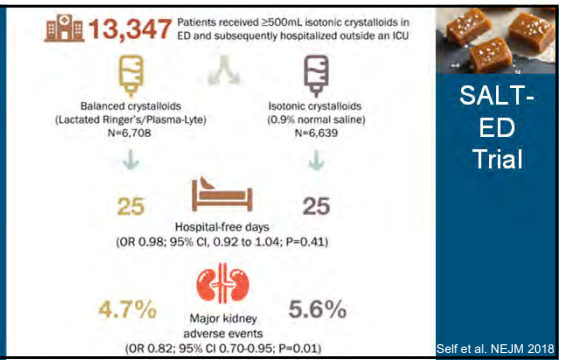
Volume Status: The Holy Grail

Classic debate b/w specialties: hospitalists are often the 'arbiters of truth'

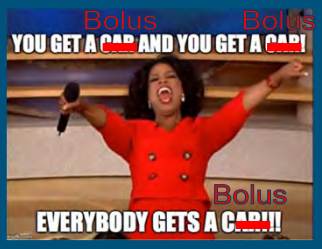
Q: When someone is hypotensive, I:

A. Start vasopressors
B. Fluid resuscitate with NS
C. Fluid resuscitate with Albumin
D. Fluid resuscitate with Plasmalyte/LR
E. POCUS, POCUS, more POCUS
F. Just lower the MAP goal.



Resist the "Lacto-Bolo Reflex"!

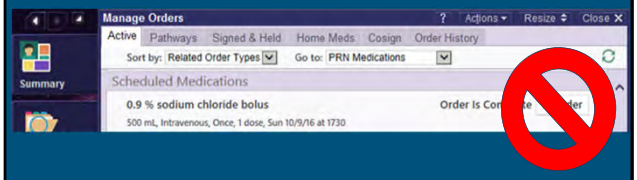
"Fluids for everyone hypotensive!"



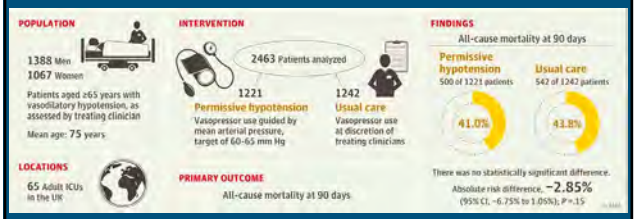
All that is Hypotensive is NOT Sepsis: Sepsis Mimics

More Common:	**More Rare:**
Hypovolemic	Anaphylactic Shock
Hemorrhagic	Adrenal Crisis
Pulmonary Embolism	Myxedema Coma
Cardiogenic	HLH
Obstructive/Tamponade	Toxidromes

Reassess Patient at the Bedside – Beyond the EHR

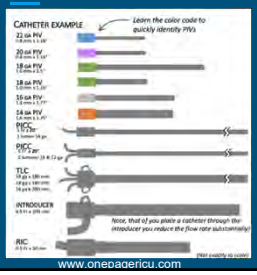


The New 65 Trial Addresses a Perennial Question



LaMontagne et al. JAMA 2020

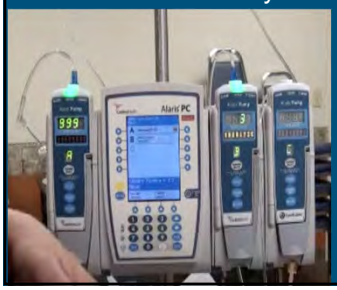
How to Resuscitate? Some Practical Tips



www.onepagericu.com

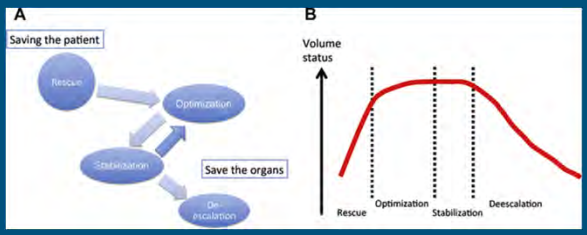
- If not responsive to fluids & escalating pressors, consider "the septic heart" – TTE
- Caution! Normal EF may actually be low in sepsis w/ vasopressors
- Smaller IVF boluses in CHF, ESRD, peri-intubation (250 ccs at a time) – reassess

New Trial! How Quickly to Resuscitate? 999 Ain't Bad!



- BaSICS RCT (Zampieri, JAMA 2021)
- 10,520 patients in ICUs – 333ml/hr (slow infusion) vs 999ml/hr (fast infusion) rate
- No mortality difference! Bolus away if you need to!

Don't forget to D/C IVF long before D/C Home!

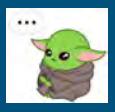


Weyker et al. Clin Chest Med 2016

Key Point

Volume status is dynamic and difficult to assess: reassess frequently and de-escalate & diurese early.

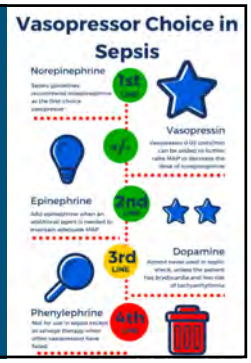
Q: My 1st line vasopressor of choice for shock is:



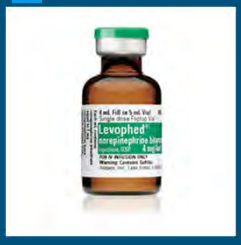
A. Norepinephrine (Levophed)
B. Phenylephrine ("Neo")
C. Dopamine
D. Vasopressin
E. Epinephrine
F. Just lower the MAP goal.

Vasopressor of Choice

- "Fill the tank" & check for volume-responsiveness
- CENSER Trial discussed early escalation to vasopressors – will need to be replicated
- Almost no role for Phenylephrine "Neo"



A Plea to Use Generic Names



Norepinephrine "Levo"

Phenylephrine "Neo"

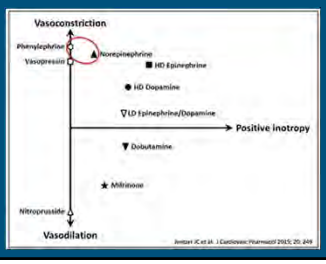
Vasopressors→ICU. But What about via PIV?

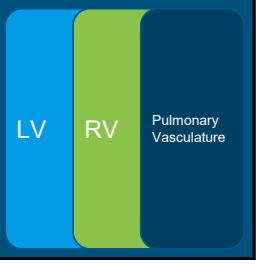
Small single-centered studies → small systematic review ~3% complications

Principle	Guidance
Vein size	> 4 mm, measured by U/S
Location	Upper extremity (no hand or wrist)
IV line size	20 g or 18 g
Assessment	RNs assess q2 hrs per protocol
Maximum dose/time	Low-dose norepi < 24 hrs

Emerg Med Austr 2020

Quick Pearl on Mixed Shock: Compartments!





Key Point

Pressors are like antibiotics: select the correct drug for the patient's physiology.

New Recs: 93 Recs in October Surviving Sepsis Guidelines!

Highlights of the New Surviving Sepsis Recs

KEEP	STOP	START
Early Abx (<1 hr)	Using qSOFA!	Balanced crystalloids
Norepi as 1st line	Starches/ gelatins!	HFNC > NIPPV
Addressing GOC early	Using Vitamin C!	?Steroids?

ICU Management Pearls for the Hospitalist

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Approach to Massive Resuscitation

What Defines a “Massive Transfusion”?

3 most common definitions:

1. Transfusion of ≥ 10 RBCs within 24 hours
   - ❑ This approximates the total blood volume of an adult!
2. Transfusion of ≥ 4 RBCs within 1 hr & anticipating more
3. Replacement of >50% total blood volume by products in 3 hrs

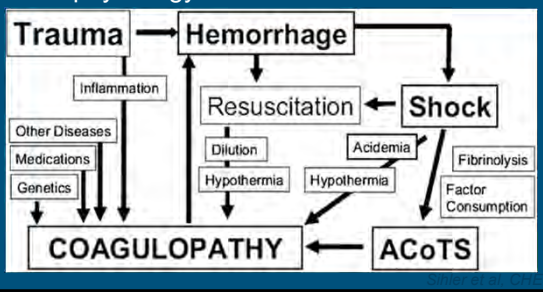
Pham et al, Br J Anesthesia, 2011

Epidemiology of Massive Transfusion

1. Major surgeries (spinal, liver transplant, cardiac cases)
2. Trauma (40% of trauma-related death 2/2 hemorrhage)
3. Obstetric hemorrhage (#1 cause of maternal mortality)
4. Gastrointestinal hemorrhage (variceal bleeding esp)
5. Hematologic malignancy

Mant et al, Crit Care Med, 2015

Pathophysiology of Massive Transfusion



Sihler et al, CHEST, 2011

Permissive Hypotension

- Conceptually part of damage-control resuscitation
- Minimize bloody vicious triad
- Maintain organ perfusion & avoid rebleed & vasoconstriction
- Caveat: CPP = MAP - ICP

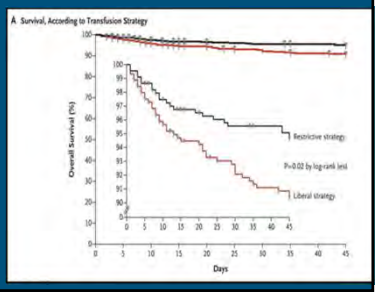
Kahn et al, Trauma Reports, 2013

Key Point

For massive resuscitation, permissive **hypotension is ok**, except for **brain & spinal cord injury** pts

GI Bleed Trials: A Classic Trial

- Villaneuva et al NEJM 2013 study



Villaneuva et al, NEJM 2013

Quick Pearls: Jehovah's Witnesses

- The Case: 60yo woman, Jehovah's Witness, admitted with Hb of 4 and hypotension.
- Humans can tolerate severe anemia!
- Consider fluids, FeSO4, EPO as adjunct therapies
- Try to get source control; consider Ethics consultation

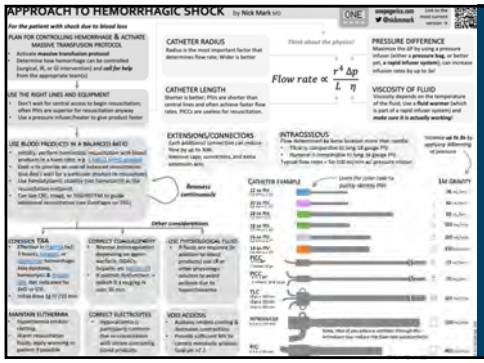
Berend et al, Am J Med, 2009

Quick Pearls: End-of-Life

- The Case: 96yo woman admitted with aortoenteric fistula and hypotension
- Key Point: Massive transfusion is a bridge
- Knowing when to stop is equally important . . .

Key Point

ICU 1 Pager on Massive Resuscitation



ICU Management Pearls for the Hospitalist

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Q: Not Indicated for Non-Invasive Ventilation?

A. Hypercapnic respiratory failure

B. Cardiogenic pulmonary edema

C. Hypoxemia in a DNR/DNI Yoda

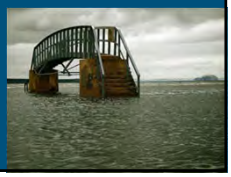
D. Weaning from the ventilator

Non-Invasive Ventilation: When to Use it?

- ❑ COPD exacerbation with hypercapnic acidosis
- ❑ Cardiogenic pulmonary edema
- ❑ Post-extubation respiratory failure

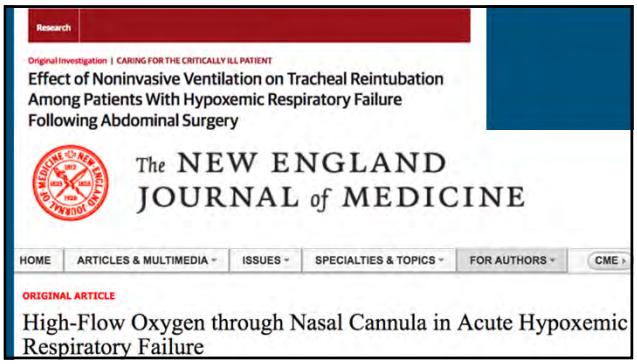
Contraindications to Non-Invasive Ventilation

- ❑ Cardiac or respiratory arrest
- ❑ Facial or neurological surgery/trauma/deformity
- ❑ Inability to protect airway/cooperate
- ❑ Inability to clear secretions
- ❑ High risk for aspiration
- ❑ Goals of care



Flow vs. Pressure: Who Wins?

NIV	HFNC
Counterbalances auto-PEEP	More comfortable than NIV
Reduces work of breathing	Higher FiO2 delivery
Improves lung compliance	Decreased dead space
Mask can be uncomfortable	Not good for hypercapnia



Key Point

Think carefully about contraindications and to what you are bridging. Continually reassess if they need intubation, whether HFNC or NIV.

ICU Management Pearls for the Hospitalist

1. **Volume, Pressors & Shock**
2. **Blood, Sweat & Tears**
3. **Non-Invasive Ventilation**
4. **Demystifying Tracheostomy**

Trach management & recovery

- Indications for tracheostomy
  - **Prolonged intubation**
  - **Facilitation of ventilation support/weaning**
  - Upper airway obstruction
  - Inability to intubate
  - Adjunct to major HEENT surgery/trauma
  - Airway protection (neurologic diseases, TBI)

Trach management & recovery

	Tracheostomy	Intubation
Advantages	· Pt comfort/decreases work of breathing · Better speech, swallowing, mobility · Easier to suction · Facilitates weaning/x-fer out of ICU	· Easily done in most settings · Not surgical (risk, $)

Trach management & recovery

	Tracheostomy	Intubation
Advantages	▪ Pt comfort/decreases work of breathing ▪ Better speech, swallowing, mobility ▪ Easier to suction ▪ Facilitates weaning/x-fer out of ICU	▪ Easily done in most settings ▪ Not surgical (risk, $)
Disadvantages	· Surgical procedure w/ related risks (incl mediastinitis) · Possible laryngeal nerve injury · Possible tracheo-arterial fistula · Stomal/cuff complications · Easily changed/managed by RNs/RTs · High mortality if inadvertently decannulated before tract matures	· Requires special expertise · Risk of tracheomalacia · Risk of laryngeal injury · Trauma to nose/mouth

Trach management & recovery

For these reasons, tracheostomy when indicated may **facilitate weaning from mechanical ventilation** → Tracheostomy is not a failure!

Trach management: What about COVID?

Highly infectious pathogen

+

Aerosol generating procedure

+

Prolonged ventilation

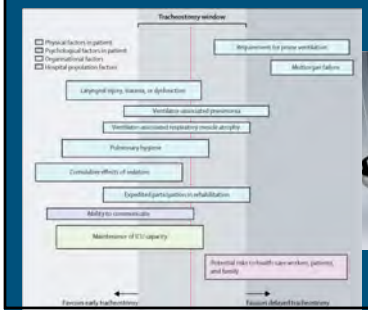
+

Prolonged sedation

+

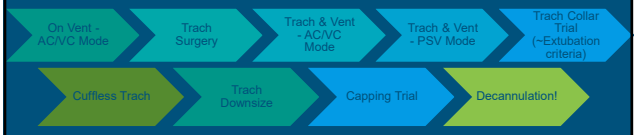
Scarce resources

Trach management: What about COVID?



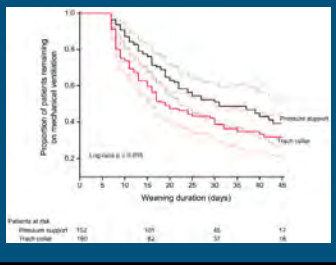
Lancet 2020

Trach management: Pathways



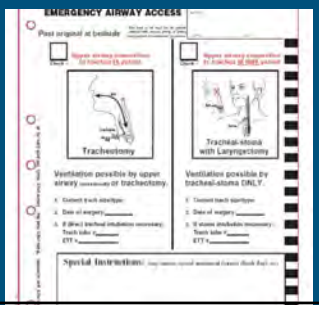
LTACHs and Weaning

Weaning at an LTACH can go more quickly than you think!



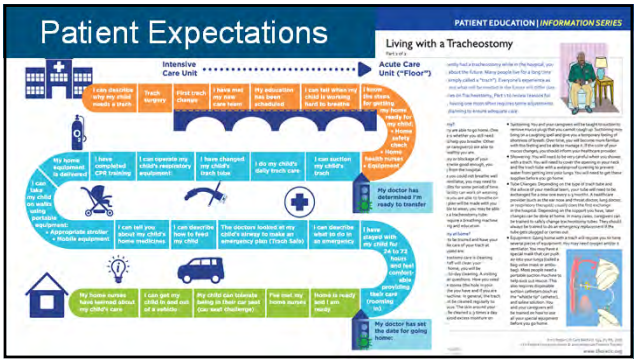
JAMA 2013 Jubran et al.

Trach Emergencies: UCSF OHNS QI



- Always know which box is checked for your patient – is your patient 'intubate-able from above' or not?
- When in doubt, call a Code Blue!

Patient Expectations



Key Point

Think about specific indications/advantages of a trach & remember a trach is not a failure. Know the progression pathway to weaning & set patient/family expectations accordingly.

ICU Management Pearls for the Hospitalist

1. Volume, Pressors & Shock
2. Blood, Sweat & Tears
3. Non-Invasive Ventilation
4. Demystifying Tracheostomy

Thank You!

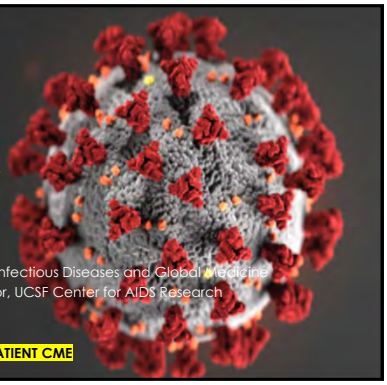
Questions?

Lekshmi.Santhosh@ucsf.edu
@LekshmiMD

NOTES

NOTES

COVID-19: Update on vaccines and variants



Monica Gandhi MD, MPH
Professor of Medicine, Division of HIV, Infectious Diseases and Global Medicine
Medical Director, Ward 86 and Director, UCSF Center for AIDS Research
October 22, 2021

MANAGEMENT OF THE HOSPITALIZED PATIENT CME

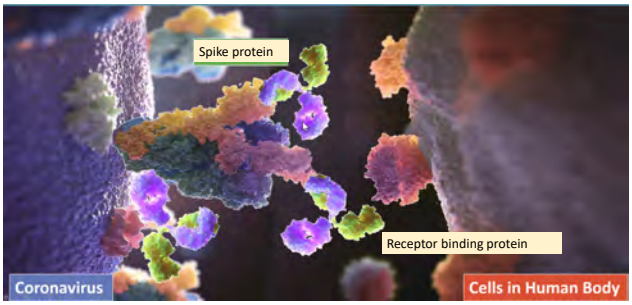
ARS: How many COVID-19 vaccines are currently being rolled out worldwide?

1. Three
2. Five
3. Six
4. Nine
5. Fifteen

Company or name	Form of publication for phase 3 data/ type of vaccine	Reference
Moderna	Peer reviewed publication/ mRNA	Baden NEJM, Feb 4, 2021
Pfizer	Peer reviewed publication/ mRNA	Polack NEJM, December 31, 2020
Johnson & Johnson	Press release only/ adenovirus + DNA	J&J press release January 29, 2021; FDA document Feb 24
AstraZeneca	Two peer-reviewed publications but ongoing (adenovirus + DNA)	Voysey Lancet December 8, 2020; Preprint Feb 1, 2021
Novavax	Press release, abstract, press release (phase 3 UK; phase 2b S. Africa; phase 3 US/Mexico)	Novavax press release June 14; Novavax NEJM June 30, 2021
Sputnik 5	Peer-reviewed publication (DNA plus adenovirus)	Logunov Lancet, February 2, 2021
Sinopharm	Publication (whole inactivated)	Sinopharm, JAMA, May 28, 2021
Sinovac	Publication (whole inactivated)	Sinovac, JAMA May 28, 2021
Bharat	Press release (whole inactivated)	Bharat Covaxin, April 21, 2021

There are actually 9 vaccines out there for COVID-19, three authorized in U.S.

6 vaccine candidates to date involve spike protein and receptor binding domain of SARS-CoV-2 either mRNA or adenoviral-vector DNA vaccines or protein adjuvant itself; 3 inactivated virus



Three types of vaccines involving spike protein

- mRNA vaccines (2)
- Adenoviral vector DNA vaccines (3)
- Spike protein + M-adjuvant vaccine (1)

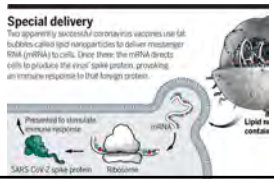
Three vaccines whole inactivated virions

Novavax

Johnson & Johnson

AstraZeneca

Sputnik V

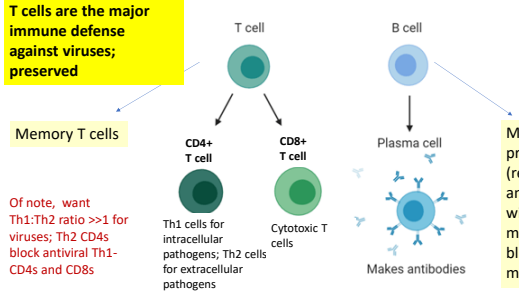


Pfizer

Moderna

Remember immunity -antibodies and cell-mediated

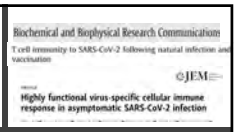
T cells are the major immune defense against viruses; preserved

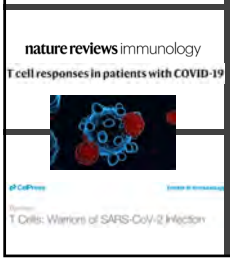


Of note, want Th1:Th2 ratio >>1 for viruses; Th2 CD4s block antiviral Th1-CD4s and CD8s

Memory B cells produce antibodies (remember antibodies will wane with time, but memory B cells are blueprint to make more)

Most vaccine trials measured antibodies and T cell responses





How does functional T-cell response modulate severity of disease?

- T cell responses modulate the severity of disease
- Strong T cell responses in all of these trials seem to have led to prevention of severe disease
- JEM study shows us that those with asymptomatic infection mounted good T cell responses to COVID-19
- If you get re-infected after natural infection or vaccine (rare), should be mild if mounted good T-cell response
- Fun fact: Study from 1918 survivors of influenza pandemic show durable B cell immunity (memory B- Ab) 90 years later!

Company	Platform	Doses	Non-clinical results	# with vaccine (same placebo)	Protection from COVID-19 hospitalization	Protection from COVID severe dz (some at home)	Efficacy against milder COVID
Moderna	mRNA-1273 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 CD4+ protection from challenge (macaques)	~15,000	90% (1 in vaccine arm after 2nd dose hospitalized)	97% (30 cases in placebo arm; 0 in vaccine reported but 1 severe per FDA)	94.1%
Pfizer	BNT162b2 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 CD4+, CD8+; protection from challenge (macaques)	~18,600	100%	100% (9 cases in placebo arm; 0 in vaccine- 1 initially severe but not)	95%
Johnson & Johnson	JNJ-78436725 Non-replicating human adenovirus/DNA	1	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; challenge protection (macaque)	~22,000 US, Latin America, S. Africa	100%	85.4% across 3 sites (7 deaths, 16 hospitalizations, all in placebo arm)	72% US; 61% Latin America; 64% S. Africa (95% B1.351)
AstraZeneca	AZD 1222 Non-replicating Chimp Adenovirus-DNA	2	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; protection from challenge (macaques)	~28,588 (UK, SA, US/Peru/ Chili)	100%	100% (UK, 15 placebo arm hospitalized, 0 in vaccine; US, 8 severe in placebo, 0 vaccine)	76% US (85% in >65 yrs); 70% UK; S. Africa halted for mild
Novavax	NVX-CoV2373 Spike protein/RBD + Matrix M adjuvant	2	Neutralizing Abs; Strong Th1 CD4 > Th2; macaque challenge protection	8833 (Phase 3 UK; 2b SA); 12.5K (Φ 3)	100%	100% (24 severe placebo in UK/SA/US /MX; 0 vaccine)	90.4% US/MX; 100% severe; 93.2% variants
Sputnik V	Ad26 and Ad5 adenovirus/DNA	2	NAbs; IFN-γ secretion PMBCs, cellular response	~14964	100%	100% (20 in placebo; 0 vaccine)	91.6%

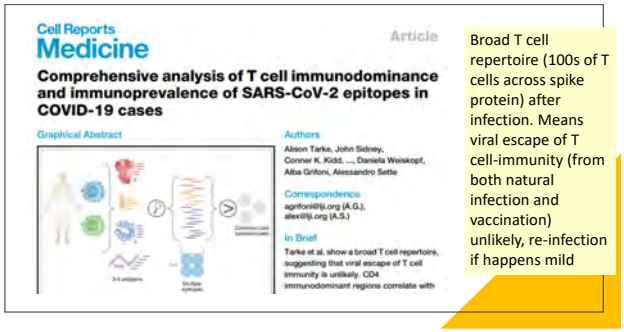
Company	Platform	Doses	Non-clinical results	# with vaccine (same placebo)	Protection from COVID-19 hospitalization	Efficacy against milder COVID
Bharat	Inactivated whole virus	2	Neutralizing Abs; Strong Th1 CD4 responses in phase II trial (Lancet)	11,000 (press release 4/21)	100%	78%
Sinovax	Whole inactivated virion	2	Neutralizing Abs; IFN-gamma assays T cell responses	13,068	100%	72.8%
Sinopharm	Whole inactivated virion	2	Neutralizing Abs; IFN-gamma assays T cell responses	13,068	100%	78.1%

Will vaccines work against variants and all against severe disease?
Short answer: yes because of T cells

New names proposed for Covid variants

Country/region	Scientific name	WHO name
Kent, UK	B.1.1.7	Alpha
South Africa	B.1.351	Beta
Brazil	P.1	Gamma
India	B.1.617.2	Delta

Why T cell response will work against variants? First look at natural infection


Cell Reports Medicine

Article

Comprehensive analysis of T cell immunodominance and immunoprevalence of SARS-CoV-2 epitopes in COVID-19 cases

Graphical Abstract

Authors

Alison Tarke, John Sidney, Conner K. Kidd, ..., Daniela Weiskopf, Alba Grifoni, Alessandro Sette

Correspondence

agrifoni@lji.org (A.G.), alex@lji.org (A.S.)

In Brief

Tarke et al. show a broad T cell repertoire, suggesting that viral escape of T cell immunity is unlikely. CD4 immunodominant regions correlate with

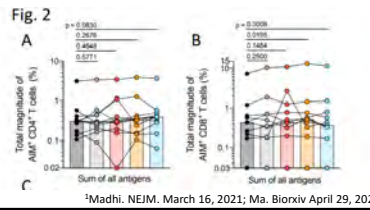
Broad T cell repertoire (100s of T cells across spike protein) after infection. Means viral escape of T cell-immunity (from both natural infection and vaccination) unlikely, re-infection if happens mild

Then look at T-cell response to variants after vaccines- still intact

bioRχiv

Negligible impact of SARS-CoV-2 variants on CD4+ and CD8+T cell reactivity in COVID-19 exposed donors and vaccinees.

Alison Tarke, John Sidney, Nils Methot, Yun Zhang, Jennifer M. Dan, Benjamin Goodwin, Paul Rubiro,



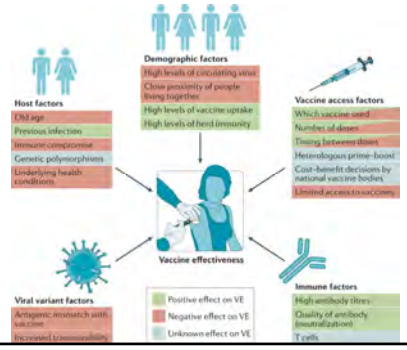
- Looked at SARS-CoV-2-specific CD4+ & CD8+ T cell responses from those with natural infection with non-variant & examined activity against alpha, beta, gamma variants
- T cell reactivity against those variants remained intact if you had natural infection or mRNA vaccination (Pfizer/Moderna)
- Same finding from UCSF paper- after vaccines, T cell response intact against alpha, beta variants

[1]Madhi. NEJM. March 16, 2021; Ma. Biorxiv April 29, 2021

Are vaccines waning in effectiveness with delta?

We need to first discuss B versus T cells!

Vaccine effectiveness – depends on many factors



Courtesy of Muge Cevik MD

Efficacy of mRNA vaccines against severe disease in settings where Delta variant is circulating, Sept 2021

Study Location (reference)	Vaccine	Effectiveness vs. severe disease or hospitalization	Lower limit of 95% CI	Upper limit of 95% CI
USA, Southern California KPSC (1)	BNT162b2 or mRNA-1273	93	84	96
USA, Minnesota (2)	BNT162b2	75	24	94
	mRNA-1273	81	33	96
USA, New York (3)	BNT162b2; mRNA-1273; Ad26.COV2.S	94.4	92.7	95.7
USA 13 jurisdictions (5)	BNT162b2; mRNA-1273; Ad26.COV2.S	90.4	87.7	92.5
USA, 7 locations VISION network (7)	BNT162b2	87	85	90
	mRNA-1273	91	83	93
USA, 9 States VISION network (8)	BNT162b2	80	73	85
	mRNA-1273	95	92	97
USA, 5 VA Medical Centers (9)	mRNA-1273	89	80	94
USA (14)	mRNA-1273	96	91	98
Israel, (4)	BNT162b2	88	94	91
Qatar (10)	BNT162b2	89.7	61	98.1
Qatar (11)	mRNA-1273	100	41.2	100
Singapore (12)	BNT162b2 or mRNA-1273	93	66	98
UK (13)	BNT162b2	96	86	99

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Morbidity and Mortality Weekly Report (*MMWR*)

SARS-CoV-2 Infections and Hospitalizations Among Persons Aged ≥16 Years, by Vaccination Status — Los Angeles County, California, May 1–July 25, 2021

You are 29.2 times more likely to get hospitalized if unvaccinated than vaccinated in time of delta

ARS: What is the protection against hospitalization from Moderna in the US (with delta)

1. 63%
2. 72%
3. 80%
4. 88%
5. 93%

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Morbidity and Mortality Weekly Report (*MMWR*)

Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021

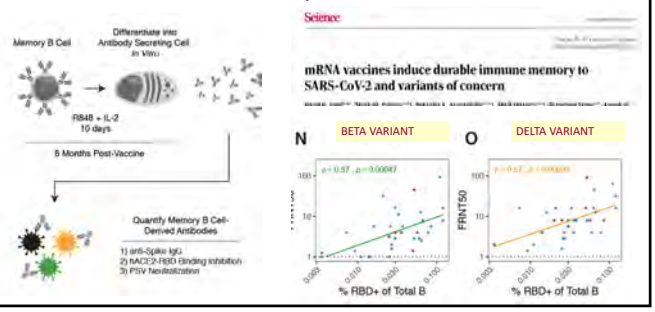
Protection against hospitalization with delta: 18 states

Moderna 93%

Pfizer 88%

Johnson and Johnson 71%

Memory B cells from vax or infection happily adapt to whatever variant they see

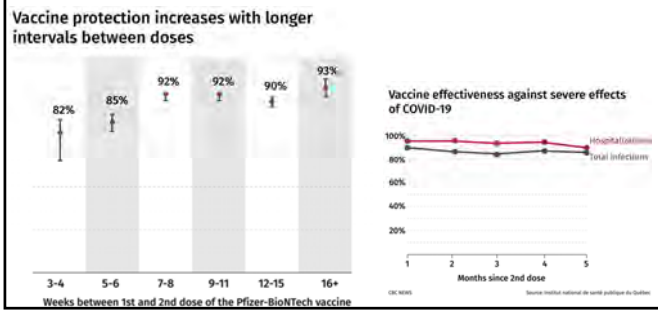


Why have we seen more symptomaticc breakthroughs with delta?

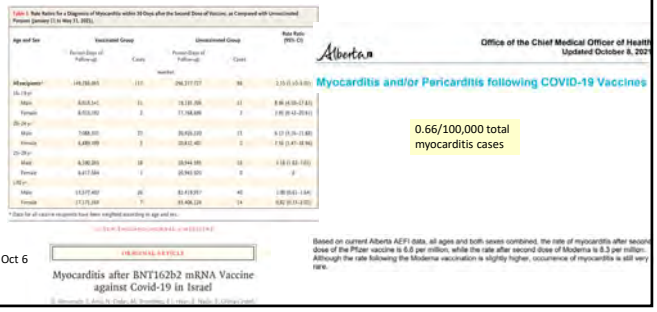
- Could be higher viral load
- **Think more likely waning antibodies with time** (protection in nose
- Increasing duration between doses leads to higher antibodies[1] (e.g. 8-12 weeks done in Canada and UK), less symptomatic breakthroughs in those two countries
- Less re-infection with Moderna than Pfizer[2] (Mayo Clinic study with delta) – Moderna given at 4 weeks, Pfizer at 3 weeks
- Luckily, waning antibodies NORMAL, not a GLITCH and are made anew by memory B cells – that is what they do

[1]https://www.nature.com/articles/d41586-021-01299;
[2]https://www.science.org/doi/10.1126/science.abm0829

Data from Canada shows Pfizer works better if extend interval to 7-8 weeks



Myocarditis (although mild/rare) more common with Pfizer q3 weeks (Israel) than longer intervals (usually 8)



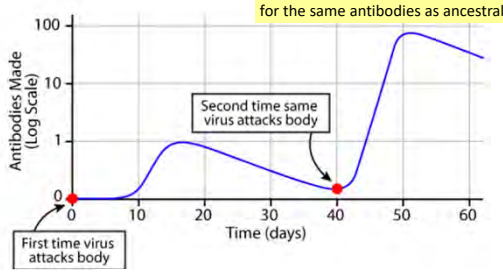
Oct 6

Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel

So, boosters for everyone or a tiered approach?

Antibodies come down naturally but memory B cells produce more if see virus again

Memory B cells ADAPT their antibodies they produce to cover variants; a booster will code for the same antibodies as ancestral strain



1https://www.science.org/doi/10.1126/science.abm0829

2https://www.medrxiv.org/content/10.1101/2021.05.28.21258025v1

Given J&J data from CDC, strong reason to boost J&J:
Meeting OCTOBER 15 FDA meeting

Boosters approved for

- **Immunocompromised**
- **>65 years**
- **18-64 with medical conditions**
- **Lots of exposure**

- Received an organ transplant and are taking medicine to suppress the immune system
- Received a stem cell transplant within the last 2 years or are taking medicine to suppress the immune system
- Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids or other drugs that may suppress your immune response

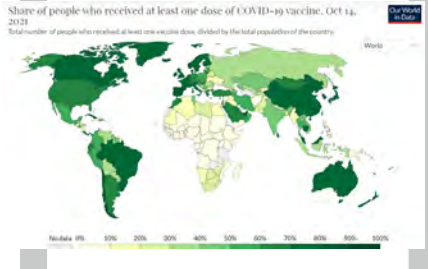
CDC

ARS: Of the 6.6 billion doses given out worldwide, what % have been administered in low-income countries?

1. 20%
2. 10.2%
3. 5.8%
4. 2.7%
5. 1.2%

6.6 billion doses administered worldwide

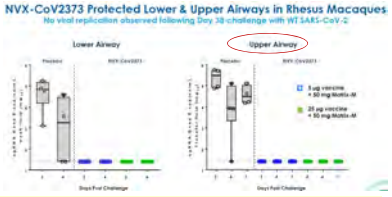
- **And should we give boosters to immuncompetent?**
- **Or focus on global vaccine equity instead!**



Do vaccines reduce transmission?

Yes, but with delta less so

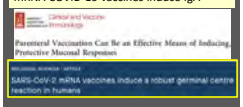
Will vaccines decrease transmission? Biological plausibility (4 main reasons)



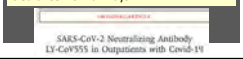
4. Challenge experiments with macaques in pre-clinical trials show blocking of viral replication (or no/low viral RNA) in BAL and nasal swabs (Mercado Nature J&J vax, 2020; Guebre-Xabier Vaccine Novavax 2020)

1. IgG antibodies measured in trials found in high levels in nasal mucosa

2. Systemic vaccines induce IgA (mucosal immunoglobulin) and recent study shows mRNA COVID-19 vaccines induce IgA



3. Monoclonal antibodies hasten viral clearance from airways



PRIOR TO THE DELTA VARIANT		
Setting	% reduction in asymptomatic infection or transmission	Reference
Healthcare workers in England	**85%**	Hall Lancet, **April 23, 2021**
Healthcare workers in Israel	**75% and 86%**	Amit, Lancet, **March 6**; Angel JAMA **May 6**
Patients in Mayo Clinic health system	**88.7%**	Pawlowski medRxiv, **February 27, 2021**
Israel Ministry of Health (nationwide)	**94% (largest study)**	**Pfizer** press release, **March 11, 2021 (and** Goldberg Medrxiv, **April 24, 2021)**
Israel general population (Pfizer)	**90%**	Dagan NEJM, **February 24, 2021**
Pre-surgical patients in Mayo Clinic system swabbed asymptomatically	**80%**	Tande Clin Inf Dis, **March 10, 2021**
Healthcare workers in Cambridge University Hospitals	**75%**	Weekes Authorea, **February 24, 2021**
First-line responders and HCWs in US	**90%**	Thompson A. MMWR, **March 30, 2021**
Israel population (>16) with children unvaccinated	**For every 20-point increase in adult vaccination, rates of kids testing positive halves**	Milman O. Medrxiv. **March 31, 2021**
Long-term care facility, Spain	**90%**	Salazar P. Medrxiv. **April 13, 2021**
Nursing homes, U.S. (two studies)	**100%**	Cavanaugh MMWR, **April 21 and** Terran MMWR, **April 30**

Nasal viral load values most important determinant of transmissibility (Lancet study, Spain); Viral loads from post-vaccination exposures are low and likely noninfectious per CT values (use rapid antigen tests after vaccination if test symptomatic or incorporate CT)

Health

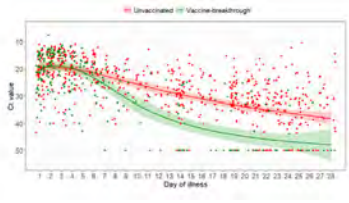
How Provincetown, Mass., stress-tested the coronavirus vaccine with summer partying and delta

Showed us that

1) Delta variant likely to transmit from symptomatic breakthroughs but less so – will explain (no evidence from asymptomatic)
2) lots of exposure, lots of mild breakthroughs "stress test' but vaccines held up to their promise- prevented severe disease!

Delta variant not as infectious in vaccinated as unvaccinated though

- More transmissible
- Likely not as infectious from vaccinated than unvaccinated (Provincetown outbreak data looked at one point in time of CT values of PCR tests in vaccinated & unvaccinated being same)
- Singapore study of delta breakthroughs **did serial testing** and found viral loads (by CT) drop more quickly among the vaccinated
- NPIs work against delta



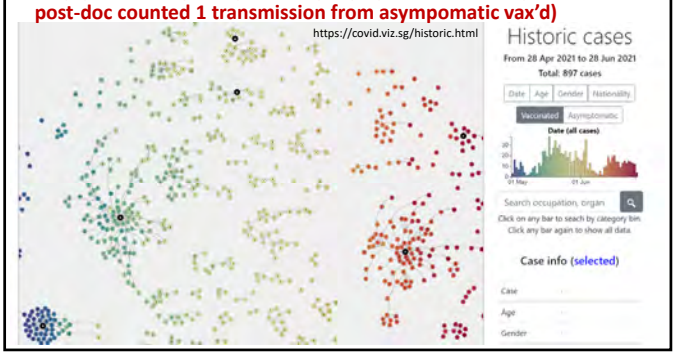
Delta variant outbreak in Singapore: https://www.medrxiv.org/content/10.1101/2021.07.28.21261295v1.full.pdf

Looked at culture data from delta breakthroughs in vaccinated HCWs

Less likely to be infectious by culture data

Bottom line: Vaccinated people can likely spread if symptomatic with delta, but less than unvaccinated

Singapore tracing study showing asymptomatic vax'd spread rare (our post-doc counted 1 transmission from asympomatic vax'd)

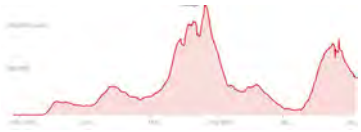


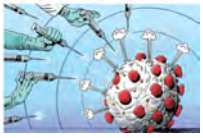
CDC breakthrough data

- CDC keeping track of breakthrough infections in U.S
- Out of >187 million Americans who are fully vaccinated against COVID-19
  - 13,775 hospitalized breakthroughs (0.01%) – 67% >65 years
  - Deaths 0.003% for COVID-19 (85% >65 years)

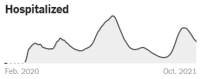
https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html

State of the pandemic



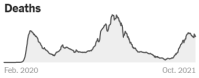


Hospitalized



Feb. 2020 Oct. 2021

Deaths



Feb. 2020 Oct. 2021

USA cases coming down but occurred fastest in states with high rates of vaccination

California Now Has Nation's Lowest Virus Transmission Rate

COVID-19 likely to be controlled not eradicated – so frequency of boosters will depend on if we tamp down transmission WORLDWIDE

- **Control:** Reduction of disease incidence to acceptable levels
- **Elimination**: Reduction to zero incidence in a defined geographical area
- **Eradication**: Permanent reduction to zero worldwide
- **Extinction:** Infectious agent no longer exists in nature or laboratories.

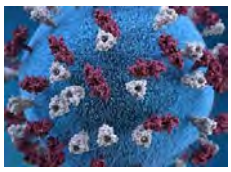
ARS: What are the only two infectious diseases that have been eradicated worldwide?

1. Polio and smallpox
2. Filariasis and smallpox
3. Rinderpest and smallpox
4. Measles and smallpox
5. Filariasis and polio

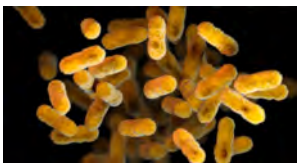
Features of eradicable infectious diseases – like smallpox

- No animal reservoir
- Clear pathogenic features
- Short period of infectiousness
- Immune for life and then highly effective vaccine

- (COVID-19 looks like other respiratory illnesses, can spread when presymptomatic, in animals, vaccine good)



Measles

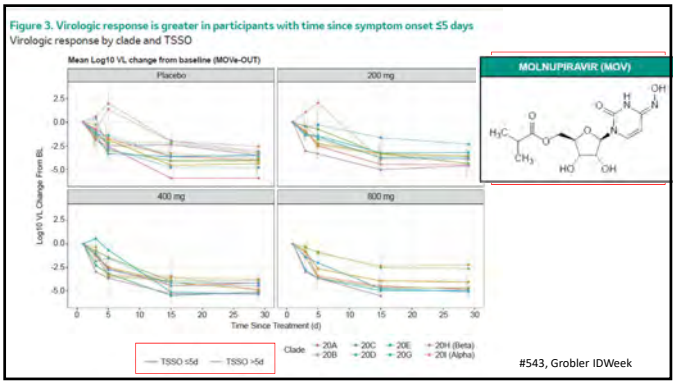


Pertussis

Comes under control/elimination with vaccines (measles) and vaccines/treatment (pertussis)

ARS: What is the only outpatient oral treatment for COVID-19 that looks like it works?

1. Hydroxychloroquine
2. Ivermectin
3. Molnupiravir
4. Monoclonal antibodies
5. AZT



#543, Grobler IDWeek

NEWS RELEASE

Merck and Ridgeback's Investigational Oral Antiviral Molnupiravir Reduced the Risk of Hospitalization or Death by Approximately 50 Percent Compared to Placebo for Patients with Mild or Moderate COVID-19 in Positive Interim Analysis of Phase 3 Study

10/1/2021

"MOVe-OUT"

- Outpatients with mild-moderate COVID (O2 sat ≥93%)
  - Symptom onset w/in 5 days
  - One or more risk factors for severe COVID (including age>60, obesity, diabetes, CAD)
  - 800mg BID x 5 days vs Placebo
- Interim analysis of 775 patients of planned n=1550
- Latin America (55%), Europe (23%), Africa (15%) in addition to US
- 14.1%-> 7.3% reduction in 1º endpoint of all-cause hospitalization/death
  - No deaths in MOV vs 8 deaths PCBO
- Adverse events: 35% vs 40%, Drug related 12% vs 11%, D/c due to AE 1.3% vs 3.4%
- Viral sequencing in 40%: similar efficacy in Delta, Gamma &Mu

PFIZER AND BIONTECH ANNOUNCE POSITIVE TOPLINE RESULTS FROM PIVOTAL TRIAL OF COVID-19 VACCINE IN CHILDREN 5 TO 11 YEARS

September 20, 2021

- Results are the first from a pivotal trial of any COVID-19 vaccine in children under 12 years of age
- In participants 5 to 11 years of age, the vaccine was safe, well tolerated and showed robust neutralizing antibody responses
- Companies plan to submit these data to the FDA, EMA and other regulatory agencies around the world as soon as possible
- Results in children under 5 years of age are expected as soon as later this year

Summary

- Vaccine trials show amazing efficacy and safety
- All vaccines reduce severe disease significantly, likely due to T-cell response
- Vaccines decrease transmission but more symptomatic and transmission with delta
- Variants can be managed - B cells
- Rare safety concerns – much more rare than COVID itself
- Molnupiravir, child vaccines coming – COVID getting under control

The state of the Covid-19 pandemic

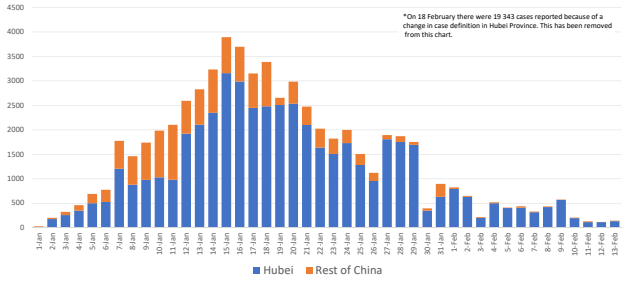
George W. Rutherford, M.D., A.M.
Professor of Epidemiology, Preventive Medicine, Pediatrics and History
Head, Division of Infectious Disease and Global Epidemiology
Department of Epidemiology and Biostatistics
School of Medicine
University of California, San Francisco

22 October 2021

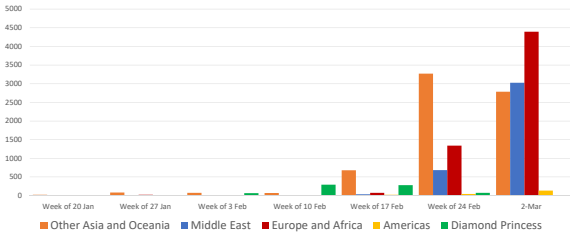
Where did we come from?

Excerpts from an early COVID lecture, 7 March 2020

COVID-19 by date of report, China, 18 February-5 March 2020



COVID-19 outside of China by region and week, 20 January to 6 March 2020



*To date, 6 March

How will this end?

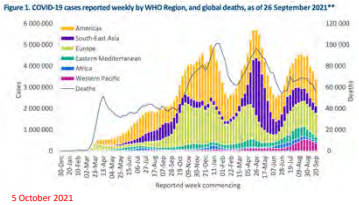
- Containment - increasingly unlikely
  - Keep large bulk of infection in China (currently 89%)
  - But large new clusters in Iran, Italy and South Korea with regional spread
  - New clusters of transmission will require aggressive follow up, isolation and quarantine
  - Spring weather may give us a break
  - Key: rapid response to suspected cases
  - Can Italy and the EU contain their outbreaks?
  - How much has it already spread in the U.S.?
- Pandemic spread
  - Spread outside of China and sustained person-to-person transmission in other countries
    - Iran, Italy and South Korea
    - U.S. (Washington state, California)
    - How the EU handles COVID-19 will be key
  - Attack rate somewhere between <1% and 20%
  - Potentially very taxing on healthcare system (5% with critical disease)
  - Endemic cause of viral pneumonia?
  - Summer Olympics in Tokyo – what will happen?

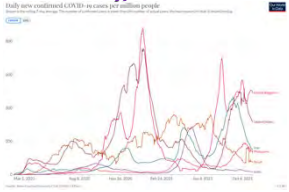
Where do we stand?

Worldwide, national, statewide and local epidemiology of COVID-19 and SARS-Co-2

COVID-19 cases world by day and country, 2020-2021

Worldwide:
234 809 103 total cases
+3 116 852 new cases last week (-8.62%)
4 800 375 total deaths
+54 170 last week (-3.89%)



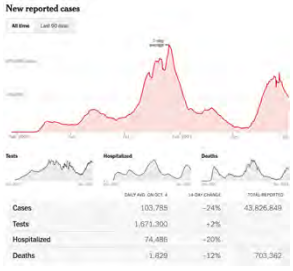


Cases in last week	
United States	644 530
The United Kingdom	236 450
Turkey	198 767
Russian Federation	169 168
India	155 916
Brazil	115 813
Philippines	102 541
Iran	90 608
Malaysia	79 330
Thailand	75 436

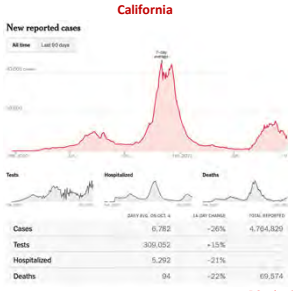
5 October 2021

COVID-19 cases and deaths are decreasing, United States and California, 2020-2021

United States



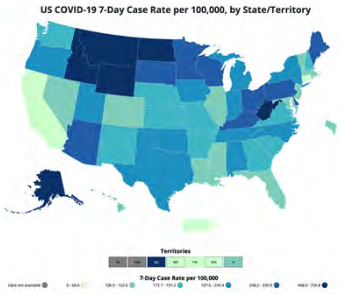
California



5 October 2021

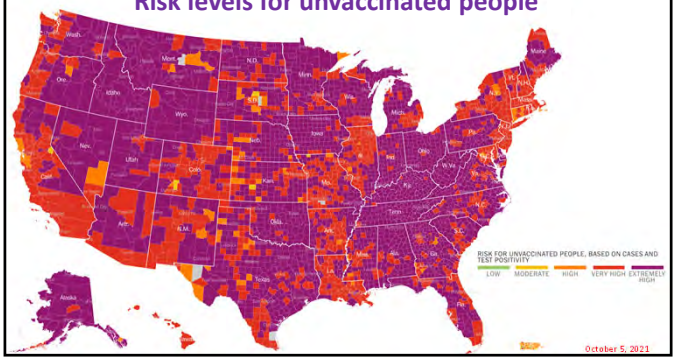
COVID-19 cases per 100,000 by state, last 7 days, United States, October 2021

	CASES DAILY AVG.	PER 100,000	14-DAY CHANGE	FULLY VACCINATED
United States	103,785	31	-24%	56%
Alaska ›	887	121	+7%	51%
Montana ›	886	83	-3%	49%
North Dakota ›	625	82	+33%	45%
Guam ›	133	79	-16%	68%
West Virginia ›	1,368	76	-25%	41%
Wyoming ›	435	75	-17%	42%
Idaho ›	1,300	73	+11%	42%
Kentucky ›	2,867	64	-32%	53%
Wisconsin ›	2,894	50	-7%	57%
Ohio ›	5,752	49	-16%	51%



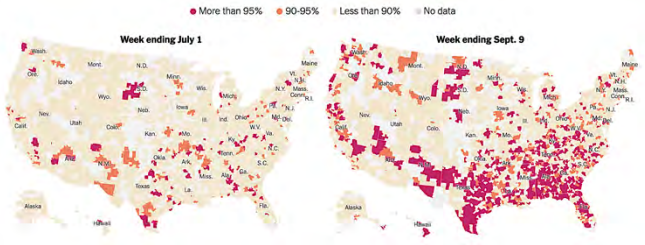
5 Oct 2021

Risk levels for unvaccinated people

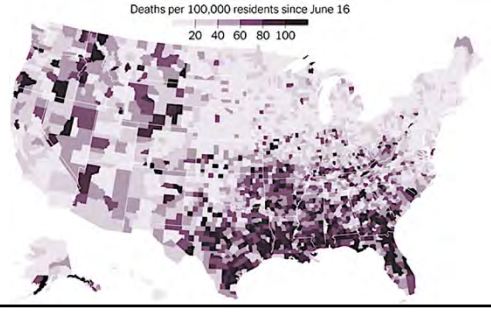


October 5, 2021

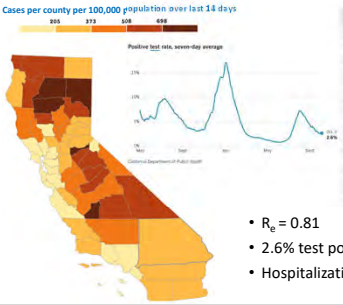
Hospital ICU utilization by catchment area, United States, July-September 2021



COVID-19 mortality rates by county, United States, June 16-October 1, 2021



Statewide indicators, SARS-CoV-2 infection, California, 2021



	CASES DAILY AVG.	PER 100,000	14-DAY CHANGE	FULLY VACCINATED
California	6,782	17	-26%	59%
Inyo ›	15	81	+70%	…
Mariposa ›	13	73	+19%	…
Trinity ›	9	72	+29%	…
Kings ›	106	69	-2%	37%
Lassen ›	21	69	-53%	31%
Tehama ›	42	65	-37%	34%
Amador ›	24	60	+33%	47%
Shasta ›	100	56	-41%	42%
Tulare ›	247	53	-22%	42%
Glenn ›	13	46	-39%	46%

- R_e = 0.81
- 2.6% test positivity
- Hospitalizations 5 292 (14-day change: -21%)

5 Oct 2021

San Francisco Bay Area

County	Total deaths	Total cases	New cases curve	Weekly change in new cases	Cases/ 10^5/ d*	R_e	%+	%FD
Santa Clara	1,872	143,324		▼160	7.5	0.9	1.1%	79.6%
Alameda	1,353	118,895		▼10	7.7	0.92	1.6%	76.5%
Contra Costa	953	98,276		▼67	10.3	0.91	2.3%	77.3%
San Mateo	589	53,452		▼137	6.6	0.84	1.1%	78.8%
San Francisco	641	53,450		▲1	8.4	0.85	1.8%	80.9%
Solano	328	45,350		▲68	11.9	0.92	2.6%	66.2%
Sonoma	383	40,295		▲6	8.4	0.93	2.1%	73.3%
Marin	242	17,467		▲2	5.5	0.97	1.9%	82.3%
Napa	96	12,649		▼2	12.6	0.93	2.8%	75.5%

583 158 total cases
+539 on 6 Oct

6 437 total deaths
+18 on 6 Oct

*Adjusted for testing rate, 7-day lag

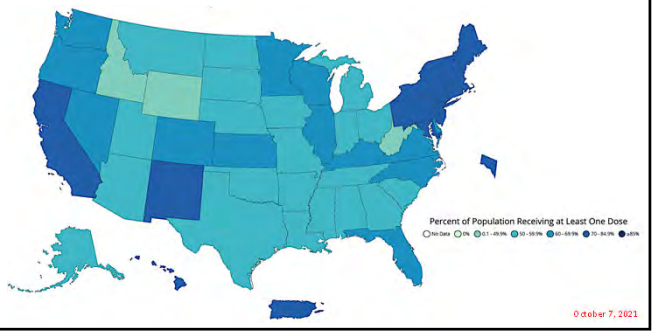
8 October 2021

Where are we going?

What can still go wrong?

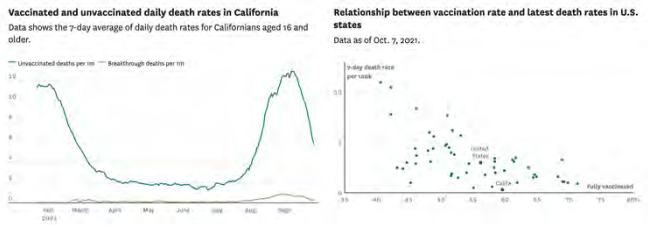
1. **Maldistribution of vaccine with substantial pockets of underimmunization that can sustain epidemic transmission**
2. Emergence of more transmissible and less immunologically susceptible variants
3. Loss of confidence in vaccines and more vaccine hesitancy
4. Underutilization of newer technologies
5. Ignoring international spread

Vaccination coverage is highly variable in the U.S.



October 7, 2021

COVID-19 death rates by vaccination status, California and United States, 2021



COVID-19 vaccine doses administered, California, 2021

Currently vaccinating
- All Californians ≥12 years old
- Those requiring third doses and booster doses

- 49 028 206 doses administered
- 91 276 average per day for the last 7 days
- 67% of Californians have received ≥1 dose
- 60.4% have been fully vaccinated
- San Francisco: 80.8% with ≥1 dose, 75.9% fully vaccinated

Share of completed vaccinations by Pfizer, Moderna or Johnson & Johnson

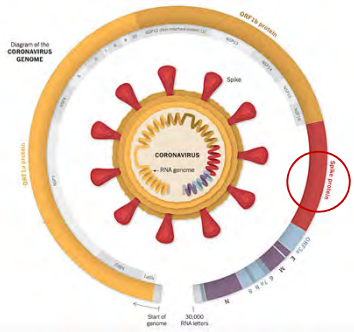
County	Doses administered	At least 1 dose	▾ Fully vaccinated
Marin »	414,666	82.2%	77.0%
San Francisco »	1,341,484	80.8%	75.9%
Santa Clara »	2,920,059	79.5%	75.0%
San Mateo »	1,147,936	78.6%	73.1%
Contra Costa »	1,679,530	77.1%	72.4%
Alameda »	2,362,779	76.3%	71.3%
Imperial »	260,880	63.3%	69.0%
Napa »	199,196	75.3%	67.3%
Sonoma »	698,373	73.2%	67.2%
Santa Cruz »	372,615	71.1%	65.8%

5 Oct 2021

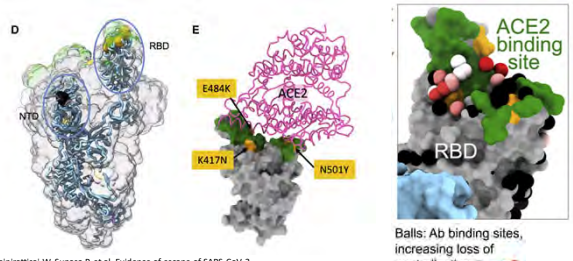
1. Maldistribution of vaccine with substantial pockets of underimmunization that can sustain epidemic transmission
2. **Emergence of more transmissible and less immunologically susceptible variants**
3. Loss of confidence in vaccines and more vaccine hesitancy
4. Underutilization of newer technologies
5. Ignoring international spread

What is a variant?

- A group of coronaviruses that share the same inherited set of distinctive mutations is called a **variant.** If enough mutations accumulate in a lineage, the viruses may evolve clear-cut differences in how they function.
- SARS-CoV-2 variants of public health interest are in the spike protein (1,273 amino acids long)



Key mutations present in variatns with reduced neutralization are around edge of ACE2 binding site



Balls: Ab binding sites, increasing loss of neutralization

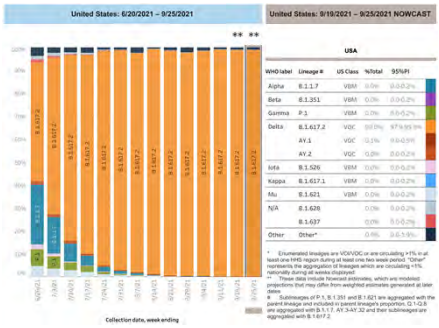
Zhou D, Dejnirattisai W, Supasa P, et al. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. Cell 2021; 189:2348-61.

SARS-CoV-2 variants of concern, United States and California, 2021

Region including:
California, Arizona, Hawaii, Nevada and all territories

B.1.617.2 (δ)	98.9%
Delta Plus (δ+)	0.6%
AY.2	0.2%
AY.1	0.4%
B.1.1.7 (α)	0.0%
P.1 (γ)	0.0%
B.1.621	0.0%
Other	0.5%

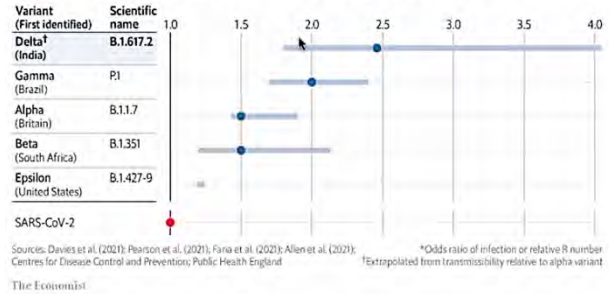
9/19/2021-9/25/2021 NOWCAST



5 Oct 2021

Rate of change

Covid-19, estimated transmissibility* of variants compared with original SARS-CoV-2 virus



Sources: Davies et al. (2021); Pearson et al. (2021); Faria et al. (2021); Allen et al. (2021); Centres for Disease Control and Prevention; Public Health England

*Odds ratio of infection or relative R number
†Extrapolated from transmissibility relative to alpha variant

The Economist

Considerations for future variant emergence

- Lower transmission = less viral replication = fewer opportunities for variants to emerge
- But, as more people are vaccinated, there will be more immune pressure and possible escape
- However, the delta variant seems to be outcompeting other variants suggesting that our worst problem is before us right now
  - And the current vaccines work pretty well against delta
- We have redundant immune systems and both cellular (T-cell) and humoral (B-cell, antibodies) immune systems
- Herd immunity is a moving target (waning immunity vs. boosters)
  - Lower transmission
  - Immunocompromised individuals will be protected by the herd

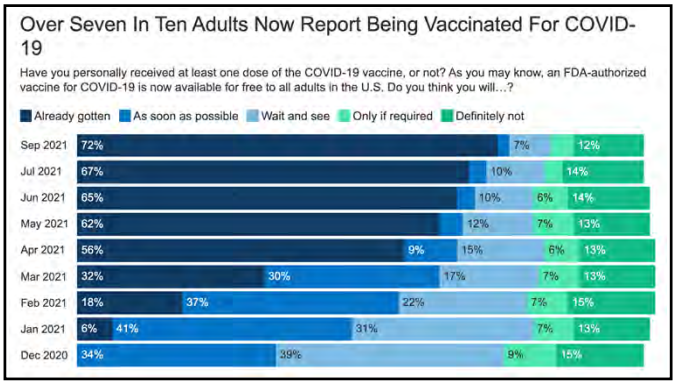
Table 2. Vaccine Effectiveness against the Alpha Variant or *S* Target–Negative Status and the Delta Variant or *S* Target–Positive Status, According to Dose and Vaccine Type.*

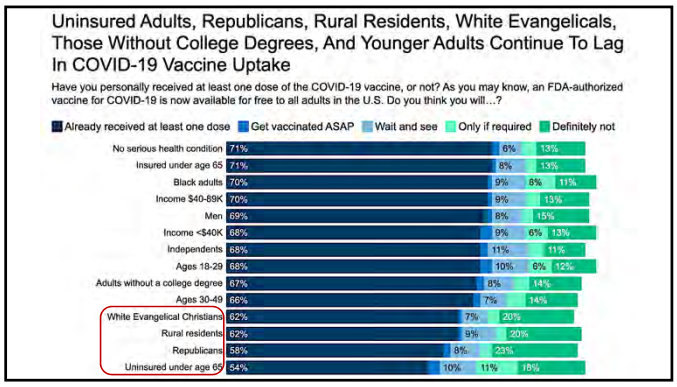
Vaccination Status	Test-Negative Status		Alpha Variant or *S* Target–Negative Status			Delta Variant or *S* Target–Positive Status		
	Controls	Cases	Case:Control Ratio	Adjusted Vaccine Effectiveness (95% CI)	Cases	Case:Control Ratio	Adjusted Vaccine Effectiveness (95% CI)
	no.	no.		%	no.		%
Unvaccinated	96,371	7313	0.076	Reference	4043	0.042	Reference
Any vaccine							
Dose 1	51,470	2226	0.043	48.7 (45.5–51.7)	1493	0.029	30.7 (25.2–35.7)
Dose 2	23,993	143	0.006	87.5 (85.1–89.5)	340	0.014	79.6 (76.7–82.1)
BNT162b2 vaccine							
Dose 1	8,641	450	0.052	47.5 (41.6–52.8)	137	0.016	35.6 (22.7–46.4)
Dose 2	15,749	49	0.003	93.7 (91.6–95.3)	122	0.008	88.0 (85.3–90.1)
ChAdOx1 nCoV-19 vaccine							
Dose 1	42,829	1776	0.041	48.7 (45.2–51.9)	1356	0.032	30.0 (24.3–35.3)
Dose 2	8,244	94	0.011	74.5 (68.4–79.4)	218	0.026	67.0 (61.3–71.8)

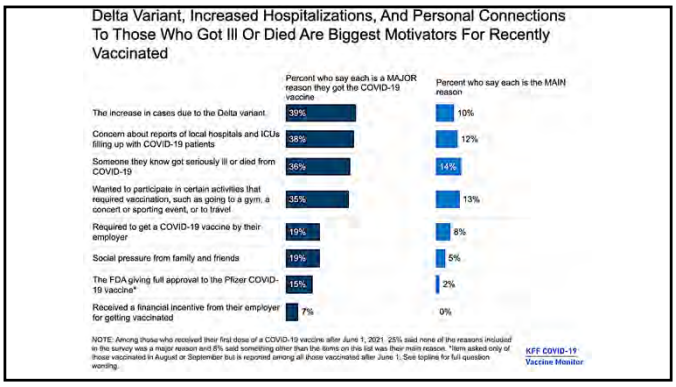
* The adjusted analysis of vaccine effectiveness was adjusted for period (calendar week), travel history, race or ethnic group, sex, age, index of multiple deprivation, clinically extremely vulnerable group, region, history of positive test, health or social care worker, and care home residence. CI denotes confidence interval.

Bernal JL, Andrews N, Gower C, et al. Effectiveness of Vocid-19 vaccines against the B.1.617.2 (delta) variant. N Engl J Med 2021; Jul 21 [Epub ahead of print].

1. Maldistribution of vaccine with substantial pockets of underimmunization that can sustain epidemic transmission
2. Emergence of more transmissible and less immunologically susceptible variants
3. **Loss of confidence in vaccines and more vaccine hesitancy**
4. Underutilization of newer technologies
5. Ignoring international spread







Reasons for vaccine failure

- Mishandling
- Immunocompromise
- Therapeutics (e.g., tocilizumab)
- Genetic drift – variants
- Waning immunity

Failure to vaccinate (or to seek vaccination)

Vaccine effectiveness by time since vaccination, United States, 2021

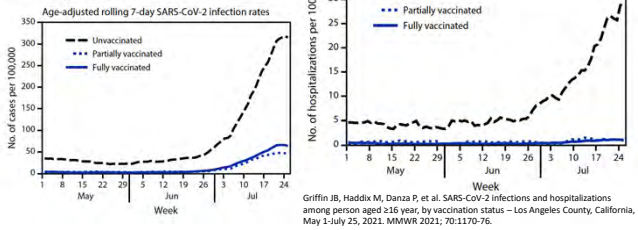
TABLE 2. COVID-19 vaccine effectiveness* against COVID-19–associated hospitalization among adults without immunocompromising conditions, by vaccine product — 21 hospitals in 18 U.S. states,† March–August 2021

Vaccine/Period	Vaccinated patients/Total patients (%) Case-patients	Control-patients	VE against COVID-19 hospitalization (95% CI)
Moderna VE after full vaccination			
Full surveillance period§	54/1,517 (3.6)	422/1,321 (31.9)	93 (91–95)
14–120 days after full vaccination	36/1,499 (2.4)	345/1,244 (27.7)	93 (90–95)
>120 days after full vaccination	18/1,481 (1.2)	77/976 (7.9)	92 (87–96)
Pfizer-BioNTech VE after full vaccination			
Full surveillance period	128/1,591 (8.0)	610/1,509 (40.4)	88 (85–91)
14–120 days after full vaccination	65/1,528 (4.3)	495/1,394 (35.5)	91 (88–93)
>120 days after full vaccination	63/1,526 (4.1)	115/1,014 (11.3)	77 (67–84)
Janssen (Johnson & Johnson) VE after full vaccination			
Full surveillance period	37/1,500 (2.5)	76/975 (7.8)	71 (56–81)
>28 days after full vaccination	33/1,496 (2.2)	59/958 (6.2)	68 (49–80)

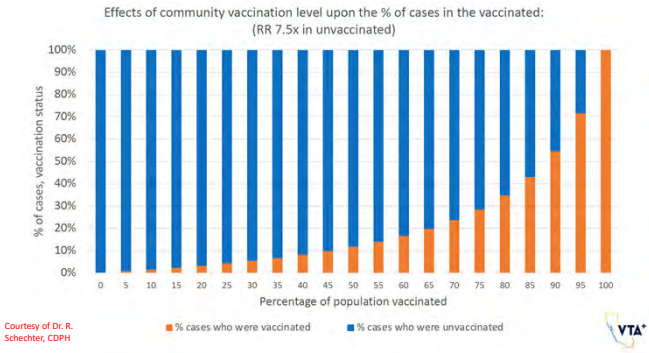
Self WH, Tenforde MW, Rhoads JP, et al. Comparative effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) vaccines in preventing COVID-19 hospitalizations among adults without immunocompromising conditions – United States, March-August 2021. MMWR 2021 Sep 17 [Early release].

COVID-19 cases by vaccination status, Los Angeles County, May-July, 2021

FIGURE 1. Age-adjusted rolling 7-day SARS-CoV-2 infection and hospitalization rates,* by vaccination status† — Los Angeles County, California, May 1–July 25, 2021



Griffin JB, Haddix M, Danza P, et al. SARS-CoV-2 infections and hospitalizations among person aged ≥16 year, by vaccination status – Los Angeles County, California, May 1-July 25, 2021. MMWR 2021; 70:1170-76.



Courtesy of Dr. R. Schechter, CDPH

FDA and CDC recommend booster dose for certain Pfizer-BioNTech vaccine recipients

- Newest recommendations
  - All adults ≥65 years old
  - Residents of long-term care facilities
  - People with underlying medical conditions that place them at risk of severe COVID-19
    - 50-64 years olds can self refer
    - 18-49 years olds need to be assessed individually
  - Persons whose occupations but them at risk of exposure
    - Healthcare workers
    - Certain frontline institutional workers
- Moderna and J&J boosters will be considered on October 14-15

Alisha Jucevic for The New York Times

Who's eligible for Pfizer-BioNTech booster?

- People with certain medical conditions that place them at higher risk of severe COVID-19 outcomes (50-64 years old should, 18-49 may)
  - Cancer
  - *Chronic kidney disease**
  - Chronic lung diseases
  - Dementia or other neurologic conditions
  - Diabetes mellitus
  - Down syndrome
  - Heart conditions
  - HIV infection
  - *Immunocompromised state**
  - Liver disease
  - Overweight and obesity
  - Pregnancy and recent postpartum
  - Sickle cell disease or thalassemia
  - Smoking, current or former
  - *Solid organ or blood stem cell transplant**
  - Stroke or cerebrovascular disease
  - Substance use disorders
- People aged 18–64 years at increased risk for COVID-19 exposure and transmission because of occupational or institutional setting
  - First responders (healthcare workers, firefighters, police, congregate care staff)
  - Education staff (teachers, support staff, daycare workers)
  - Food and agriculture workers
  - Manufacturing workers
  - Corrections workers
  - U.S. Postal Service workers
  - Public transit workers
  - Grocery store workers

*Should receive additional dose regardless of age or primary series

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html

Status of pediatric COVID-19 vaccines


'IT'LL MAKE US ALL A LITTLE BIT SAFER'

Vaccine for younger kids could come soon

- Pfizer announced results today
- Study of >2,000 5-11 year olds
- Comparable neutralizing antibody levels as in previous study of 16-25 year olds (proxy marker)
- Common side effects: pain, fatigue, headaches, chills, mild fever, myalgia for 1-3 days; no cases of myocarditis
- Now goes to FDA for approval of extended EUA (October 26)

San Jose Mercury News, September 21, 2021

1. Maldistribution of vaccine with substantial pockets of underimmunization that can sustain epidemic transmission
2. Emergence of more transmissible and less immunologically susceptible variants
3. Loss of confidence in vaccines and more vaccine hesitancy
4. **Underutilization of newer technologies**
5. Ignoring international spread

SARS-CoV-2 antigen tests

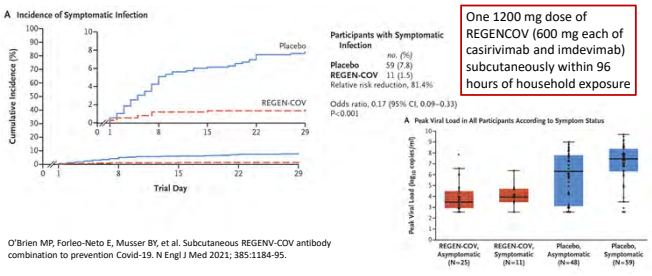
- Test for the presence of viral proteins rather than viral RNA (which is what PCR tests for)
- Lower sensitivity than PCR but highly sensitive during period of peak infectiousness
- Several are available over the counter or by prescription for home use
- Additionally, two nucleic acid tests have been authorized for home use

FDA-Authorized SARS-CoV-2 antigen tests for home use

Name	Manu-factuer	How to use	Retail price
BinaxNOW	Abbott	2-3X with 24-36 hours between tests	$14-24 fpr two
Flowflex	ACON	One time	$23 for one test
Ellume	Ellume	One test	$26-39 for one
QuickVue	Quidel	2X with 24-36 hours between tests	$24-25 for two

Other authorized home tests: Becton Dickinson (BD Veritor), Access Bio (CareSAtart), OraSure (inteliSwab)

Post-exposure prophylaxis with REGEN-COV antibody, household contacts of COVID-19 patients



One 1200 mg dose of REGENCOV (600 mg each of casirivimab and imdevimab) subcutaneously within 96 hours of household exposure

O'Brien MP, Forleo-Neto E, Musser BY, et al. Subcutaneous REGENV-COV antibody combination to prevention Covid-19. N Engl J Med 2021; 385:1184-95.

1. Maldistribution of vaccine with substantial pockets of underimmunization that can sustain epidemic transmission
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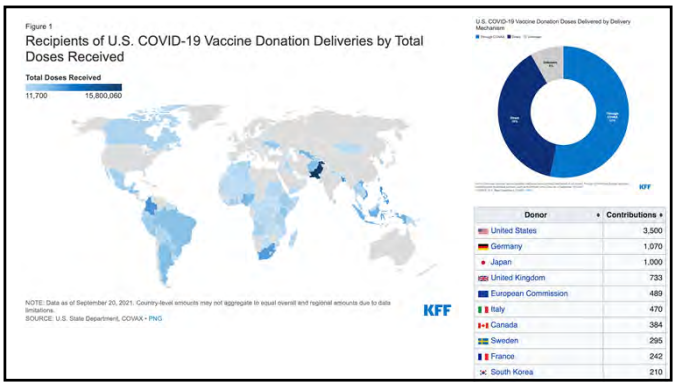


U.S. will support compulsory licensing of of COVID vaccines

- Waiver of intellectual property for public health emergencies
- WTO allows under TRIPS
- Countries who apply for waiver can manufacture their own vaccines or biologics without IP infringement

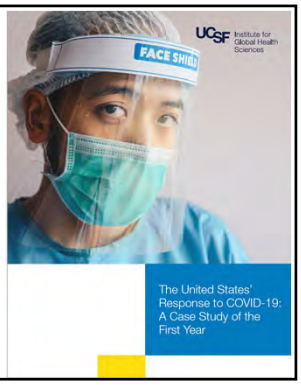

Los Angeles Times
latimes.com
U.S. will support vaccine patent waiver
By Emily Baumgaertner
A KEY STEP FOR GLOBAL VACCINE ACCESS

What have we learned?

What could we have done differently and how do we respond next time?

Lessons learned for future pandemics

- Early warning systems are key with focus on human-animal interfaces (OneHealth approach)
- Internationalism is essential
- Employ private sector solutions for manufacturing and distributing early prototype diagnostic and screening tests
- Strengthen domestic and global health architecture for pandemic preparedness and response
- Invest in public health and rebuild public health infrastructure



In summary

- As with any vaccine preventable disease, primary reason for incident cases is *failure to vaccinate*
  - Counties with highest incidence have lowest immunity (natural plus vaccine-acquired immunity)
  - Breakthroughs remain rare (about 1/3600 fully vaccinated people)
- We seem to be coping with the delta variant (at least in California)
- Likely to continue to see outbreaks in non-immune populations through fall – will we see another winter peak like in 2020-2021?
- What eventually happens in school children will depend on (1) community levels of transmission, (2) 12-to-17-year-old vaccination coverage (currently very high) and (3) how soon mRNA vaccine will be approved for 5-to-11-year-old students (FDA will review on 26 October)
- Potential for influenza A and RSV syndemics

NOTES

High Yield Neurological Examination

Vanja Douglas, MD
Sara & Evan Williams Foundation Endowed Neurohospitalist Chair
Director, Neurohospitalist Division
Associate Professor of Clinical Neurology
UCSF Department of Neurology

Disclosures

None

Purpose of Neuro Exam

- Screen asymptomatic patients
- Screen patients with symptoms that could indicate a focal neurologic lesion (e.g. back pain, headache, seizure)
- Localize the lesion in patients with neurologic deficits
  - Generate a differential diagnosis
  - Decide what test to get next (e.g. brain MRI, spine MRI, EMG/NCS, CK)

Typical "Screening" Neuro Exam

- Mental Status: Level of alertness, orientation, attention, language, memory
- Cranial Nerves: II through XII
- Motor: Bulk, tone, power in all muscles in both arms and legs
- Sensory: Light touch, vibration/joint position sense, pain/temperature, Romberg
- Reflexes: Biceps, triceps, brachioradialis, knees, ankles, plantar response
- Coordination: Finger-nose-finger, heel-knee-shin
- Gait: Observe gait, include tandem, heel, and toe walking

High Yield Screening Neuro Exam

- Mental Status
- Cranial Nerves
- Motor
- Sensory
- Coordination
- Reflexes
- Gait

Language

Expressive Aphasia	
Fluency	Impaired
Comprehension	Intact
Repetition	Impaired

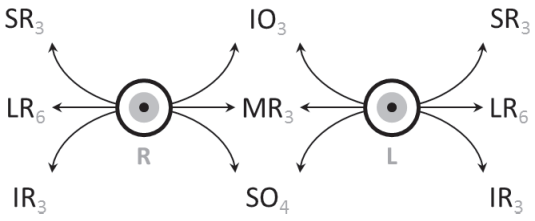
Receptive Aphasia	
Fluency	Intact
Comprehension	Impaired
Repetition	Impaired

Conduction Aphasia	
Fluency	Intact
Comprehension	Intact
Repetition	Impaired

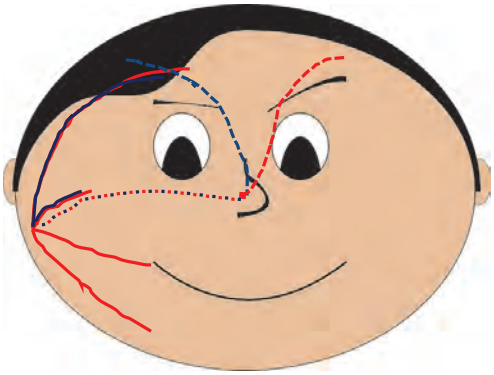
High Yield Screening Neuro Exam

- Mental Status: language, orientation, and attention
- Cranial Nerves
- Motor
- Sensory
- Coordination
- Reflexes
- Gait

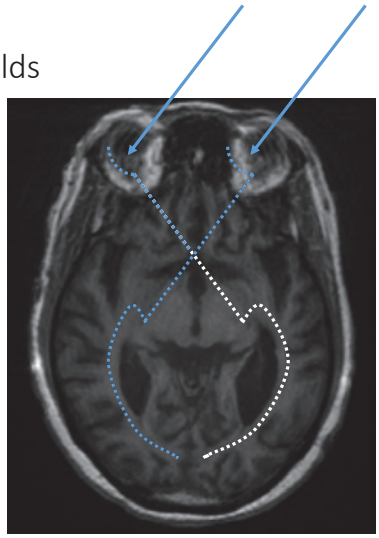
Extraocular Movements



Facial Symmetry



Visual Fields



High Yield Screening Neuro Exam

- Mental Status: language, orientation, and attention
- Cranial Nerves: visual fields, eye movements, and facial symmetry
- Motor
- Sensory
- Coordination
- Reflexes
- Gait

Motor System

2 minute screen for upper motor neuron weakness:

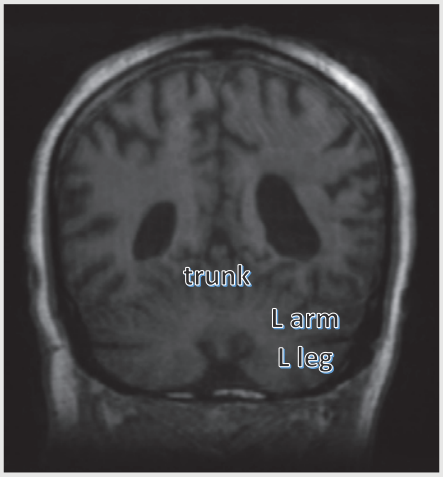
- Pronator Drift
- Finger taps & Foot taps
- Distal extensor power:
  - Finger extensors
  - Tibialis anterior

High Yield Screening Neuro Exam

- Mental Status: language, orientation, and attention
- Cranial Nerves: visual fields, eye movements, and facial symmetry
- Motor: Pronator drift, finger and foot taps, finger extensor and extensor hallucis longus power
- Sensory
- Coordination
- Reflexes: Biceps, knees, and ankles
- Gait

Coordination & Gait

- Hemispheres:
  - Finger-nose-finger
  - Heel-knee-shin
- Vermis:
  - Gait



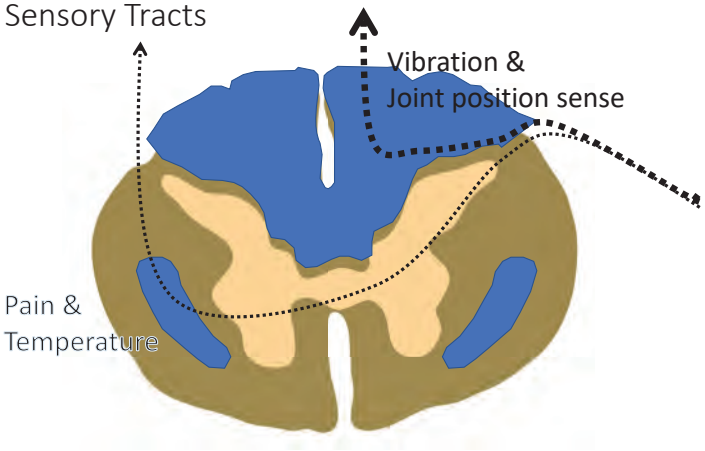
High Yield Screening Neuro Exam

- Mental Status: language, orientation, and attention
- Cranial Nerves: visual fields, eye movements, and facial symmetry
- Motor: Pronator drift, finger and foot taps, finger extensor and extensor hallucis longus power
- Sensory
- Coordination: Finger-nose-finger and heel-knee-shin (can replace HKS with gait)
- Reflexes: Biceps, knees, and ankles
- Gait: Observe gait (base, stride, posture, arm swing, turn), tandem

Why Do A Sensory Exam?

- If there are sensory complaints
- If there are balance complaints or a gait disorder
- If there is weakness

Sensory Tracts



High Yield Screening Neuro Exam

- Mental Status: language, orientation, and attention
- Cranial Nerves: visual fields, eye movements, and facial symmetry
- Motor: Pronator drift, finger and foot taps, finger extensor and extensor hallucis longus power
- Sensory: (If done, do pain OR temp + vibration OR JPS)
- Coordination: Finger-nose-finger and heel-knee-shin (can replace HKS with gait)
- Reflexes: Biceps, knees, and ankles
- Gait: Observe gait (base, stride, posture, arm swing, turn), tandem

Think Like A Neurologist

- Chief Complaint: suspected localization
- History: refine the localization
- Exam: pick maneuvers that rule in or rule out your suspicions

Let's practice!

Case Scenarios

Patient #1

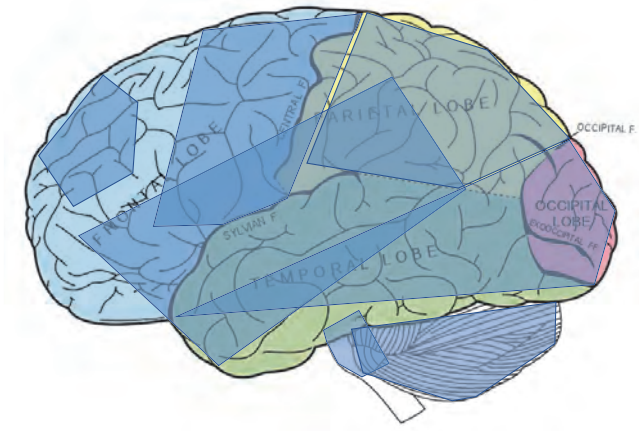
- A 23 y/o woman with a history of migraine headaches is admitted to the hospital with left leg cellulitis. On hospital day 2, she complains of a new headache. She says it's different from her previous migraines because it is "much worse" and is wondering if she needs an MRI.

Headache

Suspected localization

- Focal brain lesion

Hypothesis-Driven Neuro Exam



Patient #2

- 57 y/o man hospitalized with MI is altered after his cardiac cath. He is somnolent but arousable, mumbling incoherently. His family is very concerned that he has had a stroke.

Altered Mental Status

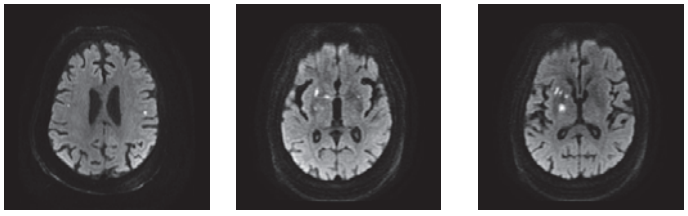
Suspected localization

- Bilateral hemispheres
- Brainstem

Patient #2 Exam

- Arouses to touch
- Names simple objects, repeats short phrases, follows simple commands
- Disoriented and unable to test attention
- EOMI; face symmetric; blinks to threat bilaterally
- Left arm drifts and hand is clumsy
- Withdraws less briskly to pain in the left leg
- Head CT is normal

Multifocal Strokes



Patient #3

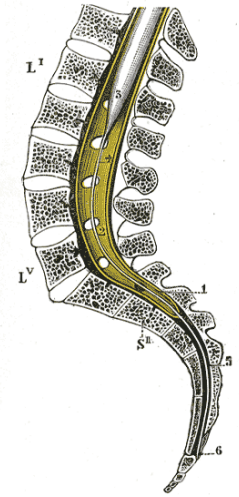
- A 65 y/o man with prostate cancer presents with bilateral leg weakness and urinary urgency.

Bilateral Leg Weakness

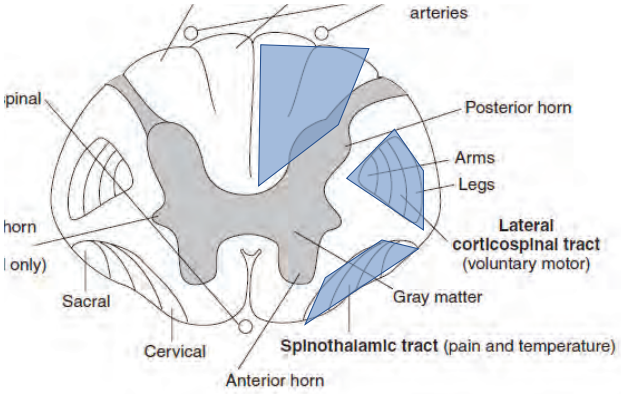
Suspected localization

- Spinal cord
- Cauda equina
- Neuropathy
- Neuromuscular junction
- Muscle

	UMN	LMN
Pattern of Weakness	Pyramidal	Variable
Function/Dexterity	Slow alternate motion rate	Impairment of function is mostly due to weakness
Tone	Increased	Decreased
Tendon Reflex	Increased	Decreased, absent or normal
Other signs	Babinski sign, other CNS signs (e.g. aphasia, visual field cut)	Atrophy (except with problem of neuromuscular junction)



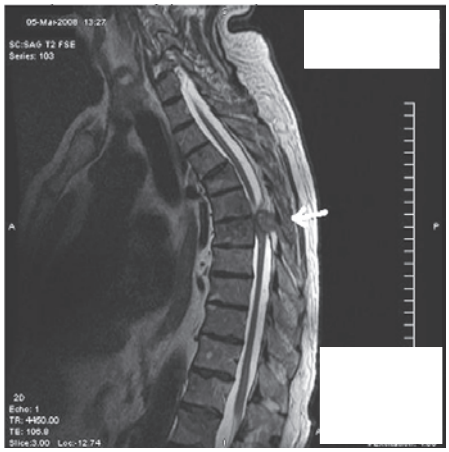
Spinal Cord Cross-Section



Patient #3: Exam

- Decreased EHL power bilaterally
- Slow foot taps
- Brisk knee jerk and ankle jerk reflexes
- Reduced joint position sense in toes
- Sensory level to pinprick at T5

Metastastic Spinal Cord Compression



Patient #4

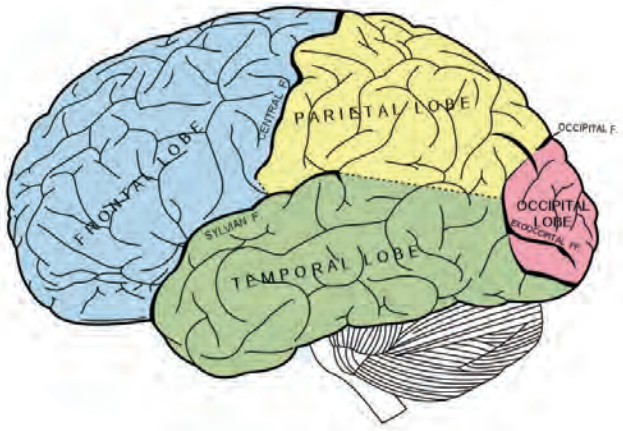
- A 30 y/o woman with lupus, APLAS, and history of endocarditis on gentamycin presents with acute vertigo.

Vertigo

Suspected localization

- Brainstem (central)
- Cerebellum (central)
- Inner ear (peripheral)

Hypothesis-Driven Neuro Exam



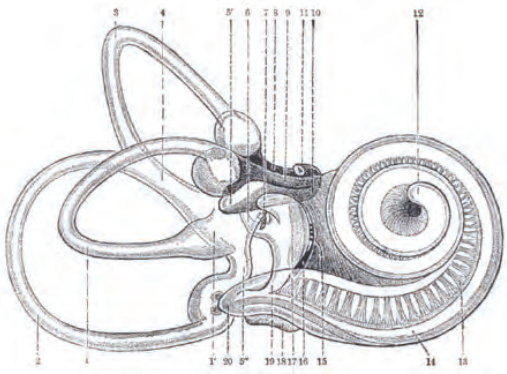
HINTS

- Head Impulse Test
  - Abnormal = peripheral
- Nystagmus
  - Unidirectional = peripheral
  - Direction-changing = central
- Test of Skew
  - Skew deviation = central
- https://youtu.be/1q-VTKPweuk

Patient #4: Exam

- Left beating nystagmus in left-gaze only
- Positive head thrust test to the right

Gentamycin Toxicity



Summary

- High yield screening exam
- Hypothesis driven approach to:
  - Suspected focal brain lesion
  - Altered mental status
  - Suspected spinal cord lesion
  - Vertigo

Bonus Case

- A 32 y/o woman presents with tingling in the hands and feet that progressed to diffuse weakness in the arms and legs over four days. She is now so weak she can no longer sit up.

Diffuse Weakness

Suspected localization

- High spinal cord
- Neuropathy
- Neuromuscular junction
- Myopathy

Localization of Weakness

	Pattern of weakness	**Tone**	**Bulk**	**Reflexes**	**Sensory Loss**	**Other**
Upper Motor Neuron	Pyramidal	Spastic	Normal	Increased	Varies	
Anterior Horn Cell	Pyramidal or myotomal	Spastic or normal	Atrophy	Increased or decreased	None	Fascic-ulations
Peripheral Nerve	In distribution of root or nerve	Normal or reduced	Atrophy	Decreased	Prominent	
Neuro-muscular Junction	Diffuse	Normal	Normal	Normal (myasthenia) or Absent (botulism)	None	Ptosis and ophthalmo -paresis
Muscle	Proximal > Distal	Normal	Normal or patterned atrophy	Normal	None	

Bonus Case

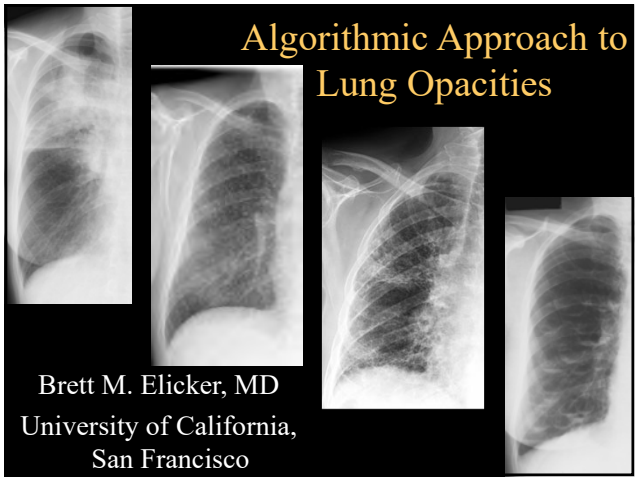
- Diffuse weakness throughout both arms and legs in both flexors and extensors
- No sensory level
- Decreased pinprick sensation in the feet
- Diffusely absent reflexes

Next Step?

- Lumbar puncture:
  - Protein 143
  - WBC 2
- Guillain-Barre Syndrome

Acknowledgements

- Hooman Kamel
- Andy Josephson
- Dan Lowenstein
- Ann Poncelet
- Kamel et al, A randomized trial of hypothesis-driven vs screening neurologic examination. Neurology Oct 2011, 77(14) 1395-1401.

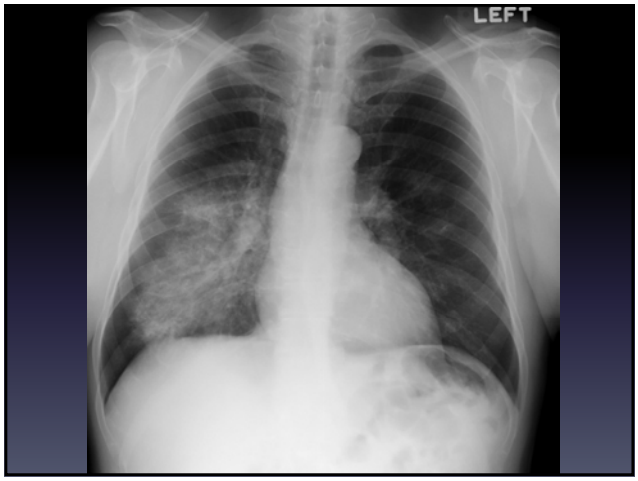


Algorithmic Approach to Lung Opacities

Brett M. Elicker, MD
University of California, San Francisco

Approach to lung opacities

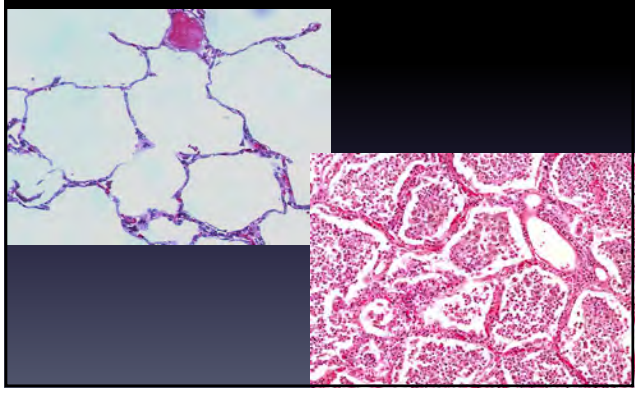
- This is hard!
- You will not be an expert today
- Approach
- Practice
- Think like a pathologist



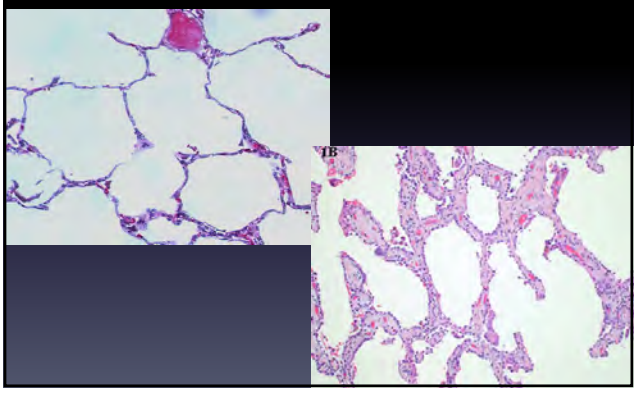
Categories of lung opacities

- 1. Consolidation
- 2. Interstitial (diffuse lines or nodules)
- 3. Airways
- 4. One or a few nodules

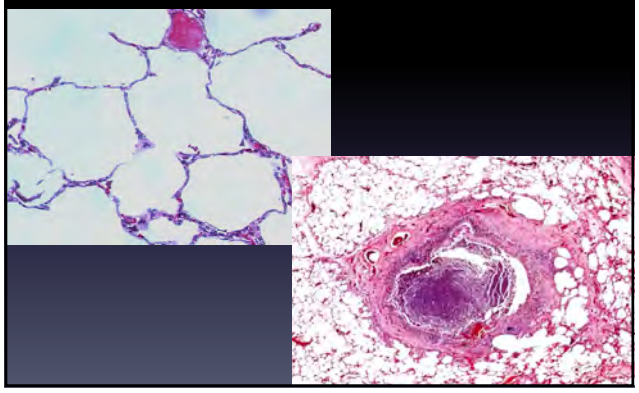
Alveolar



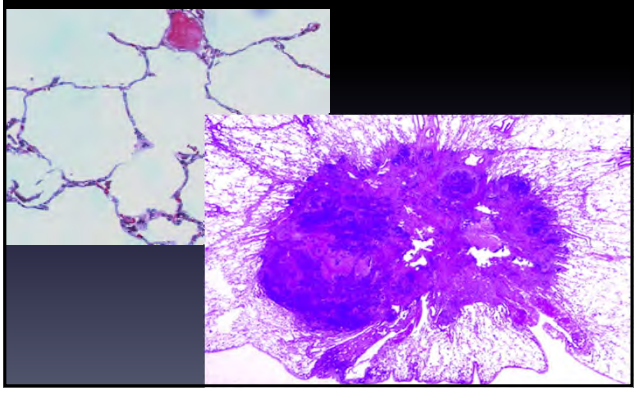
Interstitial



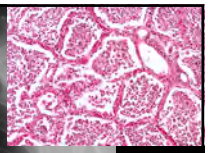
Airways



Not applicable

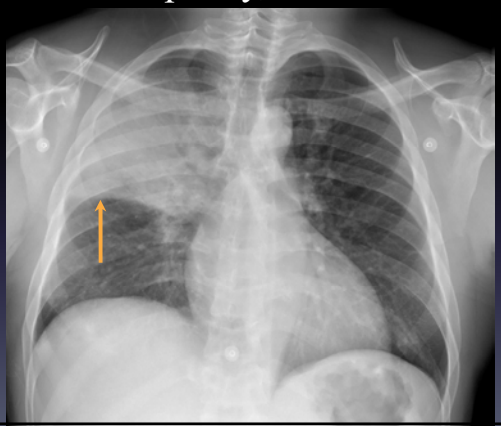


Consolidation

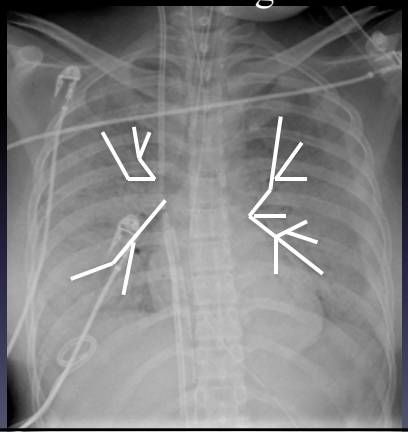


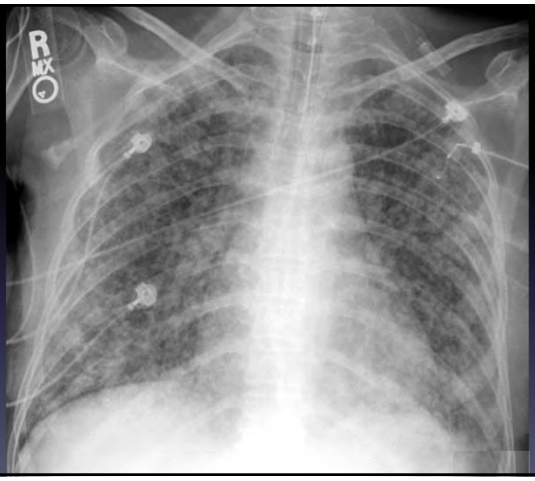
- Confluent opacity
- Fluffy around periphery
- Air bronchograms
- Lack of volume loss

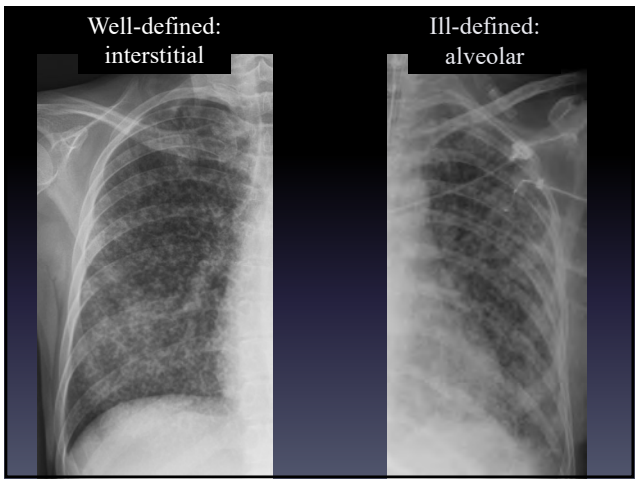
Confluent opacity, no volume loss



Air bronchograms

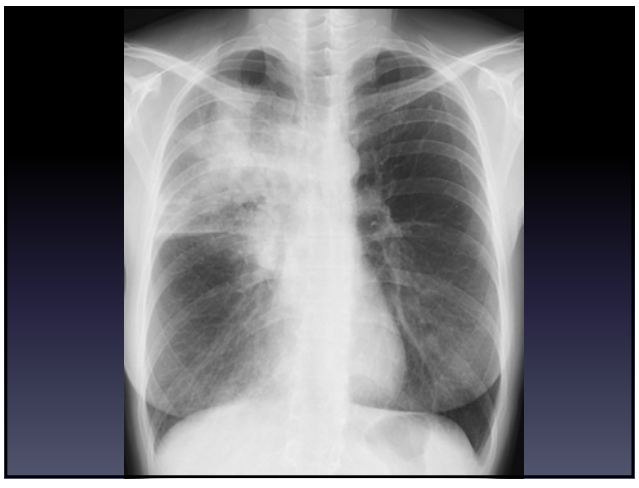


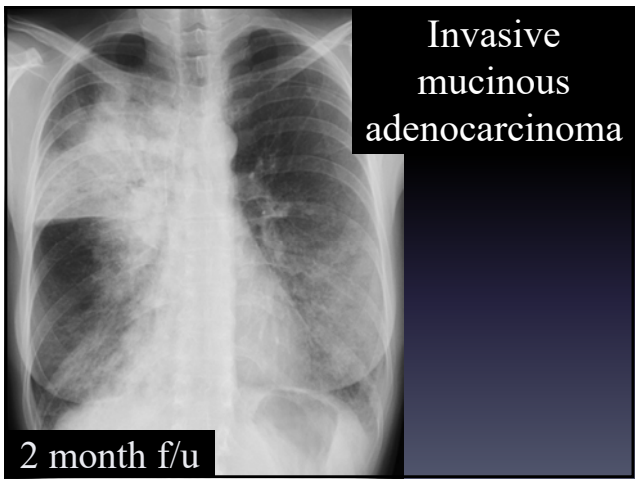




Consolidation

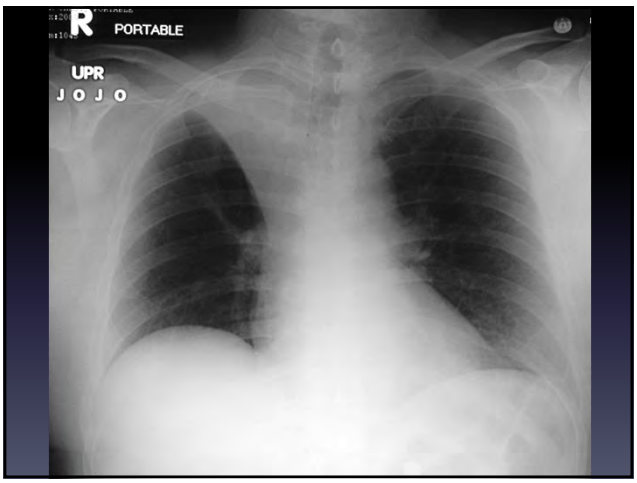
- Acute vs. chronic symptoms
- Distribution
- Acuity of changes
- Differential diagnosis in acute setting
  - Focal: pneumonia/aspiration, hemorrhage
  - Diffuse: edema, acute lung injury, pneumonia, hemorrhage



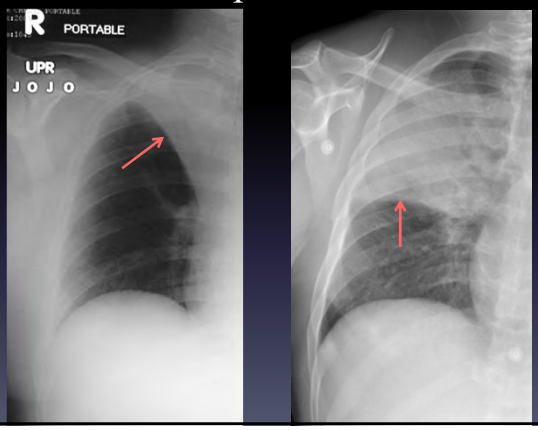


Chronic alveolar disease

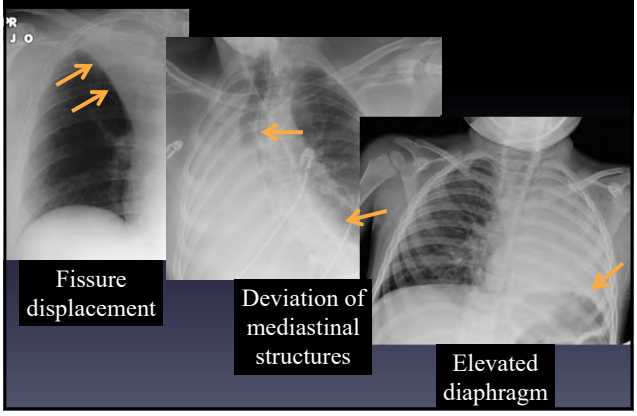
- Tumor
  - Invasive mucinous adenocarinoma (aka multifocal bronchoalveolar CA)
  - Lymphoma (recurrent or 1° pulmonary)
- Inflammatory
  - Organizing pneumonia
  - Chronic eosinophilic pneumonia
  - Sarcoidosis
- Other
  - Lipoid pneumonia
  - Alveolar proteinosis



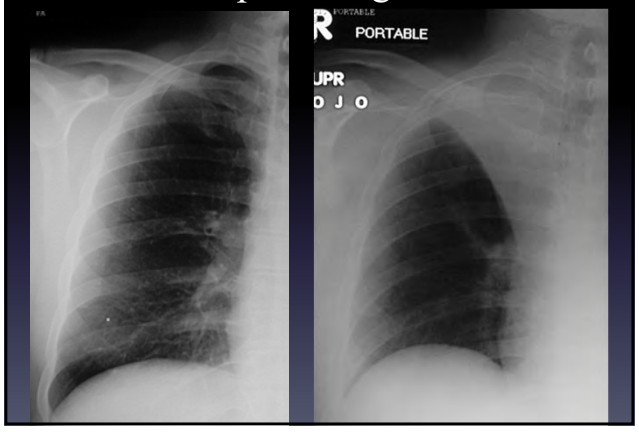
Comparison



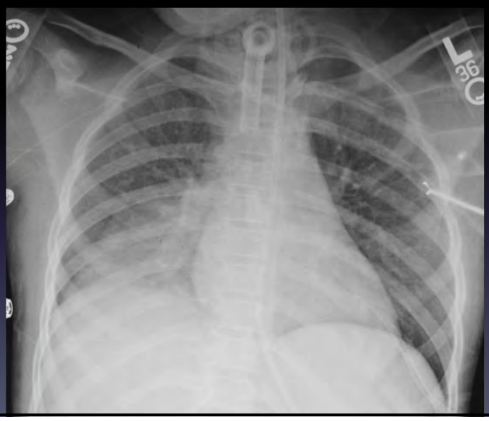
Signs of atelectasis: volume loss



Rapid change

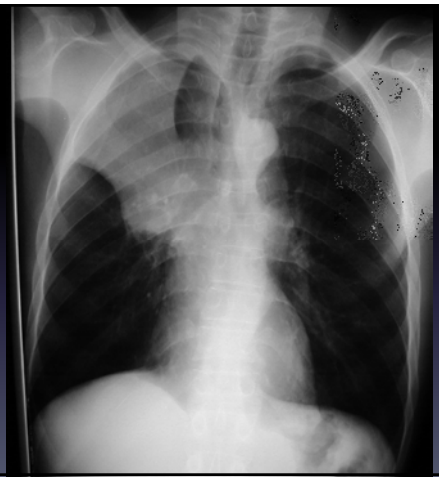


? atelectasis or an alveolar process

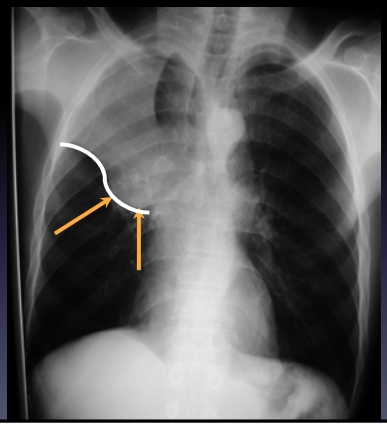


Atelectasis (types)

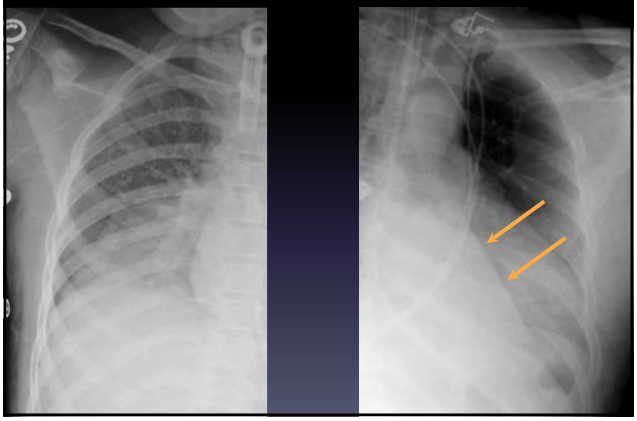
- Obstructive/resorptive (obstruction of bronchus)
- Passive (compression of lungs)
- Cicatricial (related to scarring)
- Adhesive (surfactant deficiency)



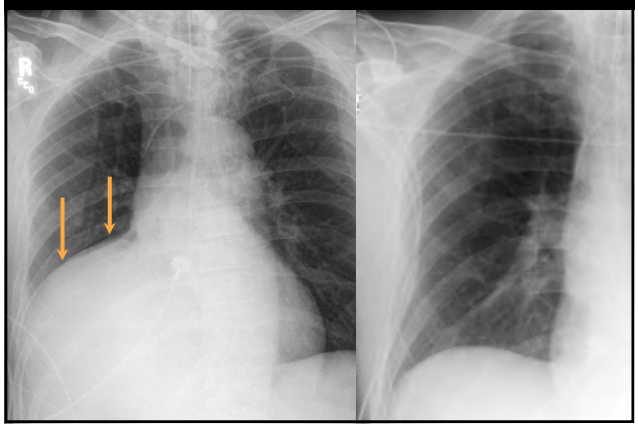
Lung cancer (Golden S sign)

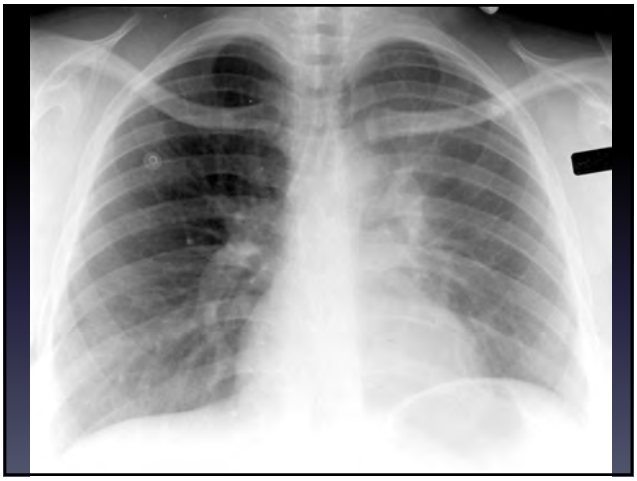


Lower lobe atelectasis

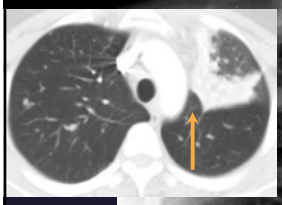


Combined RML/RLL atelectasis

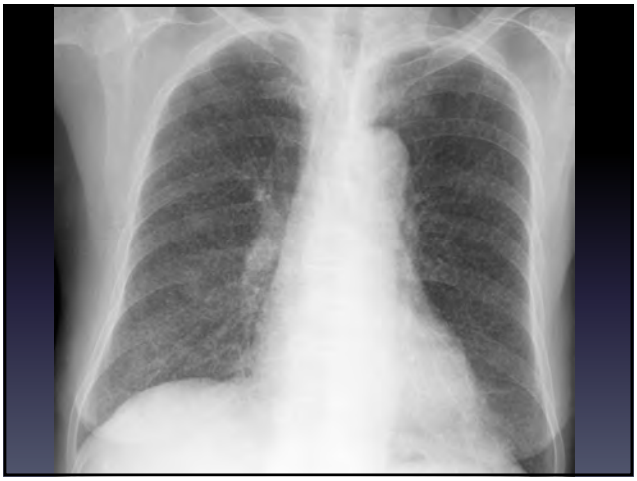




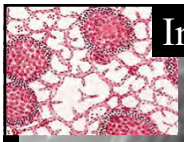
Left upper lobe collapse

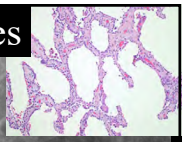


- 1. Veil-like density
- 2. Volume loss
  - Elevated diaphragm
  - Elevated left PA
- Luftsichel sign



Interstitial opacities





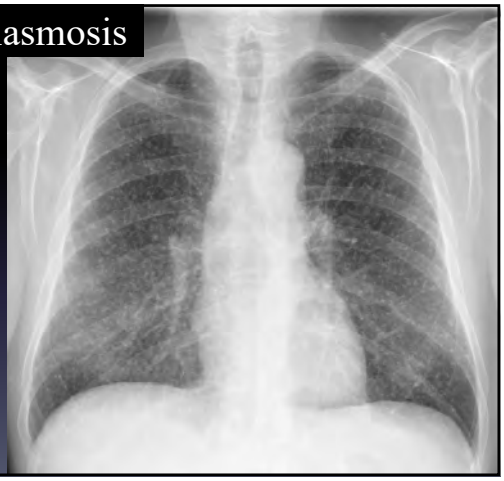
Nodules

Lines

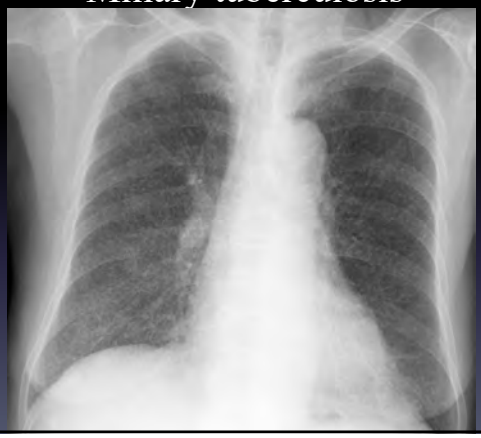
Nodules: diff dx

- Hematogenous spread
  - Miliary tuberculosis
  - Miliary fungal infection (e.g. cocci)
  - Metastases
- Lymphatic spread
  - Sarcoidosis
  - Lymphangitic spread of tumor
  - Pneumoconioses (e.g. silica)

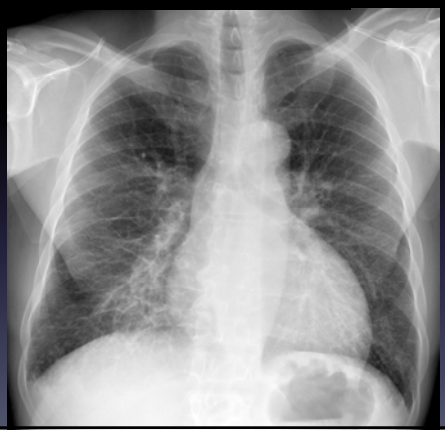
Histoplasmosis



Miliary tuberculosis



Interstitial: lines



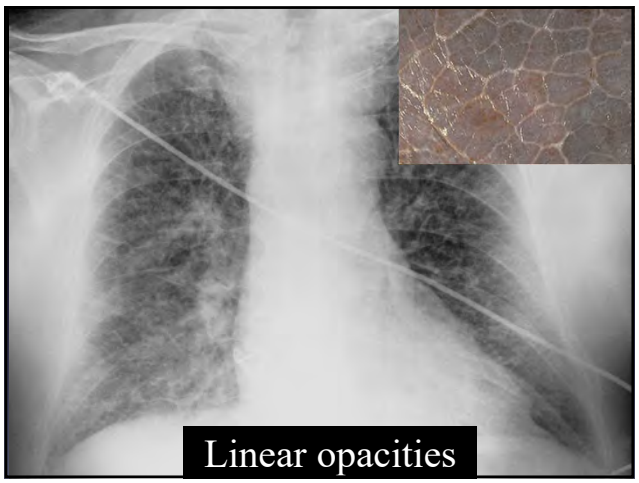
Causes of interstitial lines

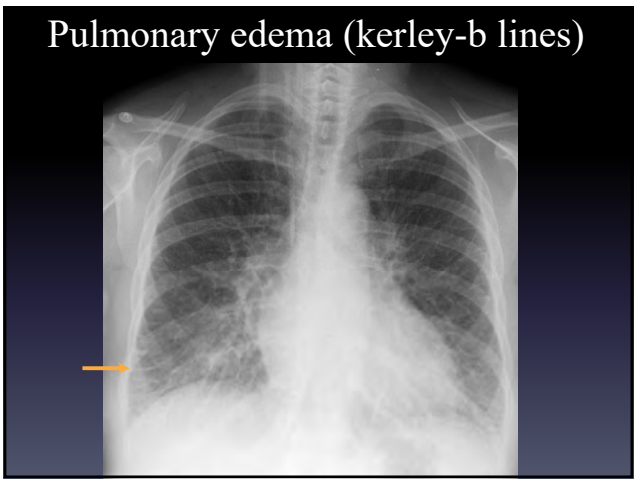
- Edema
- Malignancy

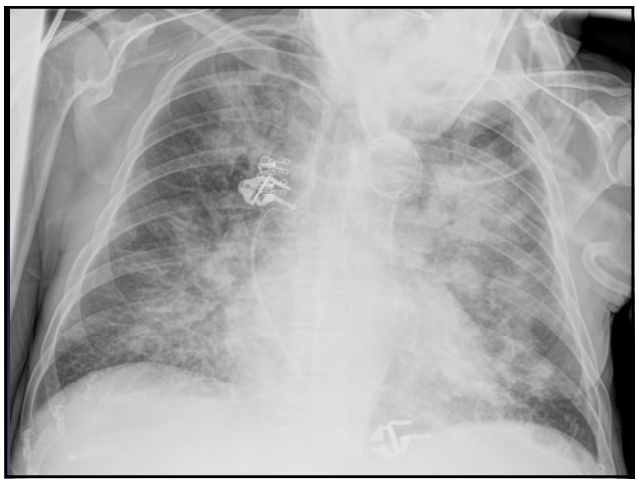
Kerley-b lines may be present

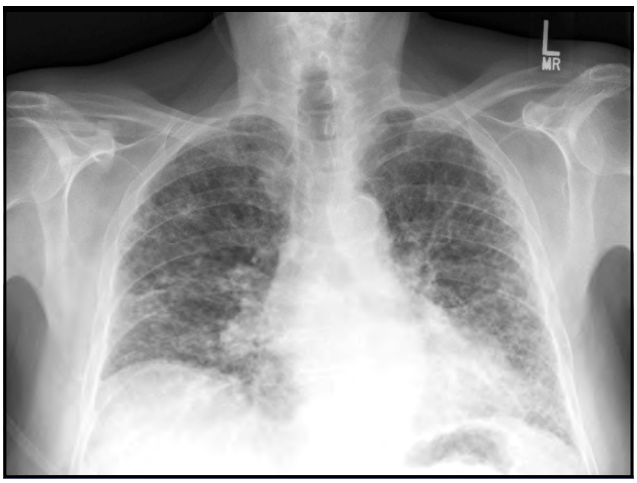
- Fibrotic lung diseases (this is a long list)

These lines are typically thick, wavy and irregular


Linear opacities


Pulmonary edema (kerley-b lines)

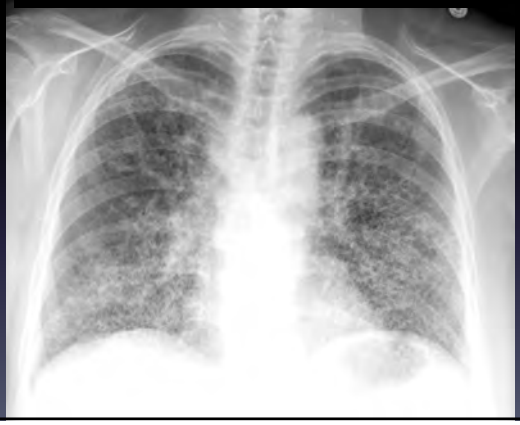



L
MR

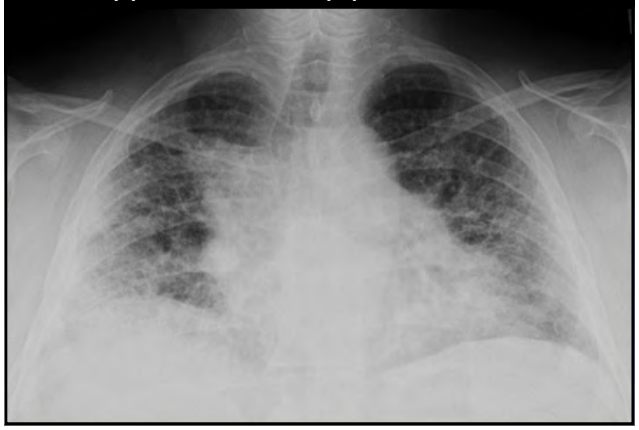
Reticular opacities (distribution)

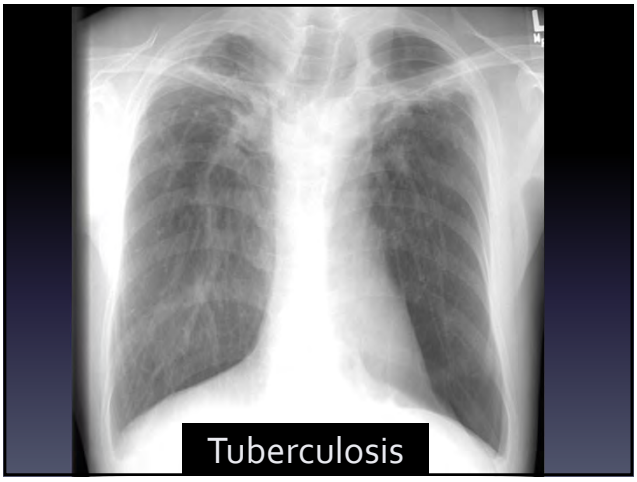
- Lower lobe predominant
  - Idiopathic pulmonary fibrosis
  - Connective tissue disease
  - Drugs
  - Asbestosis
  - Hypersensitivity pneumonitis
- Upper lobe predominant
  - Sarcoidosis
  - Prior TB/fungus
  - Pneumoconioses

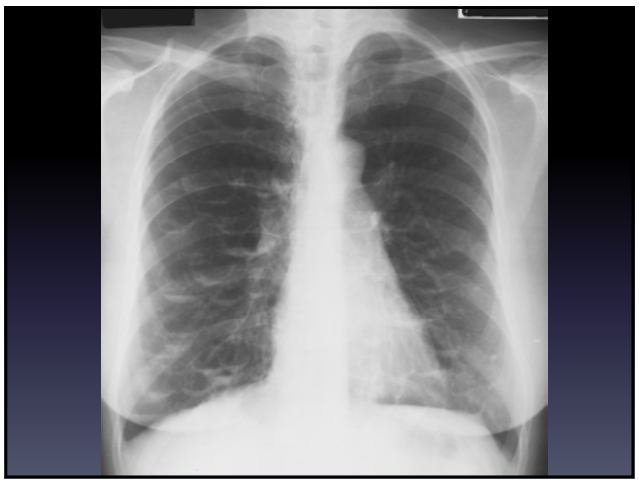
Idiopathic pulmonary fibrosis

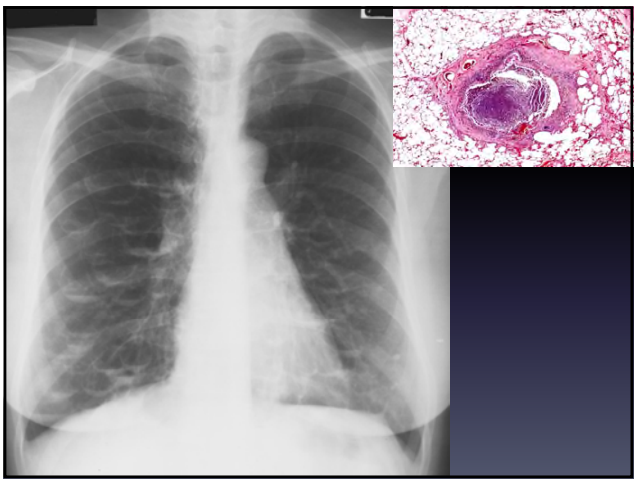


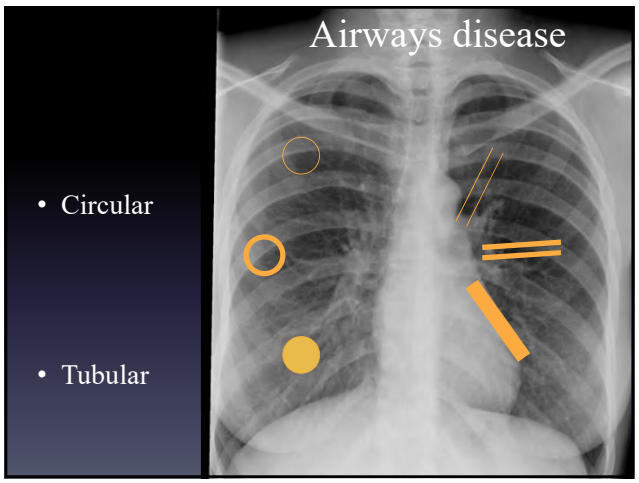
Hypersensitivity pneumonitis

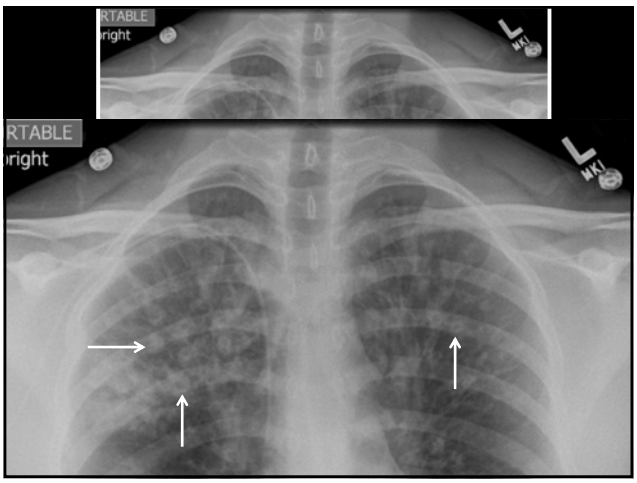








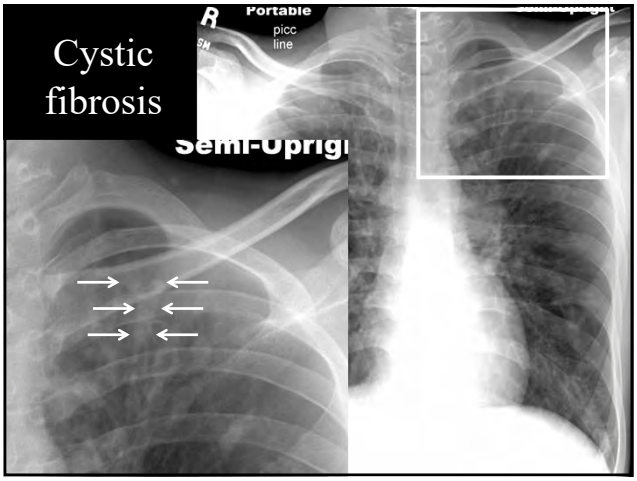

Airways disease
• Circular
• Tubular



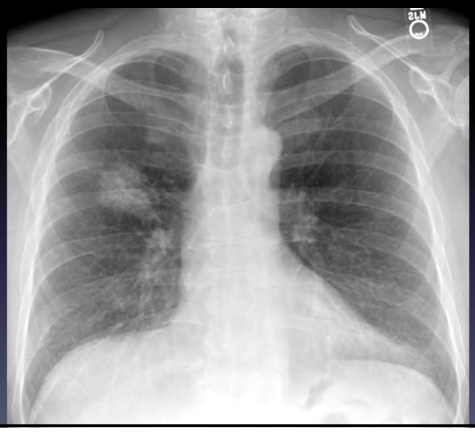
Differential diagnosis of airways disease

- Mild:
  - Asthma
  - Viral infection
  - Chronic bronchitis
  - Etc.
- Severe:
  - Bronchiolitis obliterans
  - Immunodeficiency
  - Ciliary dyskinesia
  - Cystic fibrosis
  - ABPA
  - Tuberculosis
  - Cartilage diseases

Cystic fibrosis

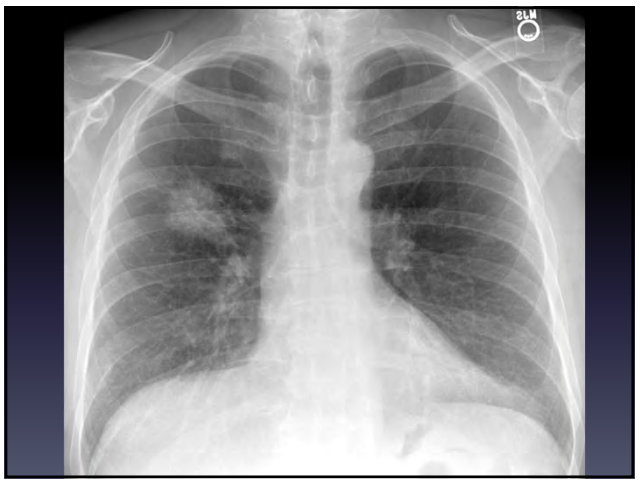


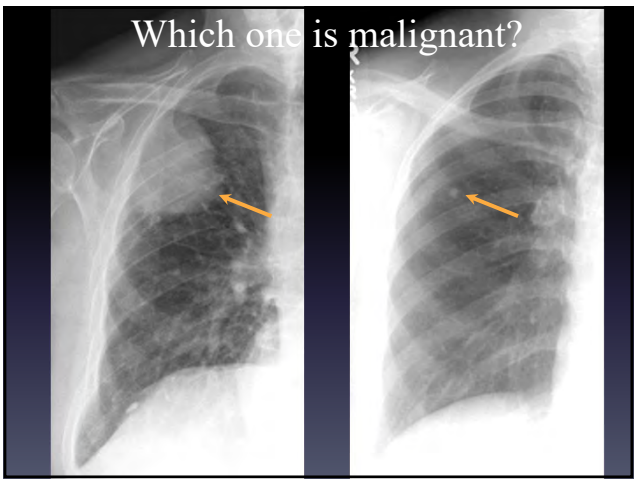
Which compartment of lung is affected?



Solitary pulmonary nodule: differential diagnosis

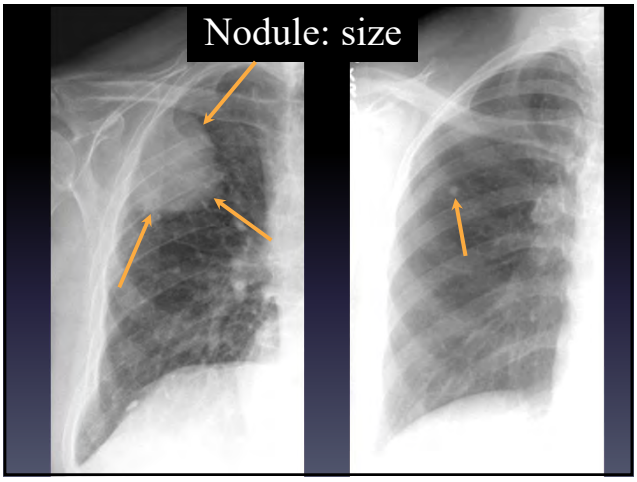
- Granuloma
- Hamartoma
- Primary bronchogenic carcinoma
- Metastasis
- Lots of others

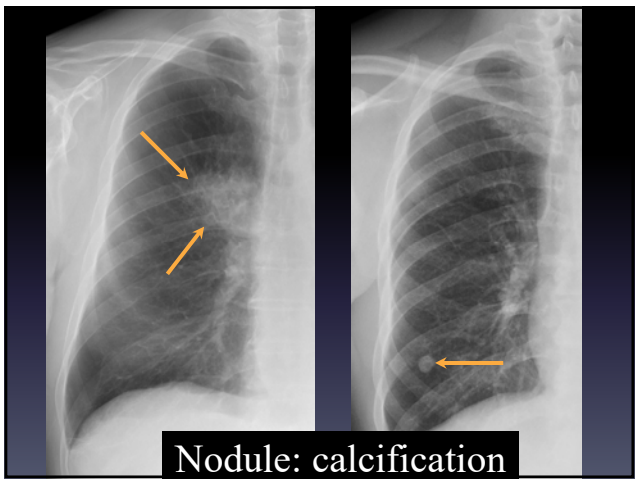


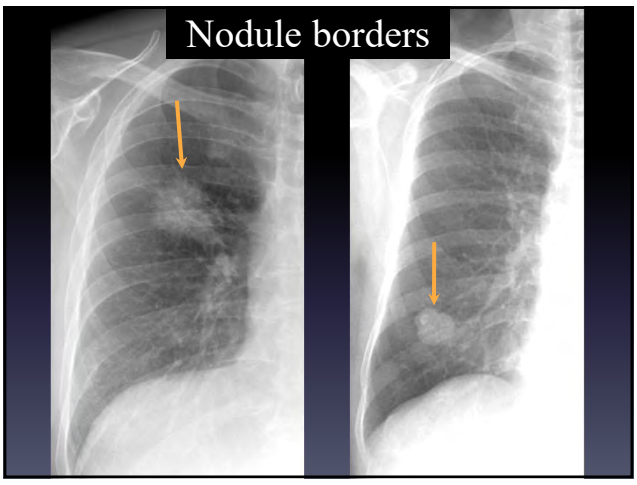


Nodules: benign vs. malignant

Benign	Malignant
Small size	Large size
Smooth border	Spiculated border
Diffuse calcification	No or irregular calcification
Stability over time	Growth over time

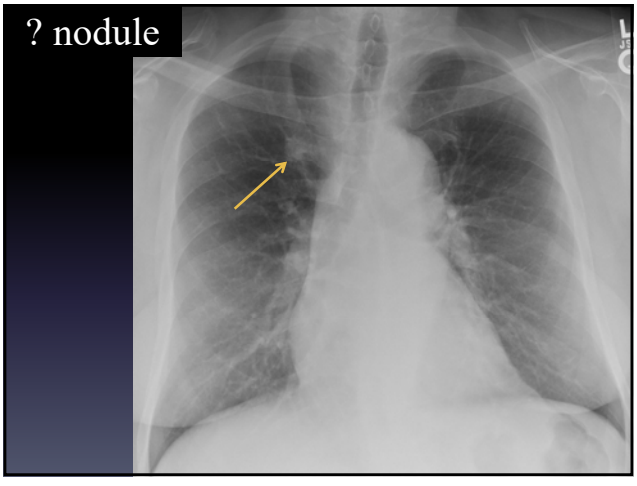




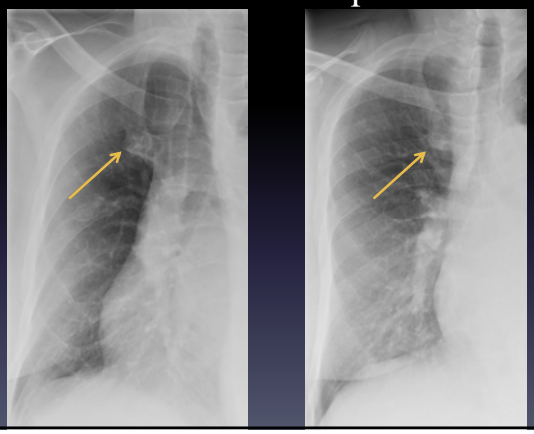


So you see a nodule on CXR…

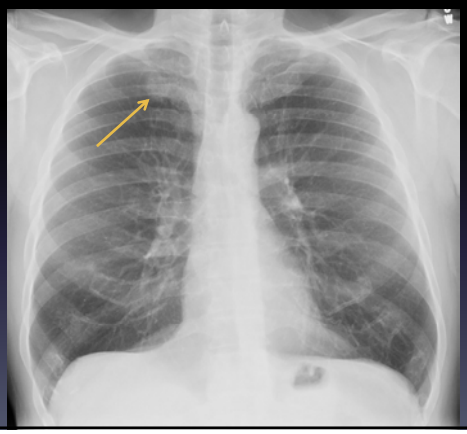
- 1. Is it actually a nodule?



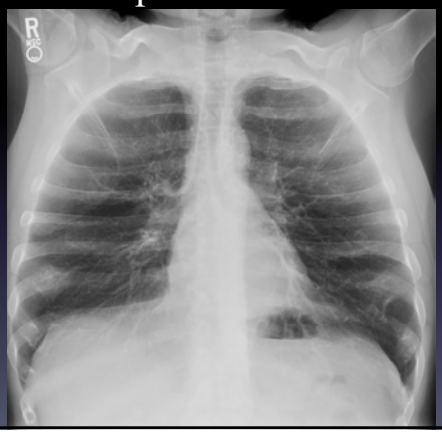
Shallow obliques



? nodule



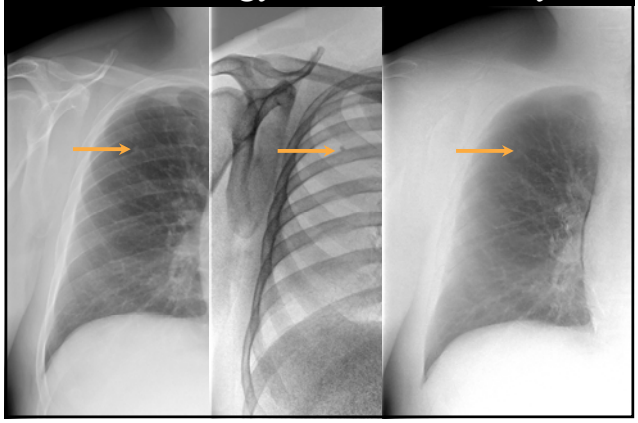
Apical lordotic



So you see a nodule on CXR…

- 1. Is it actually a nodule?
- 2. Look for prior films?
- 3. Is diffuse calcification present?

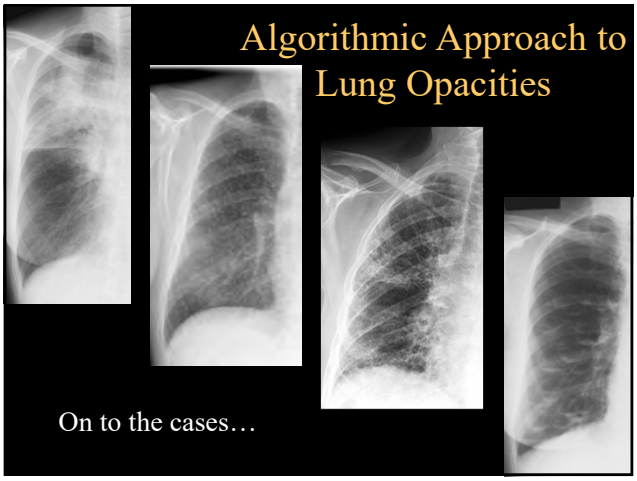
Dual energy subtraction x-ray



So you see a nodule on CXR…

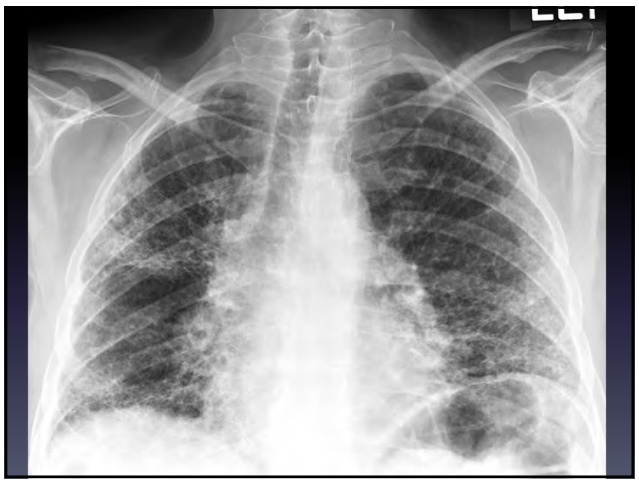
- 1. Is it actually a nodule?
- 2. Look for prior films?
- 3. Is diffuse calcification present?
- 4. Get a CT scan or a follow-up CXR

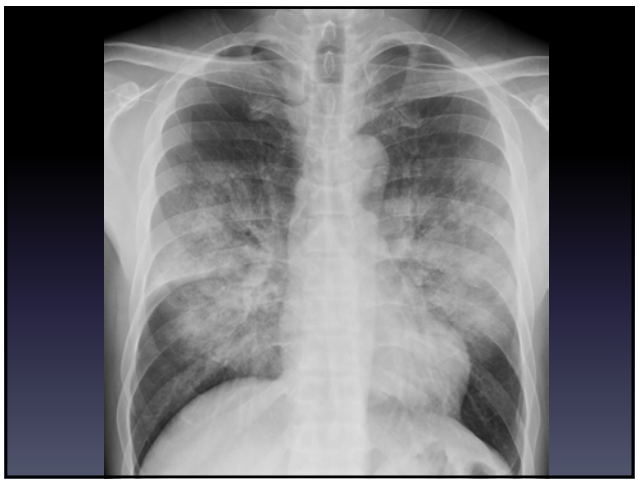
Category	Subcategory	CXR features	Common causes
Alveolar		•Confluent opacities •Air bronchograms •Fluffy edges	•Edema •Acute lung injury •Infection
Interstitial	Nodules	•Small, well-defined nodules •Opacities not confluent •Normal lung between nodules	•Tuberculosis •Fungal infection •Metastases •Sarcoidosis
	Lines (kerley-b)	•Thin, fine, delicate lines •Lines at periphery of lung (kerley-b)	•Pulmonary edema •Cancer
	Lines (reticular)	•Thick, wavy, irregular lines	•Fibrotic lung disease
Airways		•Circular or tubular •Thin or thick walled	•Numerous causes
Not in a single compartment		•One or a few nodules (≤3 cm) or masses (>3 cm)	•Lung cancer •Metastasis •Granuloma •Hamartoma

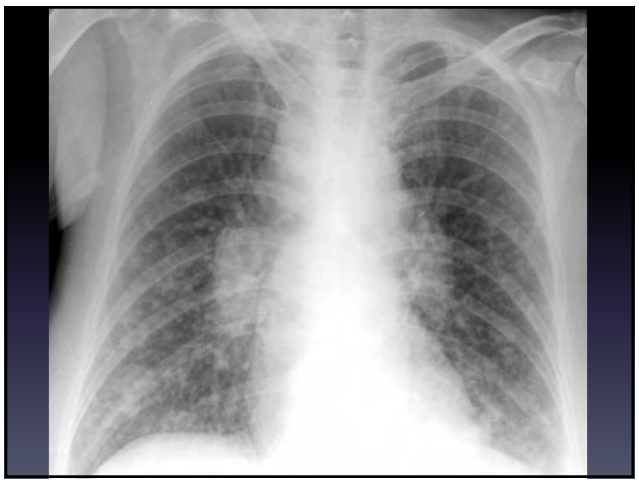


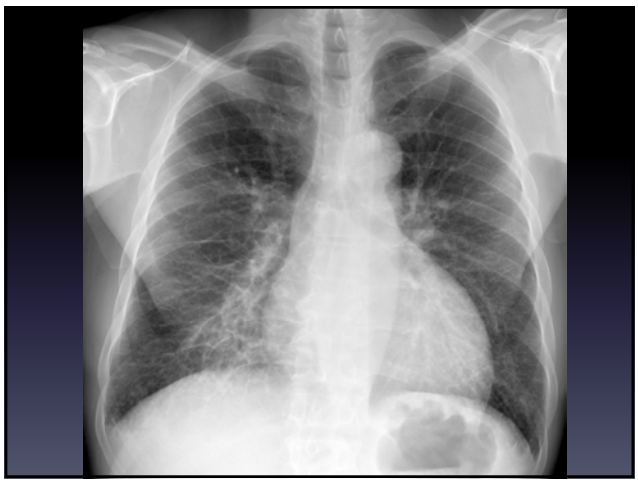
Algorithmic Approach to Lung Opacities

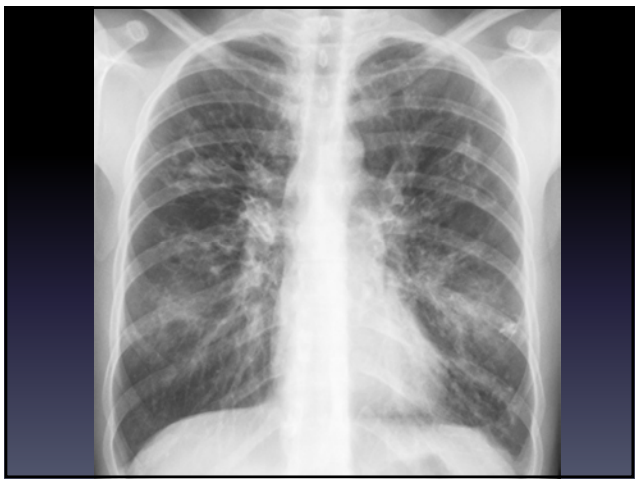
On to the cases…

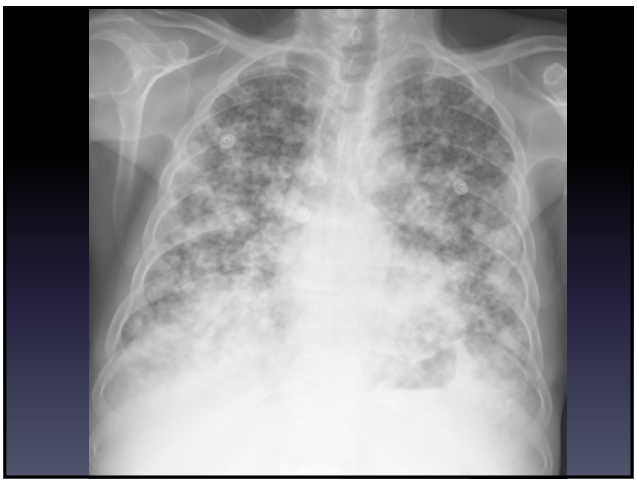












Cardiac & Pulmonary Risk Assessment in the Surgical Patient

Hugo Quinny Cheng, MD
Division of Hospital Medicine
University of California, San Francisco

Preoperative Evaluation Guidelines

Cardiac:

Fleisher L *et al.* 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery (2014). *J Am Coll Cardiol.* doi: 10.1016/j.jacc.2014.07.944.

Pulmonary:

Qaseem A *et al.* Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: a guideline from the American College of Physicians. *Ann Intern Med*, 2006; 141:575-80.

Preoperative Cardiac Evaluation

1. Is this patient at increased risk for perioperative cardiac complications?
2. Does the patient need further preoperative medical tests to clarify this risk?
3. What should be done to reduce the risk of cardiac complications?

Clinical Risk Prediction

What increases this patient's risk for perioperative cardiac complications?

70-y.o. man with progressive weakness due to cervical myelopathy need spinal decompression & fusion. He needs help with some ADLs and walks slowly with a cane.

He has stable coronary artery disease & HTN

He is an active smoker.

Question 1: What increases this patient's risk for perioperative cardiac complications?

1. History of coronary disease
2. History of HTN
3. Current smoker
4. Limited functional status
5. All of the above

Identifying Higher Risk Patients

Heart disease (and equivalents) predicts risk

Heart disease risk factors do not

Risk Factor	Odds Ratio
Ischemic heart disease	2.4
Congestive heart failure	1.9
Diabetes	2.8
History of Stroke or TIA	3.2
Poor functional status	*1.8*

Surgery Specific Risk

High (> 5 % risk)	Major aortic or peripheral vascular surgery Emergent major surgery Long cases w/ large fluid shifts or blood loss
Intermediate (< 5 % risk)	Carotid endarterectomy Head & Neck Abdominal & Thoracic Orthopedic
Low (< 1% risk)	Endoscopic procedures Skin & Breast

Revised Cardiac Risk Index

Predictors:

- Ischemic heart disease
- Congestive heart failure
- Diabetes requiring insulin
- Creatinine > 2 mg/dL
- Stroke or TIA
- "High Risk" operation (intraperitoneal, intrathoracic, or suprainguinal vascular)

# of RCRI Predictors	Complications *MI & cardiac arrest*
0	0.4%
1	1%
2	2.4%
≥ 3	5.4%

RCRI ≥ 2 is "Elevated Risk"

Devereaux PJ et al. CMAJ 2005; 173:627.

NSQIP Cardiac Risk Prediction Tool

Derived from National Surgical Quality Improvement Program (NSQIP) database:

- > 400,000 patients in derivation & validation cohorts
- Wide range of operations
- "Complication" = 30-day incidence of MI & cardiac arrest

Independent Predictors	1. Type of surgery 2. Age 3. Serum creatinine > 1.5 mg/dL 4. Functional status (dependency for ADLs) 5. American Society of Anesth (ASA) class

Gupta PK et al. Circulation 2011; 124:681

What is ASA Classification?

American Society of Anesthesiologists Physical Classification:

1. Healthy, normal
2. Mild systemic disease
3. Severe systemic disease
4. Severe systemic disease that is a constant threat to life
5. Moribund patient not expected to survive without surgery

70-y.o. with h/o CAD, now undergoing cervical spine surgery. Needs help with some ADLs.

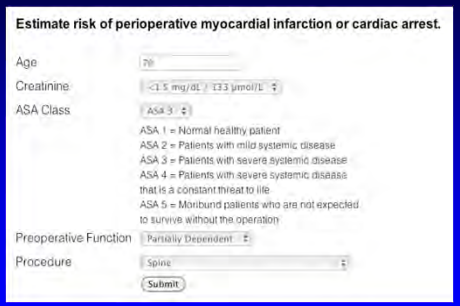
Age 70

Cr < 1.5

ASA Class 3

Partially dependent

Spine surgery



https://qxmd.com/calculate/calculator_245/gupta-perioperative-cardiac-risk

70-y.o. with h/o CAD undergoing cervical spine surgery for progressive weakness.

Estimated risk of perioperative myocardial infarction or cardiac arrest: 0.72%

www.qxmd.com/calculate-online/cardiology/gupta-perioperative-cardiac-risk

NSQIP Prediction Tool:

- Excellent performance (AUC = 0.88)
- Doesn't account for all available information
- ACC/AHA defines risk > 1% as "elevated risk"

Which Prediction Tool is Better?

	RCRI	NSQIP
Sample size	~ 4000	~ 400,000
# of hospitals	1	> 200
Currency of data	1989 – 94	2007 – 08
Screen for MI?	CK-MB, ECG	No

2014 ACC/AHA guideline endorses both tools:

- Elevated risk defined as RCRI ≥ 2 or NSQIP risk > 1%

ACC/AHA: When is Risk Excessive?

- Unstable coronary syndromes
  - Recent MI with post-infarct ischemia
  - Class III or IV angina
- Decompensated CHF
- Significant arrhythmia
  - High grade atrioventricular block
  - Symptomatic ventricular arrhythmia
  - Supraventricular arrhythmia with uncontrolled rate
- Severe valve disease (e.g., critical aortic stenosis)

ACC/AHA: When is Risk Excessive?

Severe or unstable cardiac disease that requires urgent evaluation & treatment, regardless of planned surgery

Utility of Stress Testing

Is further preoperative cardiac testing indicated?

A 63 y.o. man will undergo a Whipple procedure for newly diagnosed pancreatic cancer. He had a remote myocardial infarction, diabetes, and HTN. He has not had chest pain in the past year. Fair functional capacity.

Meds: lovastatin, atenolol, glyburide, benazepril, ASA
PEx: BP=115 / 70 HR=60; normal heart & lung exam
ECG: NSR, LVH, otherwise normal

Question 2:

63 y.o. man s/f Whipple procedure. Remote MI, long-standing diabetes & HTN. No chest pain.

Should this patient receive further preoperative tests?

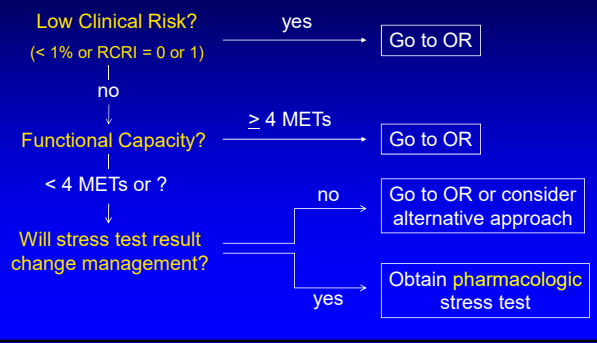
1. No further testing
2. Yes, perform a stress test

Noninvasive Stress Testing

Predictive value:

- Mainly studied in vascular surgery patients
- Strong negative predictive value ~ 98% (neg LR = 0.1 - 0.2)
- Weak positive predictive value ~10 - 20% (pos LR = 2 - 3)
- Adds little information to lower risk patients
- More useful for cases with increased risk

2014 ACC/AHA Guideline



Revascularization

Should this patient have coronary revascularization?

A 63 y.o. man pancreatic cancer is being considered for a Whipple procedure. History of remote MI, diabetes, HTN. No chest pain in the past year. Fair functional capacity. Persantine-Mibi last year showed mild inferior reversibility. Coronary cath showed a 75% RCA lesion and normal LVEF. He did not receive PCI.

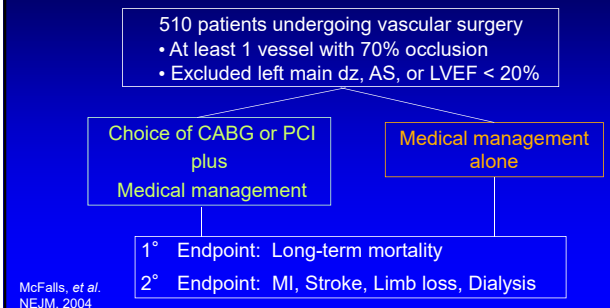
Question 3:

63 y.o. man with CAD undergoing Whipple procedure. His P-Mibi showed mild inferior reversibility. Angiogram showed a 75% RCA lesion and normal LVEF.

Should this patient have coronary revascularization?

1. No, proceed to surgery
2. Consult cardiologist for possible PCI

CARP Trial: **C**oronary **A**rtery **R**evascularization **P**rophylaxis



McFalls, *et al.* NEJM, 2004

CARP: Complications After CABG or PCI

Complication	%
Mortality	1.7%
MI	5.8%

McFalls EO, et al. *N Engl J Med.* 2004;351:2795-2804.

CARP: Outcomes After Vascular Surgery

	Revascularized (n=225)	Med Mgt Only (n=237)
Death before surgery	10 (4%)	1
Death < 30 days post-op	7 (3%)	8 (3%)
Postoperative MI	26 (12%)	34 (14%)
Long-term mortality (2.7 yrs after randomization)	70 (22%)	67 (23%)

p = NS for all comparisons

McFalls EO, et al. *N Engl J Med.* 2004;351:2795-2804.

ACC/AHA Guidelines for PCI

- Indications for PCI are same as for nonsurgical patients
- Avoid PCI if antiplatelet drugs will need to be held prematurely
- Delay elective surgery after elective PCI:
  - Bare metal stent: 30 days
  - Drug eluting stent: 6 months (optimal)
    3 months (if harm in delay)
- Continue or restart antiplatelet agents (especially ASA) as soon as possible, unless bleeding risk precludes

Medical Management

Question 4:

Which medication(s) should before surgery?

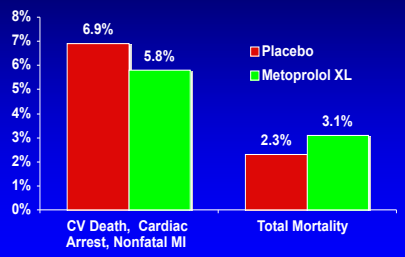
80-y.o. woman with a remote stroke, diabetes, and HTN will undergo repair of hip fracture. She has been out of care, and she is not taking any medications other than metformin for diabetes.

1. Metoprolol
2. Aspirin
3. Atorvastatin

Rise & Fall of Beta-blockers

- Early trials showed that starting beta-blockers prevented postoperative MI and reduce mortality
- Subsequent studies less impressive, and some positive studies discredited for fraud
- Largest study found small benefit on MI prevention, but increased overall mortality

POISE Trial Results



Metoprolol XL:

Reduced cardiac events (mostly nonfatal MI)

but

Increased risk of stroke & total mortality

Lancet, 2008; DOI:10.1016/S0140- 6736(08)60601-7

2014 ACC / AHA Guideline for β-blockers

Definite indications to continue if… (Helps)

- Already using β-blocker to treat angina, HTN, arrhythmia

Reasonable to consider initiation if… (Maybe)

- High clinical risk (RCRI score ≥ 3)
- Ischemia seen on preoperative stress test
- Compelling indication for long-term beta-blockade

Avoid initiation… (Harms)

- On day of surgery

POISE 2: Aspirin Results

	Aspirin	Placebo	Hazard Ratio
Death or MI	7.0%	7.1%	0.99 (NS)
Non-fatal MI	6.2%	6.3%	0.98 (NS)
Major Bleeding	4.6%	3.8%	1.23 (p = 0.04)

Devereaux, PJ et al. NEJM 2014; 370:1494-03

POISE 2 – Patients with PCI

Non-prespecified analysis of subgroup of the 470 patients with history of prior PCI:

	Aspirin	Placebo	Hazard Ratio
Death or MI	6.0%	11.5%	0.50 (p = 0.036)
Non-fatal MI	5.1%	11.0%	0.44 (p = 0.02)
Major Bleeding	5.6%	4.2%	1.26 (p = 0.04)

Graham MM et al. Ann Intern Med. 2017 Nov 14. doi: 10.7326/M17-2341.

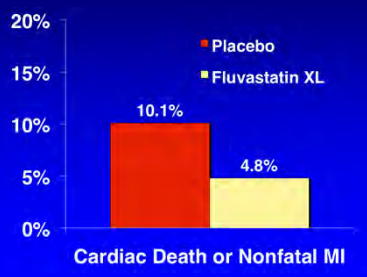
2014 ACC / AHA Guidelines

Aspirin *(for patients without stent)*

- Not unreasonable to continue ASA in elective surgery if benefits outweigh risks from bleeding (Class 2b)
- Initiation of ASA does not benefit patients undergoing elective noncardiac surgery (Class 3)

Fleischer et al. JACC (2014), doi: 10.1016/j.jacc.2014.07.944.

Trial of Statins in Vascular Surgery



Reduced nonfatal MI

No difference in rates of LFT or CPK elevation

Schouten et al. *NEJM*, 2009; 361:980-9

2014 ACC / AHA Guideline (Statins)

Definitely continue if… (Class I)
- Patient is already taking statins chronically

Reasonable to initiate if… (Class 2a)
- Patient is having vascular surgery

Not unreasonable to initiate if… (Class 2b)
- Patient has elevated clinical risk and is undergoing a moderate or high risk operation

Fleischer et al. JACC (2014), doi: 10.1016/j.jacc.2014.07.944.

Take Home Points

Use a validated clinical prediction tool:
- RCRI is easy to use & has become the "new standard"
- NSQIP tool may be more broadly applicable

Reserve stress testing for highest risk patients:
- Elevated risk and poor functional status
- Only do stress test if results will change management (e.g., cancel, delay, or modify surgery)

Take Home Points

Beware perioperative coronary revascularization:
- Indications are the same as for non-surgical patients
- Don't perform PCI if patient may have upcoming surgery that requires stopping antiplatelet therapy

Medical management:
- Only consider beta-blockers in very high risk patients after considering risks, and not immediately before surgery
- Possible role for initiating statin

Preoperative Pulmonary Evaluation

1. Is this patient at increased risk for perioperative pulmonary complications?
2. Does the patient need further preoperative medical tests to clarify this risk?
3. What should be done to reduce the risk of pulmonary complications?

Pulmonary Risk Prediction

What do you recommend for this patient?

A 65 y.o. man is to undergo repair of an abdominal aortic aneurysm. He has COPD and continues to smoke. He denies change in cough, or worsening of his chronic dyspnea when walking uphill.

Exam: Resp Rate 20 O_2 sat 95% RA
Lungs: prolonged expiration, no wheeze

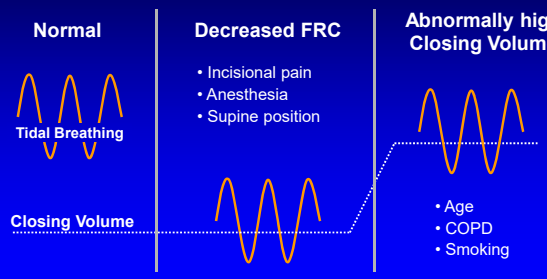
Question 5:

65 y.o. man is s/f repair of an AAA. He has COPD and smokes. No change in cough or usual chronic dyspnea.

Which of the following will be helpful?

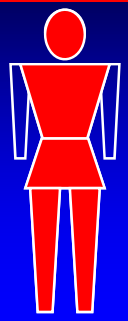
1. Obtain PFTs
2. Quit smoking first before surgery
3. Incentive spirometry after surgery

Pathophysiology of Postoperative Pulmonary Complications



Procedure Related Risk Factors

Risk Factor		Odds Ratio
Surgical Site	Neurosurgery	2.5
	Head & Neck	2.2
	Aortic	6.9
	Thoracic	4.2
	Abdominal	3.0
	Vascular	2.1
Emergency surgery		2.2
Prolonged surgery		2.3
General anesthesia		1.8



Patient Related Risk Factors

Risk Factor		Odds Ratio
Age	60 - 69	2.3
	70 - 79	5.6
Congestive heart failure		2.9
COPD		2.4

ASA Class ≥ II vs. Class I — Odds ratio = 4.9

ASA Class ≥ III vs. Class I or II — Odds ratio = 3.1

Class I: no systemic disease
Class II: mild systemic disease
Class III: severe systemic disease
Class IV: systemic disease that is a constant threat to life

Respiratory Failure Prediction Tool

- Derived from National Surgical Quality Improvement Program (NSQIP) database:
  - > 400 K patients in derivation & validation cohorts
  - Wide range of operations
  - "Respiratory Failure" = on vent > 48 hrs or reintubation

Independent Predictors

1. American Society of Anesth (ASA) class
2. Functional status (dependency)
3. Type / location of surgery
4. Emergency surgery
5. Preoperative sepsis or SIRS

Gupta PK et al. Chest 2011; 110:1207

Respiratory Failure Prediction Tool

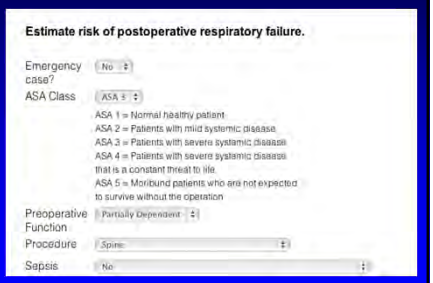
Emergency surgery?
No

ASA Class
3 (severe systemic)

Function/dependency
Independent

Surgery type Aortic

Sepsis or SIRS? No



qxmd.com/calculate/calculator_261/postoperative-respiratory-failure-risk-calculator

www.qxmd.com/calculate-online/respirology/postoperative-respiratory-failure-risk-calculator

Emergency surgery?
No

ASA Class
3 (severe systemic)

Function/dependency
Independent

Surgery type Aortic

Sepsis or SIRS? No

Estimated risk of postoperative respiratory failure: 6.7 %

Pulmonary Function Tests & Spirometry

PFT & spirometry add little to risk assessment

- Usually just tells you what you already know
- Abnormal chest exam findings more predictive of PPC
- Can't use results to identify patients with prohibitively high risk of PPC or mortality
- Use as diagnostic tool to evaluate unexplained findings

Preoperative Prevention Strategies

Optimize chronic lung disease

- Treat COPD exacerbation (steroids, antbiotics)

Smoking cessation

- Limited evidence for benefit for PPC but other benefits
- May require 8 weeks of cessation for benefit

Respiratory conditioning

- Education on lung expansion & Inspiratory muscle training
- Benefit seen in RCTs in cardiac surgery

Preoperative Smoking Cessation Counseling

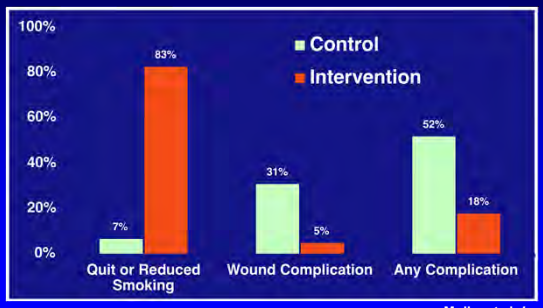
RCTs of Preoperative Smoking Cessation Counseling:

1. 120 patients undergoing arthroplasty in 6-8 weeks
2. 60 patients undergoing colorectal resection in 2-3 weeks

Intervention: Smoking cessation counseling & offer free nicotine replacement products

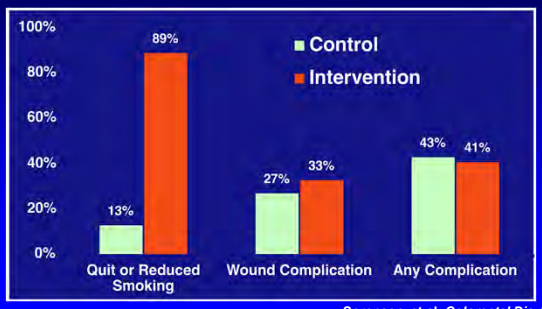
Outcomes: Postop complications, especially wound related (e.g., dehiscence, infection, hematoma)

Smoking Cessation 6-8 Weeks Before TKA or THA



Moller et al. *Lancet*, 2002

Smoking Cessation 2-3 Weeks Before Colorectal Surgery



Sorensen, et al. *Colorectal Dis*, 2003

Postoperative Prevention Strategies

Lung expansion maneuvers

- Deep breathing or incentive spirometry recommended, though quality of evidence poor
- Consideration of CPAP for very high risk patients

I COUGH – a multi-intervention strategy to prevent PPC

- Incentive spirometry, Coughing & deep breathing, Oral care, Understanding, Get out of bed tid, Head of bed elevated
- Reduced postop pneumonia and unplanned reintubation

Cassidy MR, et al. JAMA Surg. 2013 Aug;148(8):740-5

Causes of Postoperative Hypoxemia

Upper airway obstruction
- Early onset - often POD 0 or prior to leaving PACU
- Airway edema, vocal cord injury, laryngospasm, OSA

Atelectasis
- Often onset POD 1-2
- Secretion management: chest therapy, pulmonary toilet
- Positive airway pressure: CPAP, BiPAP, EzPAP

Pulmonary edema
- Often onset by POD 2
- Cardiogenic vs. non-cardiogenic

Causes of Postoperative Hypoxemia

Pneumonia
- Most common in first 5 days postop (unless on ventilator)
- Think Staph aureus & gram negative rods
- Pseudomonas? Risk with ≥ 5 days hospitalization or prior antibiotic exposure, dialysis, nursing home

Other etiologies:
- Pulmonary embolism
- Bronchospasm
- Effusions – common after abdominal surgery, usually small, exudative and usually don't require treatment

Take Home Points

Patient related risks:
- Elderly
- COPD
- Severe medical comorbidity
- Functionally dependent or generally debilitated

Procedure related risks:
- Thoracic surgery
- Abdominal surgery
- Emergency surgery
- Prolonged surgery > 3 hrs
- General anesthesia

Take Home Points

Pulmonary function tests:
- Should not be done routinely
- Consider to help evaluate unexplained symptoms

Risk reduction:
- Patients at increased risk for pulmonary complications should receive lung expansion maneuvers
- Smoking cessation likely beneficial but may require two months lead time to be effective

Thank You

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NOTES

UCSF School of Medicine

Point-of-Care Ultrasound for Hospitalists

Trevor Jensen, MD MS
Associate Professor of Medicine

October 2021

Disclosures

- Consultant for Caption Health

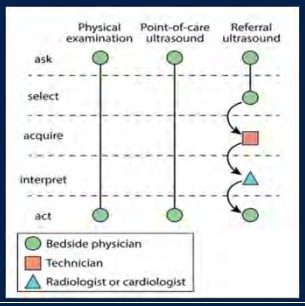
Session Outline

Point-of-Care Ultrasound (POCUS) is the future of the physical exam

- Questions we'll address around this topic:
  - What is POCUS for hospitalized patients?
  - Why learn POCUS?
  - How POCUS is used (cases + demo)?
  - How to get started with POCUS (for you & your institution)?

What is POCUS?

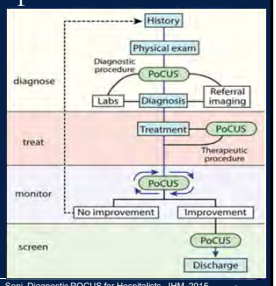
- Performed *and interpreted* by primary provider…
- …at the bedside…
- …to help answer a specific clinical question…
- …quickly



Soni, Diagnostic POCUS for Hospitalists. JHM, 2015

How we use POCUS in Hospital Medicine?

- Diagnostic
- Therapeutic (procedural guidance)
- Treatment monitoring
- Disease screening



Soni, Diagnostic POCUS for Hospitalists. JHM, 2015

Why learn POCUS?

Reason 1: It makes you a better doctor…

↓ Procedural complications

↑ Efficiency and accuracy of diagnosis

↑ Patient satisfaction

Why learn POCUS?

Reason 2: Most IM/HM doctors don't know much….

(Especially if you trained awhile ago)

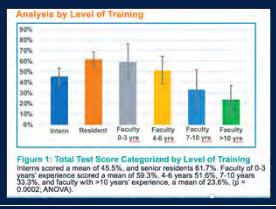


Figure 1: Total Test Score Categorized by Level of Training

Interns scored a mean of 45.5%, and senior residents 61.7%. Faculty of 0-3 years' experience scored a mean of 59.3%, 4-6 years 51.6%, 7-10 years 53.3%, and faculty with >10 years' experience, a mean of 23.6%. ($p = 0.0002$; ANOVA).

Anstey et al, SHM abstract, 2018

Why learn POCUS?

Reason 3: Despite lack of knowledge, people think its important….

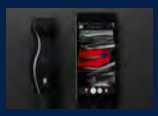
2017 Needs Assessment of UCSF Hospitalists

93%	I believe POCUS is important for diagnostic purposes in internal medicine.
88%	I believe POCUS should be a formal part of residency training.
93%	I believe faculty would benefit from faculty development in POCUS.

Conner et al, POCUS Journal

Why learn POCUS?

Its coming whether you like it or not…




AMA | ACP American College of Physicians | shm Society of Hospital Medicine | ALLIANCE for ACADEMIC INTERNAL MEDICINE

Cases: Inpatient Care as a POCUS Hospitalist

- Four common inpatient scenarios
  - Brief HPI and exam
  - Demo image acquisition and review normal anatomy/findings
  - Review abnormal images from the case
  - Discuss how POCUS impacted care delivery

Case 1: Mr. Seth is short of breath

- **HPI**: 61 M with HFrEF, COPD admitted for COPD exacerbation & CAP.
  - → nebulizers, prednisone, and antibiotics
- HD #3: increasing respiratory distress and anxiety
- **Vitals:** AF, HR 102, BP 192/97, RR 26, O2 sat 82% on RA → 93% on 6L NC
- **Exam:**
  - General: moderate distress.
  - CV: Tachycardic, no MRG. Unable to assess JVP. 1+ pitting edema of b/l LEs.
  - Lung: tachypneic, increased WOB, scattered wheeze with bilateral lower lobe rales.
- **Labs:** normal CBC and BMP, BNP 421, TnI pending, EKG non-ischemic. CXR ordered.

Case 1: Mr. Seth is short of breath + POCUS!

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- **Labs:** normal CBC and BMP, BNP 421, TnI pending, EKG non-ischemic. CXR ordered.

On admission, >3 b-lines in R anterior lung, otherwise normal. IVC 1.8cm and collapsible

Now, diffuse b-lines in bilateral lung fields, bilateral pleural effusions. IVC 2.4cm and minimally collapsible.

(You were done with your POCUS assessment by the time the CXR was ordered ☺)

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Demo: Lung Ultrasound (LZ 1-3)

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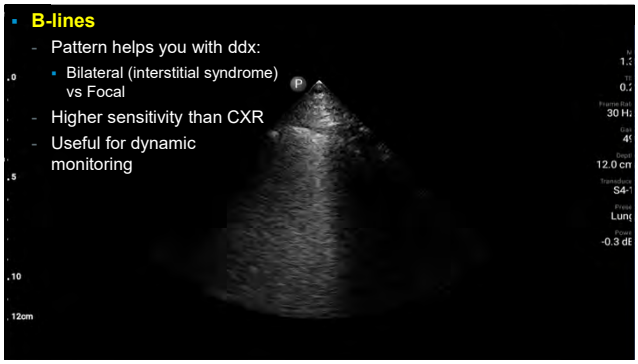
Demo: Lung Ultrasound (LZ 4)

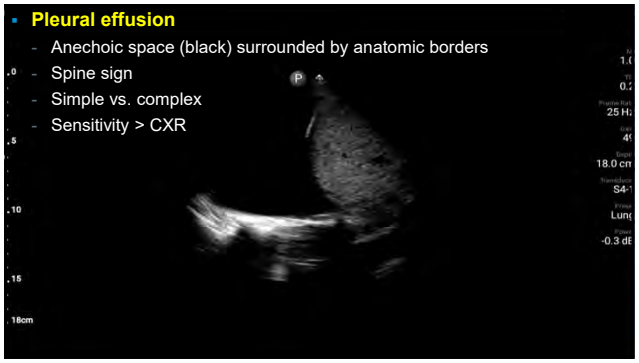
UCSF School of Medicine

Demo: IVC Ultrasound

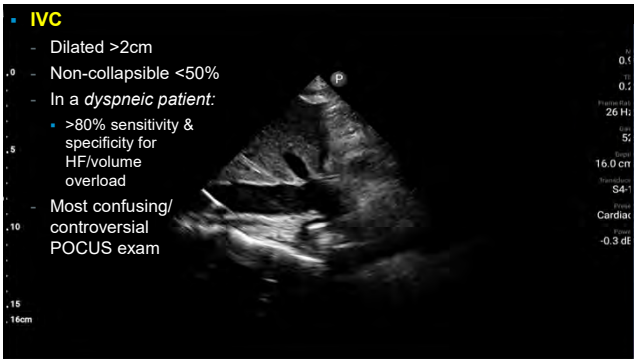
- **B-lines**
  - Pattern helps you with ddx:
    - Bilateral (interstitial syndrome) vs Focal
  - Higher sensitivity than CXR
  - Useful for dynamic monitoring



- **Pleural effusion**
  - Anechoic space (black) surrounded by anatomic borders
  - Spine sign
  - Simple vs. complex
  - Sensitivity > CXR



- **IVC**
  - Dilated >2cm
  - Non-collapsible <50%
  - In a *dyspneic patient:*
    - >80% sensitivity & specificity for HF/volume overload
  - Most confusing/ controversial POCUS exam

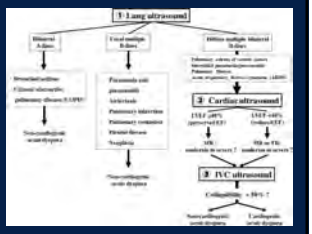


Case 1 Resolution

- POCUS diagnosis: interstitial syndrome, pleural effusions, volume overload
- You give him IV Lasix and treat his blood pressure → BP normalized and hypoxia improving
- You make a mental note to check his lung and IVC US again tomorrow to decide about thoracentesis and further need for diuretics

Case 1 Take Home Points

- POCUS
  - improved the quality of your index exam
  - helped you *quickly* identify why his condition acutely changed
- When possible:
  - Have an algorithmic approach
  - Combine multiple pcus exams and integrate with other data



Kajimoto et al, Cardiovascular Ultrasound, 2012.

Case 2: Mrs. Essig is hypotensive

- **HPI**: 52W with metastatic breast cancer c/b L malignant pleural effusion on chemotherapy p/w generalized weakness, dyspnea, lethargy, HR 123 BP 82/40
  - → given 2L IVF with improvement.
- **Vitals:** AF, HR 112, BP 90/47, RR 16, O2 sat 96% on RA
- **Exam:**
  - General: arousable but somnolent, comfortable
  - CV: Tachycardic, regular, no MRG. JVP 6cm. Chronic lymphedema of the b/l LEs
  - Lung: breathing comfortably on RA, diminished breath sounds LLB but otherwise CTA bilaterally
- **Labs:** CBC and BMP normal. Tbili 1.6, normal AST/ALT. BNP 235 (unknown baseline). TnI negative.

Case 2: Mrs. Essig is hypotensive + POCUS!

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- **Labs:** CBC and BMP normal. Tbili 1.6, normal AST/ALT. BNP 235 (unknown baseline). TnI negative.

Lungs with a-lines throughout, moderate L pleural effusion

IVC 1.8cm with ~50% collapse with inspiration

Cardiac US with mildly reduced LVEF, pericardial effusion

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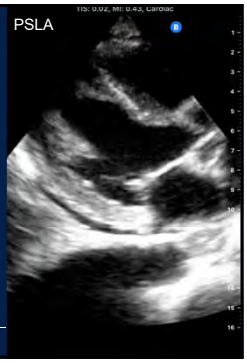
Demo: Cardiac US (Parasternal Long Axis)

UCSF School of Medicine

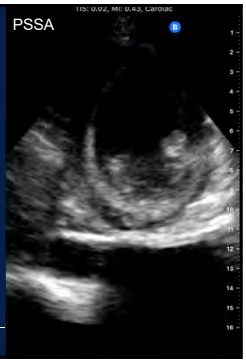
Demo: Cardiac US (Parasternal Short Axis)

- **LV Ejection Fraction**
  - Evaluation
    - End-point Septal Separation (EPSS)
    - Fractional Shortening
    - Myocardial Thickening
  - Qualitative assessment
    - Hyperdynamic
    - Normal
    - Mild-moderately reduced
    - Severely reduced
  - LV dysfunction by hospitalists: 91% sensitivity; 88% specificity



25

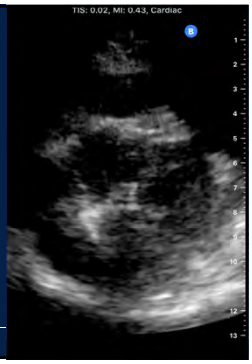
- **Pericardial Effusion**
  - Qualitative assessment:
    - Small
    - Moderate
    - Large
  - Pericardial effusion by hospitalists: 100% sensitivity; 87% specificity
  - Apical 4 chamber, sub-xiphoid best for evaluating signs of chamber collapse (tamponade)



26

Case 2 Resolution

- POCUS diagnosis: new mild-moderate LVEF reduction, new small pericardial effusion
- Repeat TTE on HD#1 confirms new EF 40%, pericardial effusion enlarging
- HD#3 she develops tamponade, undergoes pericardial drain placement. Patient and family opt for hospice referral.



27

Case 2 Take Home Points

- POCUS led you to a faster, new diagnosis of HFrEF.
  - Clinical management: more cautious with IVF
  - Further diagnostic testing: ordered TTE from admission
  - Monitoring evolution of pericardial effusion
  - Assist with prognostication & GOC

Table 4 Diagnostic Test Characteristics of Hand-Carried Echocardiography Using Standard Echocardiography as the Reference Standard in 210 Participants*

Cardiac Abnormality	Prevalence n/total n	Sensitivity* % (95% CI)	Specificity* % (95% CI)	$LR_{positive}$* (95% CI)	$LR_{negative}$* (95% CI)
LV systolic dysfunction	67/210	84 (73-92)	85 (78-90)	5.4 (3.7-8.1)	0.2 (0.1-0.3)
Pericardial effusion, moderate or large	3/210	100 (29-100)	87 (82-91)	7.7 (2.6-10.1)	0 (0-0.6)

Adapted from Lucas et al, Am J Med 2011

28

Case 3: Dr. Nye has an AKI

- **HPI**: 84M with BPH, HTN, DM2 presents with AMS, lower abdominal pain, decreased urination, K 6.4. ED POCUS shows hydronephrosis and a distended bladder
  - → foley with 400cc urine output. hyperK treatment.
- **Vitals:** within normal limits
- **Exam:**
  - General: mildly agitated but redirectable, no distress
  - Abd: soft, +suprapubic tenderness, no CVA tenderness, no distension, NABS
  - GU: foley in place draining cloudy yellow urine
- **Labs:** WBC 11.7, BUN 48, Cr 2.6, K 6.1, otherwise normal. UA +WBC, +nitrite, +LE, +blood. Urine culture pending. CTAP pending.

Case 3: Dr. Nye has an AKI

+ POCUS!

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Renal US: Bilateral hydronephrosis

Bladder still distended with foley balloon visible

FAST negative for free fluid

IVC 1.4cm, collapsible with inspiration

UCSF School of Medicine

Demo: Renal Ultrasound (RUQ)

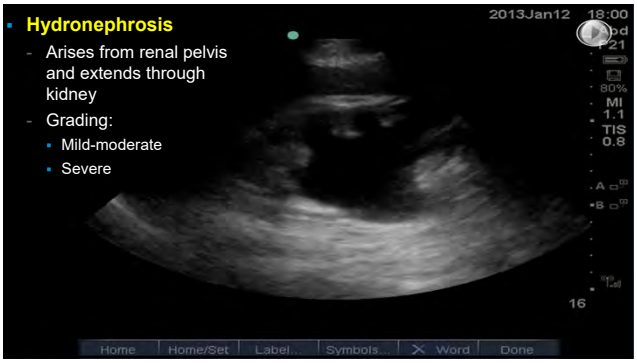
UCSF School of Medicine

Demo: Renal Ultrasound (LUQ)

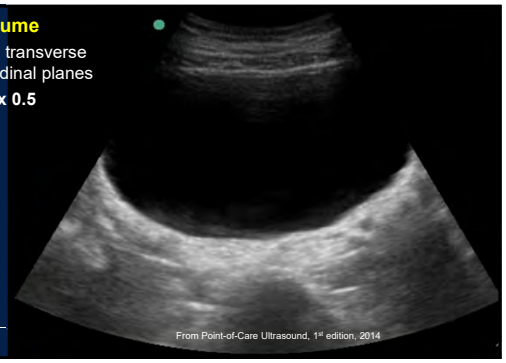
UCSF School of Medicine

Demo: Bladder Ultrasound

- **Hydronephrosis**
  - Arises from renal pelvis and extends through kidney
  - Grading:
    - Mild-moderate
    - Severe



- **Bladder Volume**
  - Measure in transverse and longitudinal planes
  - **L x W x H x 0.5**



Case 3 Resolution

- POCUS diagnosis: severe hydronephrosis, foley dysfunction with urinary retention
- Foley is flushed and repositioned → additional 800cc urine output. He is started on ceftriaxone for UTI and Tamsulosin for BPH. His abdominal pain resolves; you cancel the CT scan.
- HD #2: urine culture + for pan-sensitive E Coli → abx narrowed to cephalexin. K, Cr improved. Foley is removed and he passes a trial of void prior to discharge.

Case 3 Take Home Points

- POCUS helped you quickly identify a complication in your treatment plan
  - → avoided a potential bad outcome & unnecessary CT scan.
- Accuracy of bladder volume by POCUS > bladder scan
- Detecting hydronephrosis is a readily attainable skill
  - IM residents x5 hrs of renal US practice = 94% sensitivity; 93% specificity for moderate-severe hydronephrosis

Case 4: Ms. Nidus has cellulitis

- **HPI**: 36W with IVDU, DVT not on anticoagulation presents Saturday night with a red, swollen, and painful RLE. No fevers or chills.
  - → IVF, empiric antibiotics for cellulitis and orders a RLE Doppler
- **Vitals:** Afebrile, HR 98, BP 108/55, RR 16, O2 sat 98% RA
- **Exam:**
  - General: awake, alert, cooperative. In mild distress 2/2 pain.
  - CV: RRR, no MRG.
  - MSK: RLE tender, erythematous, warm to touch distally. No fluctuance or purulence. She is diffusely TTP overlying the area. Mild pitting edema of R>LLE. Intact pulses.
- **Labs:** WBC 12.3, CBC otherwise normal. CMP normal. Lactate 2.1. D-dimer 785. Doppler RLE is ordered, but won't be performed until the techs arrive on Monday morning.

How many people would anticoagulate her?

Case 4: Ms. Nidus has cellulitis + POCUS!

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IVC 0.9cm diameter with almost 100% collapsibility with inspiration

Normal LVEF

Soft tissue US +cobblestoning, no deep fluid pockets

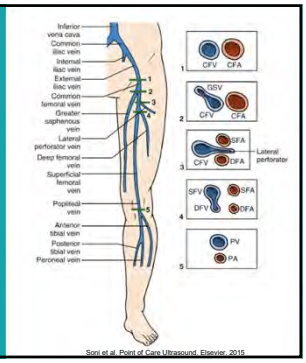
DVT US non-collapsible at level of common femoral vein

UCSF School of Medicine

Demo: Soft Tissue Ultrasound

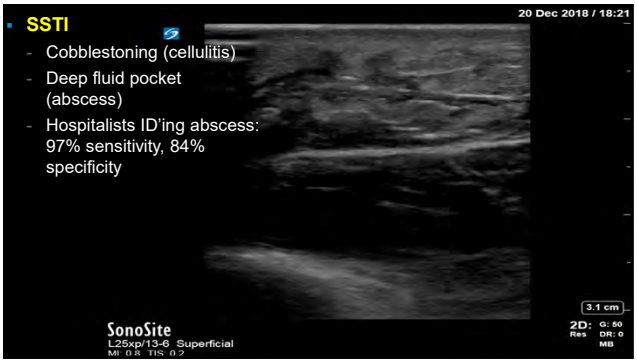
UCSF School of Medicine

Demo: DVT US

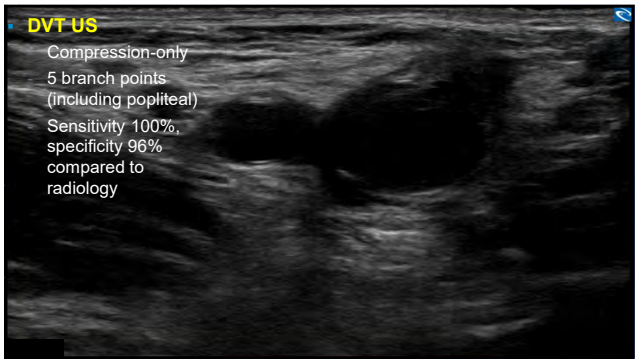


Soni et al. Point of Care Ultrasound. Elsevier, 2015

- **SSTI**
  - Cobblestoning (cellulitis)
  - Deep fluid pocket (abscess)
  - Hospitalists ID'ing abscess: 97% sensitivity, 84% specificity



- **DVT US**
  - Compression-only
  - 5 branch points (including popliteal)
  - Sensitivity 100%, specificity 96% compared to radiology



Case 4 Resolution

- POCUS diagnosis: cellulitis, no abscess, +DVT. Safe for further fluid resuscitation.
- You give an additional 1L IVF → lactate, BP normalizes
- You start her on therapeutic lovenox for DVT seen on POCUS; confirmed by radiology DVT study 36 hours later.
- She tolerates oral antibiotics well, cellulitis improves. Prior to discharge, switch to oral DOAC with plans to follow up with a community PCP

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Case 4 Take Home Points

- In a resource-limited environment (overnights, weekends) POCUS can lead to faster initiation of appropriate therapy
- POCUS can help guide fluid resuscitation in the setting of hypotension or tachycardia.
- Just because you POCUS, doesn't mean you can't order the formal study!

So why do we POCUS?

- Earlier diagnosis and treatment
- Avoids additional tests and reduces radiation exposure
- Safe treatment monitoring, prognostication
- Skills are attainable and lead to better quality care delivery than exam alone

POCUS doesn't replace the physical exam; it enhances the physical exam.

It IS the physical exam

Data for the POCUS we covered

Exam	Statistical Performance
IVC	Correlation coefficient 0.7-0.9
LVEF	LR +5.4; LR -0.2
Pericardial Effusion	LR +7.7; LR -0.0
Pulmonary Edema	Sensitivity 94%; Specificity 92%
Pleural Effusion	Sensitivity 93%; Specificity 96%
Hydronephrosis	Sensitivity 94%; Specificity 93%
DVT	Sensitivity 100%; Specificity 96%
Abscess	Sensitivity 97%; Specificity 84%

Data for POCUS Algorithms

- Rapid Ultrasound in Shock and Hypotension (RUSH)

	Shock Type Based on Final Diagnosis				
	Hypovolemic (n = 16)	Cardiogenic (n = 20)	Obstructive (n = 11)	Distributive (n = 11)	Mixed (n = 11)
Sensitivity	100%	90%	90.9%	72.7%	63.6%
Specificity	96.2%	98%	98.2%	100%	98.2%
PPV[†]	88.9%	94.7%	90.9%	100%	87.5%
NPV	100%	97%	98.3%	95.1%	93.3%
Kappa (P Value)	0.92 (0.000)	0.89 (0.000)	0.89 (0.000)	0.81 (0.000)	0.70 (0.000)

- BLUE protocol for dyspnea/hypoxia

Findings	Diagnosis	Sensitivity (%)	Specificity (%)
A lines (normal)	Asthma/COPD	89	97
Diffuse B lines (>2 lung zones)	Pulmonary edema	97	95
Loss of pleural line, consolidation, patchy B lines	Pneumonia	89	94
A lines without pleural sliding, lung point	Pneumothorax	81	100

What is the scope of POCUS in HM?

TABLE 1. Common POCUS applications for hospitalists

Cardiac	Pulmonary	Abdominal	Vascular	MSK	Procedural
LV assessment	Pleural effusion	Free fluid	DVT	Cellulitis	Paracentesis
RV assessment	Interstitial syndromes	Kidney size	AAA	Abscess	Thoracentesis
Atrial size	Alveolar syndromes	Hydronephrosis		Joint effusions	CVC placement
Right atrial pressure (IVC/JJ)	Pneumothorax	Bladder volume		Fractures	PIV placement
Pericardial effusion		Gallbladder			Arterial line placement
Chamber hypertrophy		Spleen size			Arthrocentesis
Gross valvular abnormalities		Liver size			Abscess drainage
					Lumbar puncture

Multisystem

Hypotension and shock: cardiac, RAP, pulmonary, DVT, abdominal free fluid
Resuscitation: cardiac, RAP, pulmonary
Dyspnea: pulmonary, Cardiac, RAP, DVT
Acute renal failure: renal, bladder, IVC, pulmonary

LV, left ventricle; RV, right ventricle; IVC, inferior vena cava; IJ, internal jugular vein; DVT, deep venous thrombosis; AAA, abdominal aortic aneurysm; CVC, central venous catheter; PIV, peripheral intravenous catheter; RAP, right atrial pressure.

Soni et al, "Point-of-Care Ultrasound for Hospitalists: A Position Statement of the Society of Hospital Medicine." JHM 2019

How should you integrate POCUS into your practice?

- Many factors to think through:
  - Context
  - Frequency
  - Difficulty
  - Data

Scope of POCUS in HM at UCSF

TABLE 1. Common POCUS applications for hospitalists

Cardiac	Pulmonary	Abdominal	Vascular	MSK	Procedural
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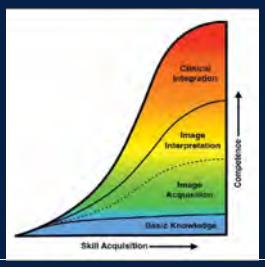
Soni et al, "Point-of-Care Ultrasound for Hospitalists: A Position Statement of the Society of Hospital Medicine." JHM 2019

Addressing Barriers

- Hardware
- Training
- Time and money constraints
- Credentialing and privileging

https://www.krestonreeves.com/news-and-events/12/07/2019/address-business-growth-barriers

POCUS Learning Pathways



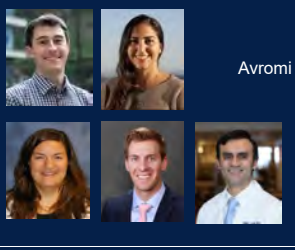
- Pursue a certificate program (SHM, CHEST)
- Attend workshops (SHM, ACP, AIUM, UCSF)
- Learn from local experts (EM, critical care colleagues)
- Self-learning, ad hoc (FOAMed)

 Soni et al. Cert of POCUS. JHM 2017 UCSF

Our institution's experience

Getting started…

- Champion(s)
- Leadership buy-in
  - Education
  - Research
  - Cost savings
  - Clinical outcomes



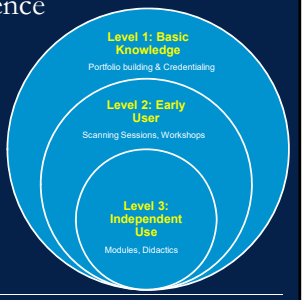
Avromi

 UCSF

Our institution's experience

Building momentum…

- Training program development
- Equipment investment



 Conner et al, POCUS Journal, in press. UCSF

Making it official

1. Privileging and Credentialing
2. Quality assurance
3. Integration into EMR and billing

IMAGE HERE:
Notary stamp?

 UCSF

"The larger issue now is to decide whether we believe that – in this case hospitalists – building competency in ultrasound among generalist physicians will enhance patient safety, quality, and value. **Personally, I do."**

- Bob Wachter, 2012

UCSF

Review of Session Goals

- What is POCUS for hospitalized patients?
- Why learn POCUS?
- How POCUS is used (cases + demo)?
- How to get started with POCUS (for you & your institution)?

POCUS is the future of the physical exam.

UCSF

Questions?

- **Trevor.Jensen@ucsf.edu**

Credit: University of South Carolina Point of Care US

NOTES

High Yield Neurological Examination

Vanja Douglas, MD
Sara & Evan Williams Foundation Endowed Neurohospitalist Chair
Director, Neurohospitalist Division
Associate Professor of Clinical Neurology
UCSF Department of Neurology

Disclosures

None

Purpose of Neuro Exam

- Screen asymptomatic patients
- Screen patients with symptoms that could indicate a focal neurologic lesion (e.g. back pain, headache, seizure)
- Localize the lesion in patients with neurologic deficits
  - Generate a differential diagnosis
  - Decide what test to get next (e.g. brain MRI, spine MRI, EMG/NCS, CK)

Typical "Screening" Neuro Exam

- Mental Status: Level of alertness, orientation, attention, language, memory
- Cranial Nerves: II through XII
- Motor: Bulk, tone, power in all muscles in both arms and legs
- Sensory: Light touch, vibration/joint position sense, pain/temperature, Romberg
- Reflexes: Biceps, triceps, brachioradialis, knees, ankles, plantar response
- Coordination: Finger-nose-finger, heel-knee-shin
- Gait: Observe gait, include tandem, heel, and toe walking

High Yield Screening Neuro Exam

- Mental Status
- Cranial Nerves
- Motor
- Sensory
- Coordination
- Reflexes
- Gait

Language

Expressive Aphasia	
Fluency	Impaired
Comprehension	Intact
Repetition	Impaired

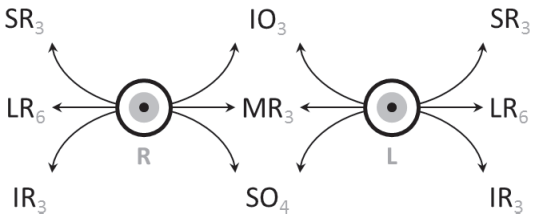
Receptive Aphasia	
Fluency	Intact
Comprehension	Impaired
Repetition	Impaired

Conduction Aphasia	
Fluency	Intact
Comprehension	Intact
Repetition	Impaired

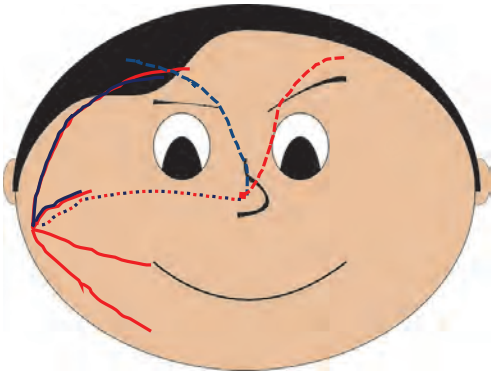
High Yield Screening Neuro Exam

- Mental Status: language, orientation, and attention
- Cranial Nerves
- Motor
- Sensory
- Coordination
- Reflexes
- Gait

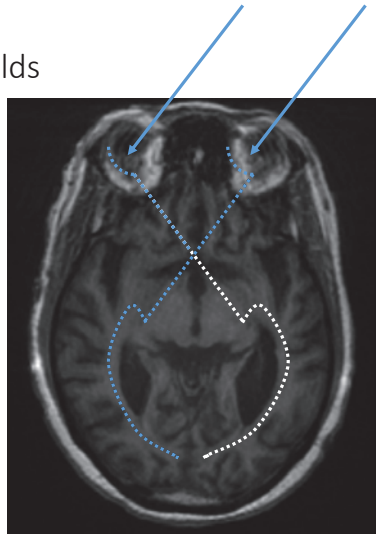
Extraocular Movements



Facial Symmetry



Visual Fields



High Yield Screening Neuro Exam

- Mental Status: language, orientation, and attention
- Cranial Nerves: visual fields, eye movements, and facial symmetry
- Motor
- Sensory
- Coordination
- Reflexes
- Gait

Motor System

2 minute screen for upper motor neuron weakness:

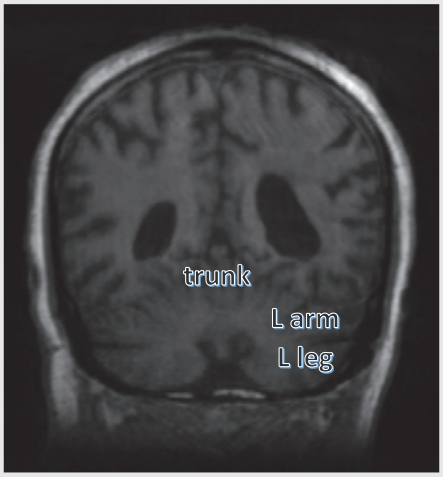
- Pronator Drift
- Finger taps & Foot taps
- Distal extensor power:
  - Finger extensors
  - Tibialis anterior

High Yield Screening Neuro Exam

- Mental Status: language, orientation, and attention
- Cranial Nerves: visual fields, eye movements, and facial symmetry
- Motor: Pronator drift, finger and foot taps, finger extensor and extensor hallucis longus power
- Sensory
- Coordination
- Reflexes: Biceps, knees, and ankles
- Gait

Coordination & Gait

- Hemispheres:
  - Finger-nose-finger
  - Heel-knee-shin
- Vermis:
  - Gait



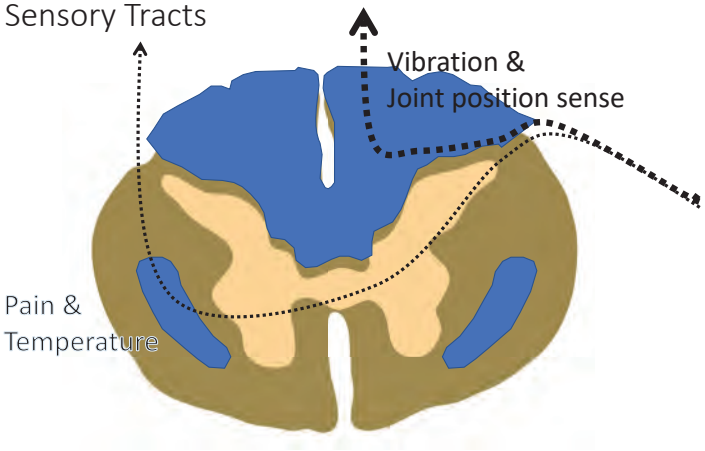
High Yield Screening Neuro Exam

- Mental Status: language, orientation, and attention
- Cranial Nerves: visual fields, eye movements, and facial symmetry
- Motor: Pronator drift, finger and foot taps, finger extensor and extensor hallucis longus power
- Sensory
- Coordination: Finger-nose-finger and heel-knee-shin (can replace HKS with gait)
- Reflexes: Biceps, knees, and ankles
- Gait: Observe gait (base, stride, posture, arm swing, turn), tandem

Why Do A Sensory Exam?

- If there are sensory complaints
- If there are balance complaints or a gait disorder
- If there is weakness

Sensory Tracts



High Yield Screening Neuro Exam

- Mental Status: language, orientation, and attention
- Cranial Nerves: visual fields, eye movements, and facial symmetry
- Motor: Pronator drift, finger and foot taps, finger extensor and extensor hallucis longus power
- Sensory: (If done, do pain OR temp + vibration OR JPS)
- Coordination: Finger-nose-finger and heel-knee-shin (can replace HKS with gait)
- Reflexes: Biceps, knees, and ankles
- Gait: Observe gait (base, stride, posture, arm swing, turn), tandem

Think Like A Neurologist

- Chief Complaint: suspected localization
- History: refine the localization
- Exam: pick maneuvers that rule in or rule out your suspicions

Let's practice!

Case Scenarios

Patient #1

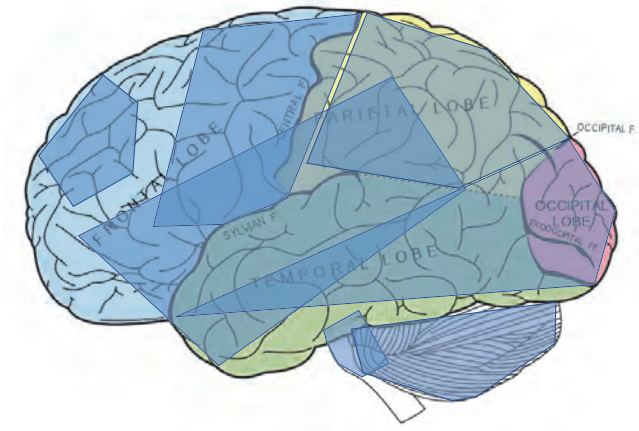
- A 23 y/o woman with a history of migraine headaches is admitted to the hospital with left leg cellulitis. On hospital day 2, she complains of a new headache. She says it's different from her previous migraines because it is "much worse" and is wondering if she needs an MRI.

Headache

Suspected localization

- Focal brain lesion

Hypothesis-Driven Neuro Exam



Patient #2

- 57 y/o man hospitalized with MI is altered after his cardiac cath. He is somnolent but arousable, mumbling incoherently. His family is very concerned that he has had a stroke.

Altered Mental Status

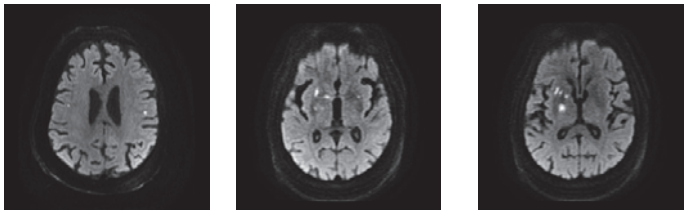
Suspected localization

- Bilateral hemispheres
- Brainstem

Patient #2 Exam

- Arouses to touch
- Names simple objects, repeats short phrases, follows simple commands
- Disoriented and unable to test attention
- EOMI; face symmetric; blinks to threat bilaterally
- Left arm drifts and hand is clumsy
- Withdraws less briskly to pain in the left leg
- Head CT is normal

Multifocal Strokes



Patient #3

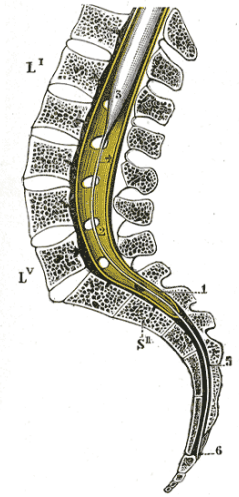
- A 65 y/o man with prostate cancer presents with bilateral leg weakness and urinary urgency.

Bilateral Leg Weakness

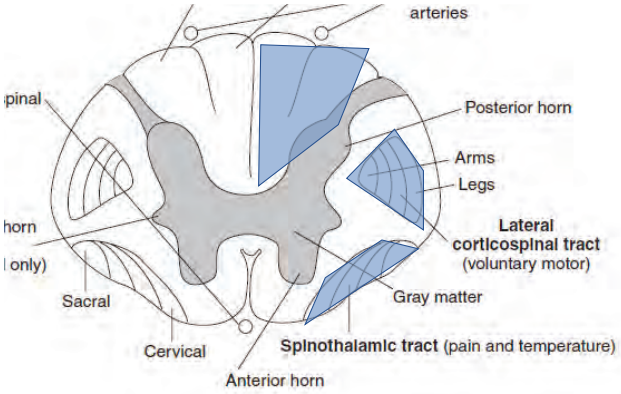
Suspected localization

- Spinal cord
- Cauda equina
- Neuropathy
- Neuromuscular junction
- Muscle

	UMN	LMN
Pattern of Weakness	Pyramidal	Variable
Function/Dexterity	Slow alternate motion rate	Impairment of function is mostly due to weakness
Tone	Increased	Decreased
Tendon Reflex	Increased	Decreased, absent or normal
Other signs	Babinski sign, other CNS signs (e.g. aphasia, visual field cut)	Atrophy (except with problem of neuromuscular junction)



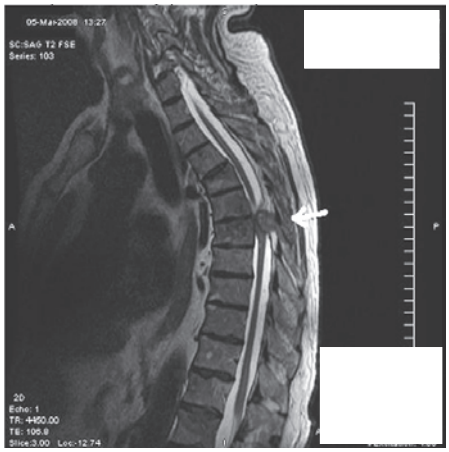
Spinal Cord Cross-Section



Patient #3: Exam

- Decreased EHL power bilaterally
- Slow foot taps
- Brisk knee jerk and ankle jerk reflexes
- Reduced joint position sense in toes
- Sensory level to pinprick at T5

Metastastic Spinal Cord Compression



Patient #4

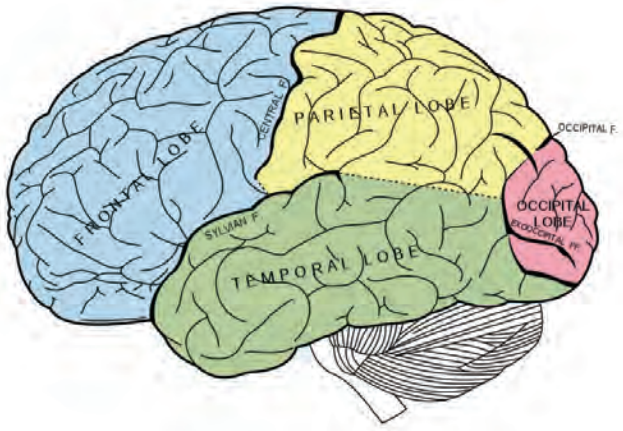
- A 30 y/o woman with lupus, APLAS, and history of endocarditis on gentamycin presents with acute vertigo.

Vertigo

Suspected localization

- Brainstem (central)
- Cerebellum (central)
- Inner ear (peripheral)

Hypothesis-Driven Neuro Exam



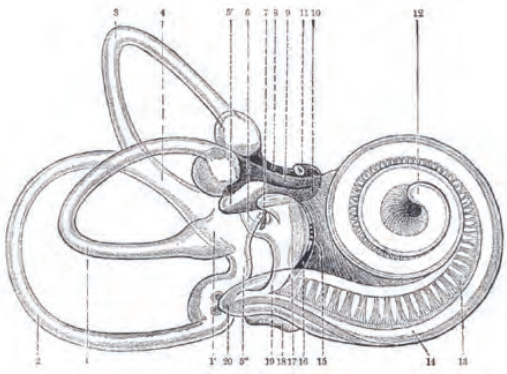
HINTS

- Head Impulse Test
  - Abnormal = peripheral
- Nystagmus
  - Unidirectional = peripheral
  - Direction-changing = central
- Test of Skew
  - Skew deviation = central
- https://youtu.be/1q-VTKPweuk

Patient #4: Exam

- Left beating nystagmus in left-gaze only
- Positive head thrust test to the right

Gentamycin Toxicity



Summary

- High yield screening exam
- Hypothesis driven approach to:
  - Suspected focal brain lesion
  - Altered mental status
  - Suspected spinal cord lesion
  - Vertigo

Bonus Case

- A 32 y/o woman presents with tingling in the hands and feet that progressed to diffuse weakness in the arms and legs over four days. She is now so weak she can no longer sit up.

Diffuse Weakness

Suspected localization

- High spinal cord
- Neuropathy
- Neuromuscular junction
- Myopathy

Localization of Weakness

	Pattern of weakness	**Tone**	**Bulk**	**Reflexes**	**Sensory Loss**	**Other**
Upper Motor Neuron	Pyramidal	Spastic	Normal	Increased	Varies	
Anterior Horn Cell	Pyramidal or myotomal	Spastic or normal	Atrophy	Increased or decreased	None	Fascic-ulations
Peripheral Nerve	In distribution of root or nerve	Normal or reduced	Atrophy	Decreased	Prominent	
Neuro-muscular Junction	Diffuse	Normal	Normal	Normal (myasthenia) or Absent (botulism)	None	Ptosis and ophthalmo -paresis
Muscle	Proximal > Distal	Normal	Normal or patterned atrophy	Normal	None	

Bonus Case

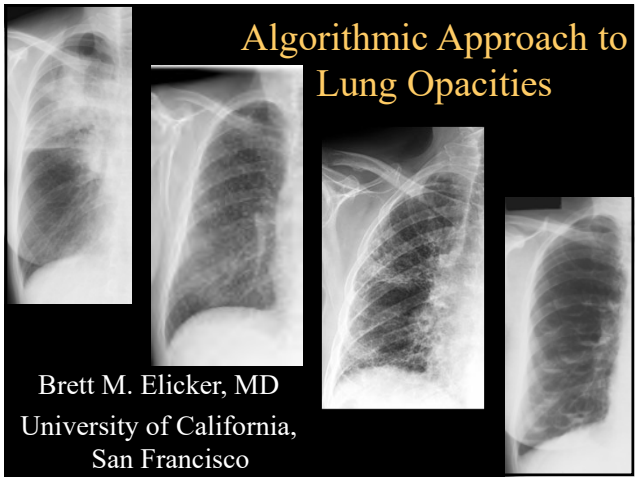
- Diffuse weakness throughout both arms and legs in both flexors and extensors
- No sensory level
- Decreased pinprick sensation in the feet
- Diffusely absent reflexes

Next Step?

- Lumbar puncture:
  - Protein 143
  - WBC 2
- Guillain-Barre Syndrome

Acknowledgements

- Hooman Kamel
- Andy Josephson
- Dan Lowenstein
- Ann Poncelet
- Kamel et al, A randomized trial of hypothesis-driven vs screening neurologic examination. Neurology Oct 2011, 77(14) 1395-1401.

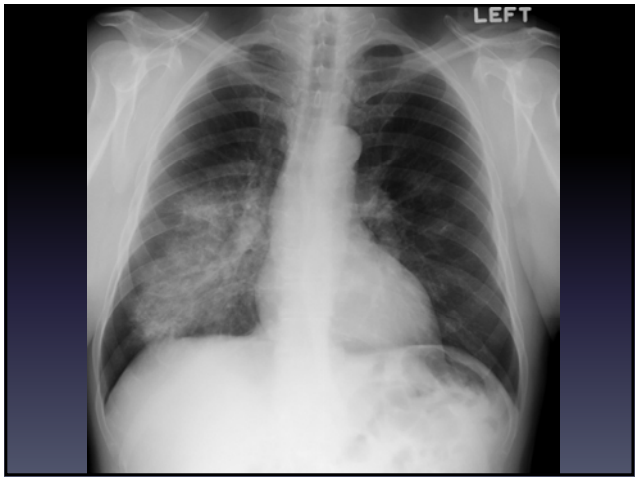


Algorithmic Approach to Lung Opacities

Brett M. Elicker, MD
University of California, San Francisco

Approach to lung opacities

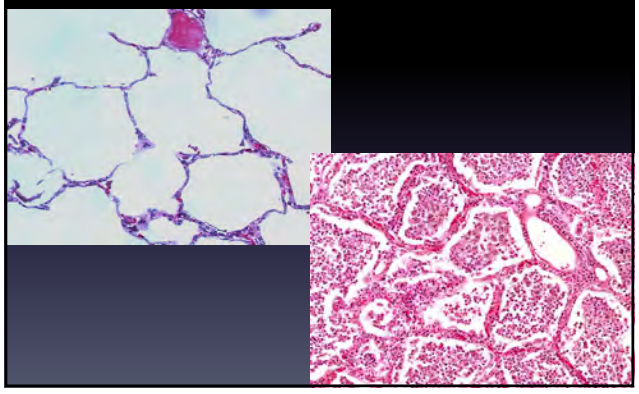
- This is hard!
- You will not be an expert today
- Approach
- Practice
- Think like a pathologist



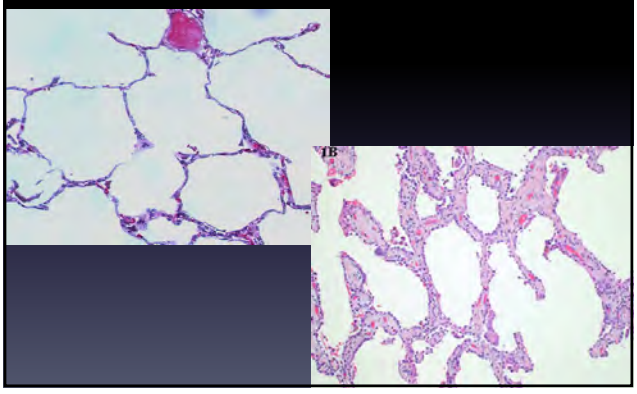
Categories of lung opacities

- 1. Consolidation
- 2. Interstitial (diffuse lines or nodules)
- 3. Airways
- 4. One or a few nodules

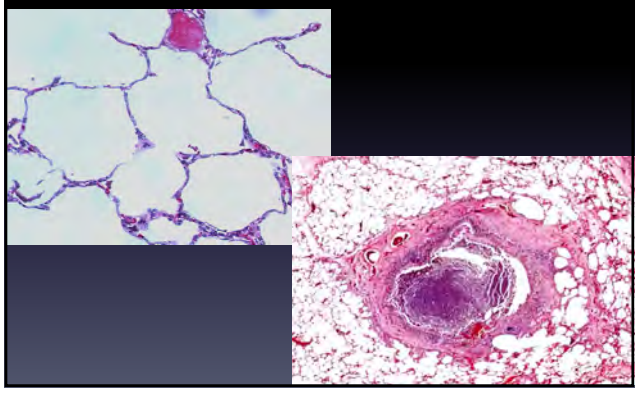
Alveolar



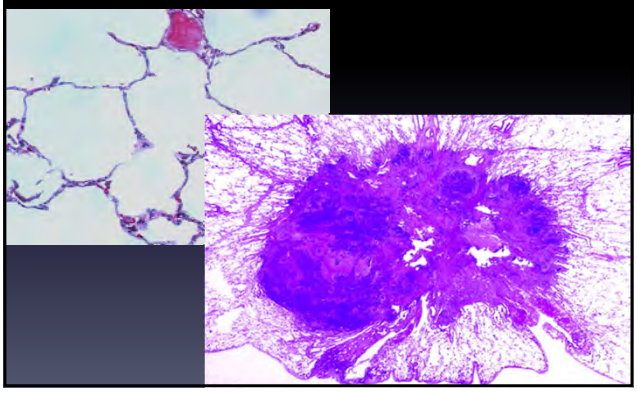
Interstitial



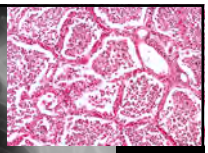
Airways



Not applicable

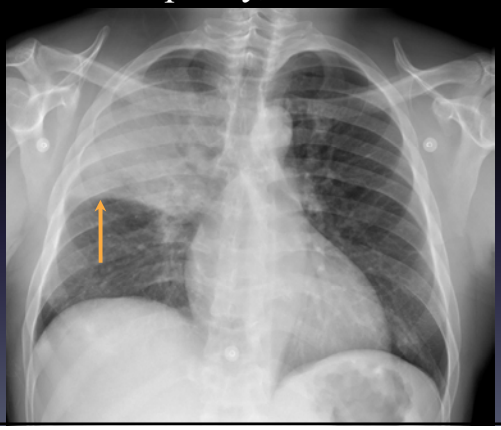


Consolidation

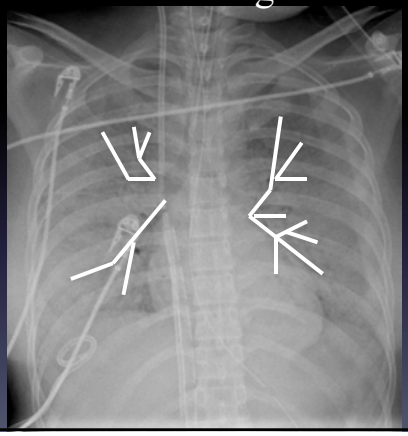


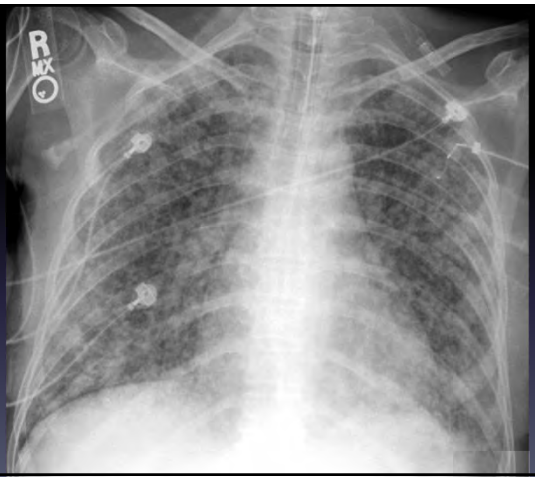
- Confluent opacity
- Fluffy around periphery
- Air bronchograms
- Lack of volume loss

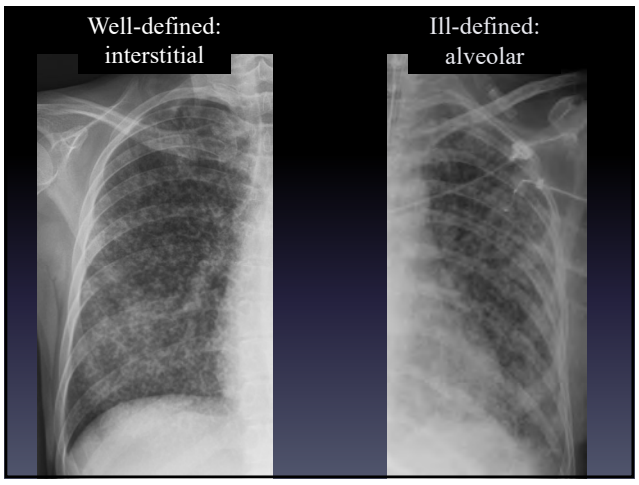
Confluent opacity, no volume loss



Air bronchograms

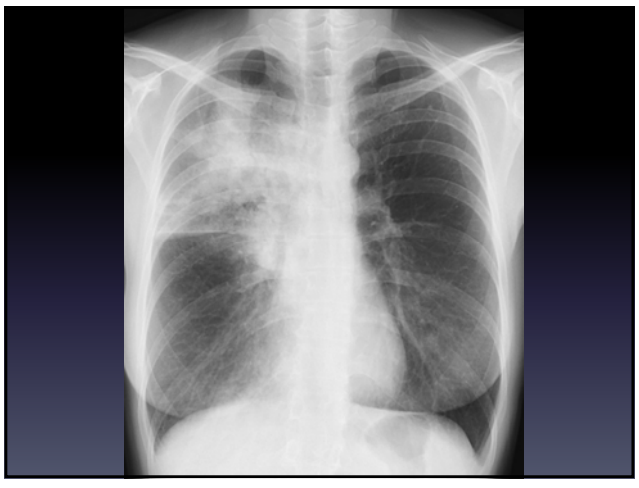


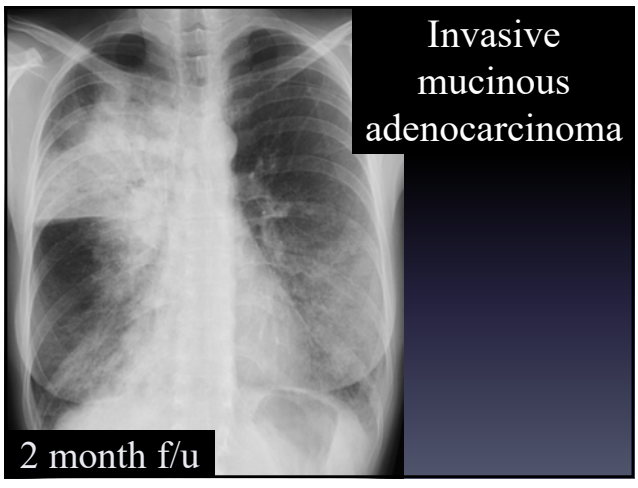




Consolidation

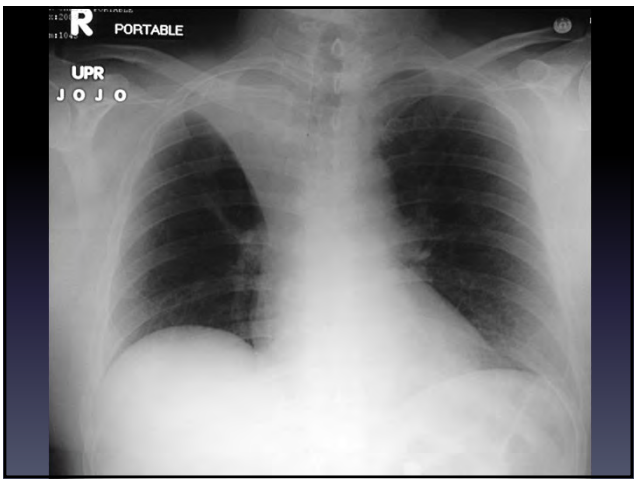
- Acute vs. chronic symptoms
- Distribution
- Acuity of changes
- Differential diagnosis in acute setting
  - Focal: pneumonia/aspiration, hemorrhage
  - Diffuse: edema, acute lung injury, pneumonia, hemorrhage



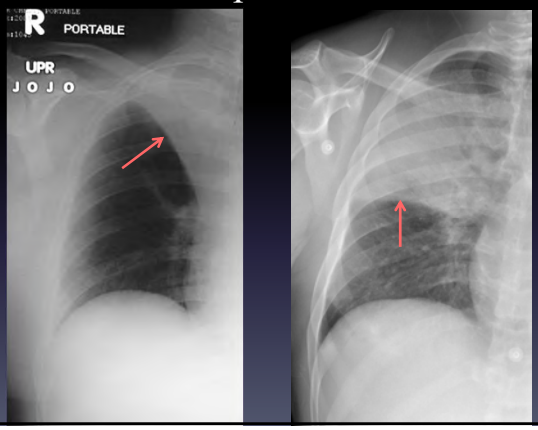


Chronic alveolar disease

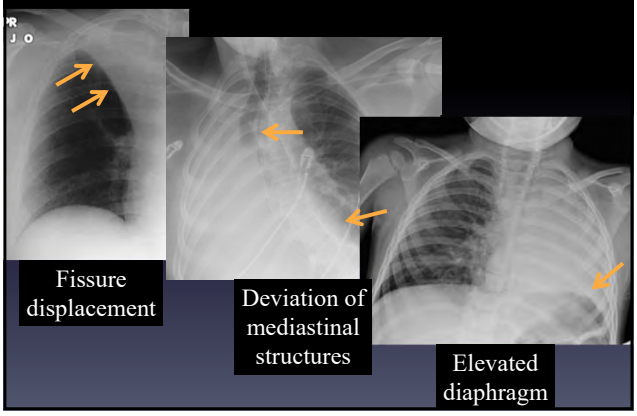
- Tumor
  - Invasive mucinous adenocarinoma (aka multifocal bronchoalveolar CA)
  - Lymphoma (recurrent or 1° pulmonary)
- Inflammatory
  - Organizing pneumonia
  - Chronic eosinophilic pneumonia
  - Sarcoidosis
- Other
  - Lipoid pneumonia
  - Alveolar proteinosis



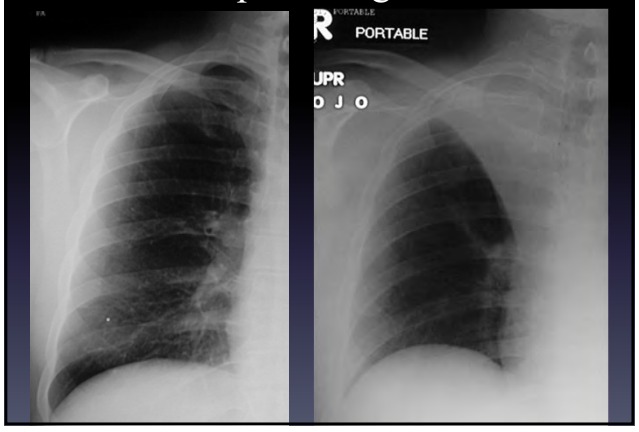
Comparison



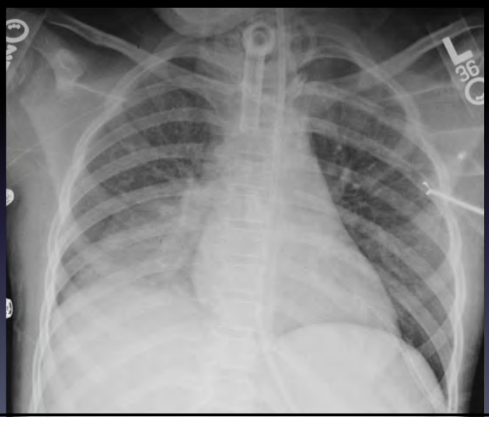
Signs of atelectasis: volume loss



Rapid change

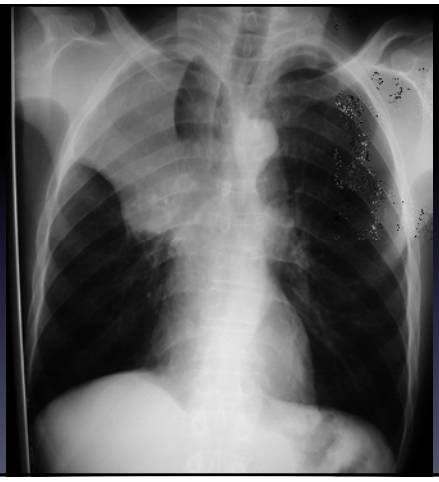


? atelectasis or an alveolar process

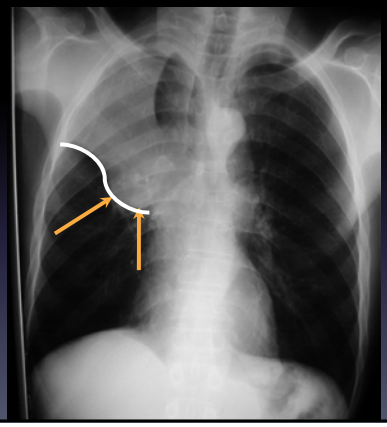


Atelectasis (types)

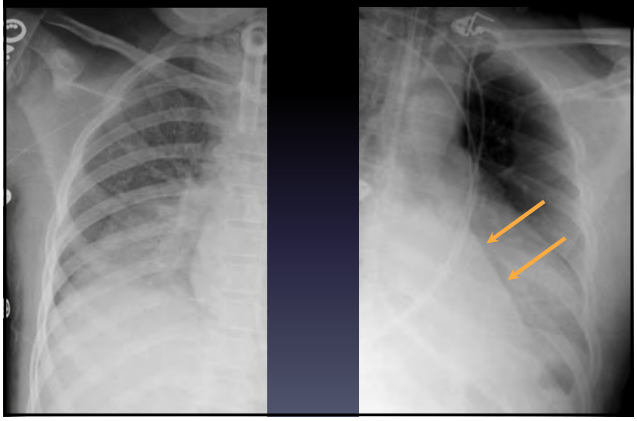
- Obstructive/resorptive (obstruction of bronchus)
- Passive (compression of lungs)
- Cicatricial (related to scarring)
- Adhesive (surfactant deficiency)



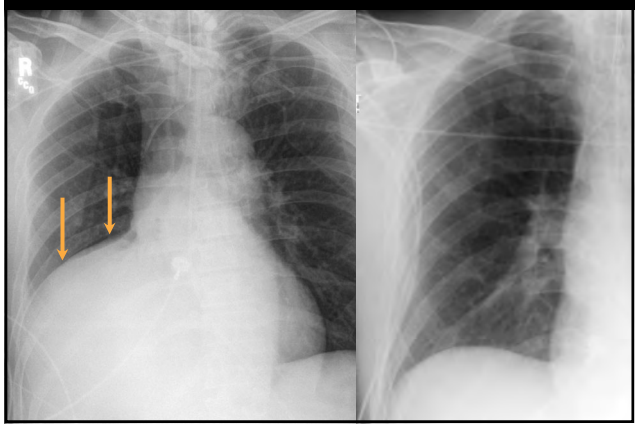
Lung cancer (Golden S sign)

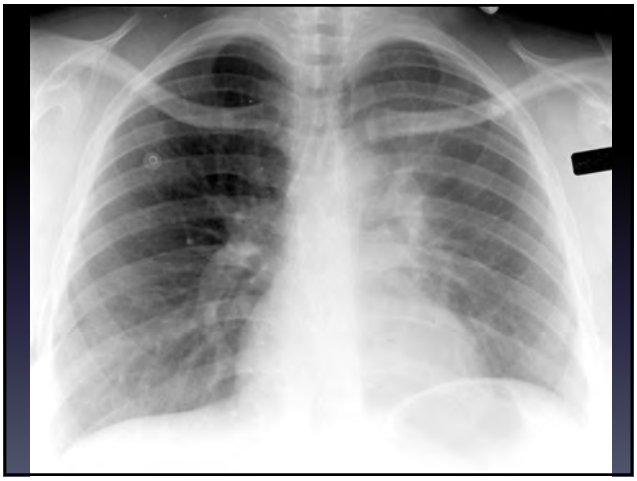


Lower lobe atelectasis

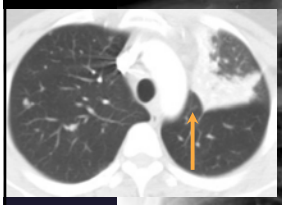


Combined RML/RLL atelectasis

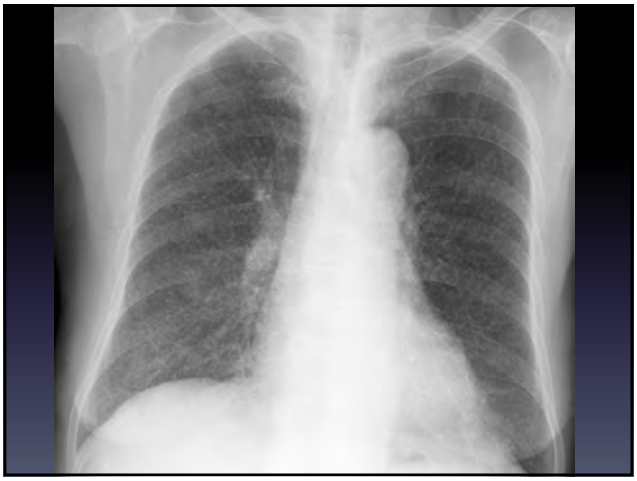




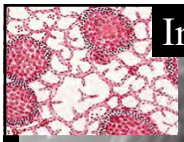
Left upper lobe collapse

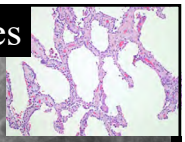


- 1. Veil-like density
- 2. Volume loss
  - Elevated diaphragm
  - Elevated left PA
- Luftsichel sign



Interstitial opacities





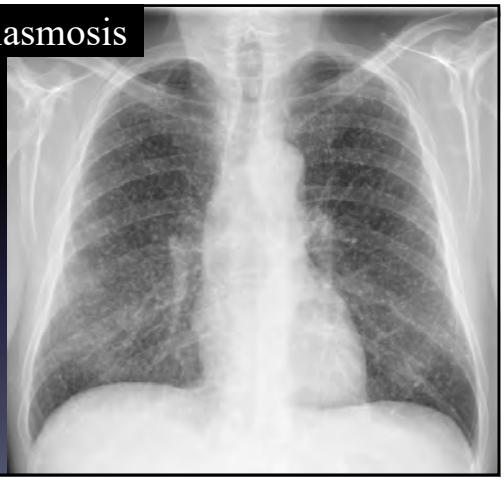
Nodules

Lines

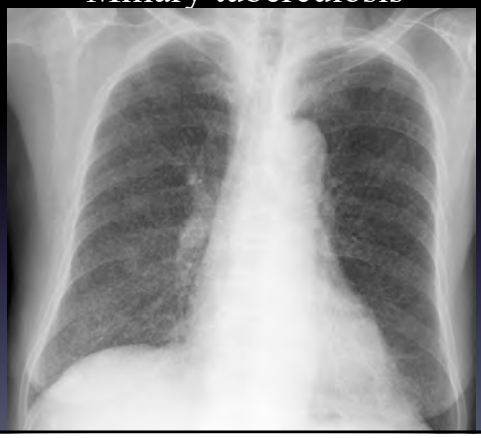
Nodules: diff dx

- Hematogenous spread
  - Miliary tuberculosis
  - Miliary fungal infection (e.g. cocci)
  - Metastases
- Lymphatic spread
  - Sarcoidosis
  - Lymphangitic spread of tumor
  - Pneumoconioses (e.g. silica)

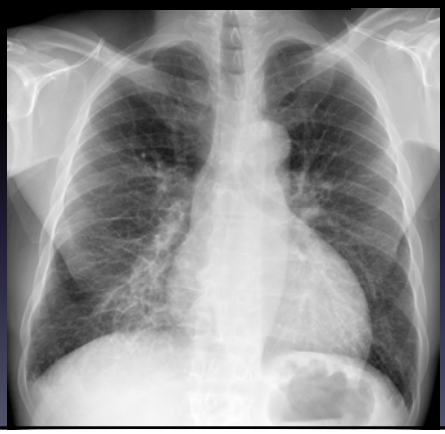
Histoplasmosis



Miliary tuberculosis



Interstitial: lines



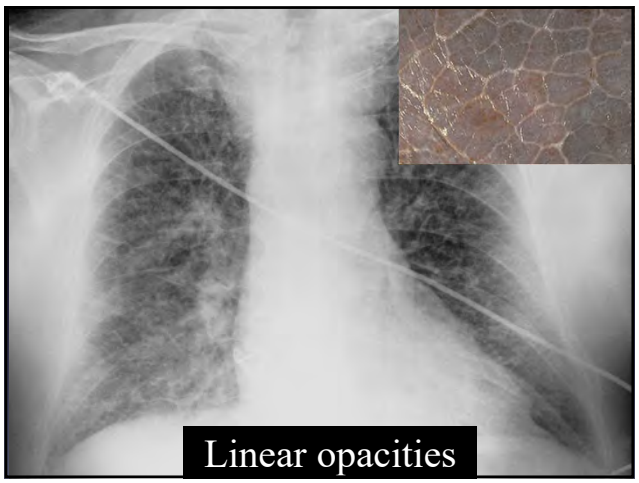
Causes of interstitial lines

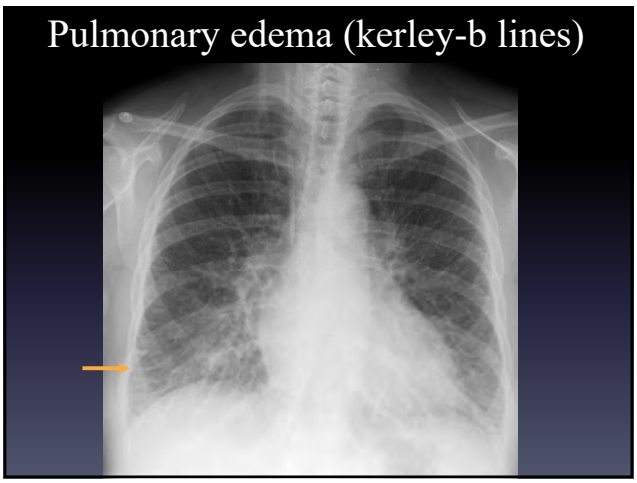
- Edema
- Malignancy

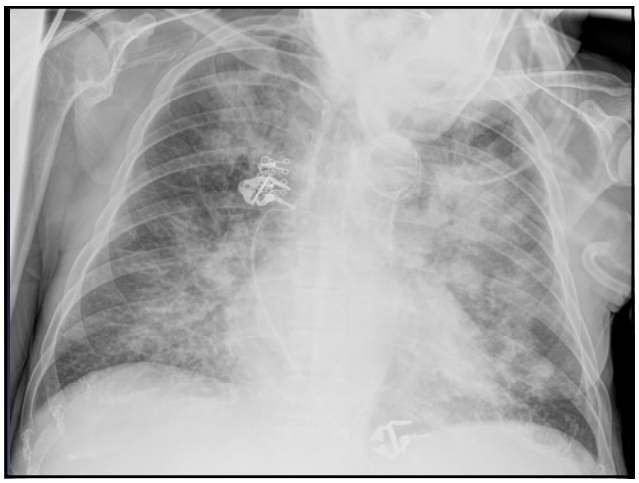
Kerley-b lines may be present

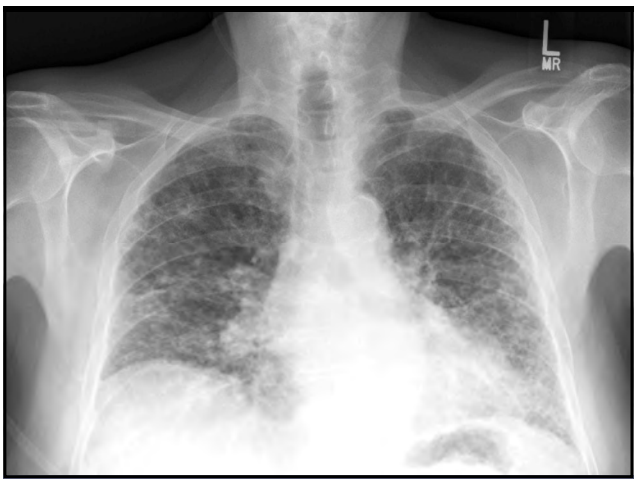
- Fibrotic lung diseases (this is a long list)

These lines are typically thick, wavy and irregular


Linear opacities


Pulmonary edema (kerley-b lines)

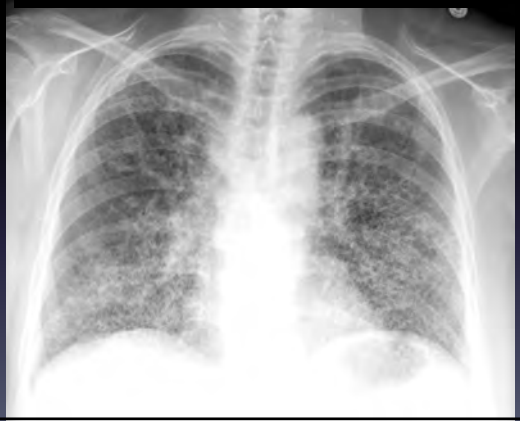



L
MR

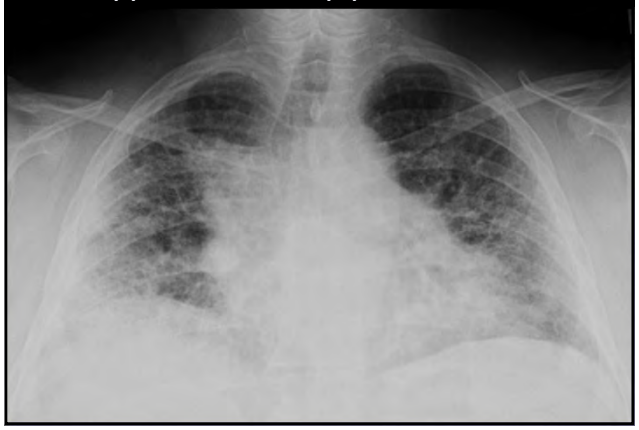
Reticular opacities (distribution)

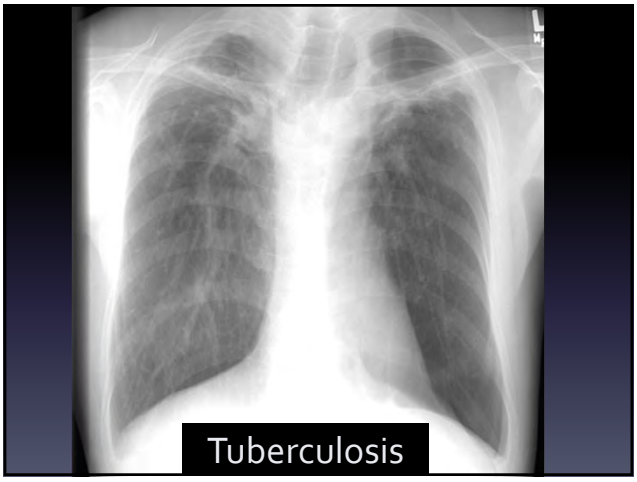
- Lower lobe predominant
  - Idiopathic pulmonary fibrosis
  - Connective tissue disease
  - Drugs
  - Asbestosis
  - Hypersensitivity pneumonitis
- Upper lobe predominant
  - Sarcoidosis
  - Prior TB/fungus
  - Pneumoconioses

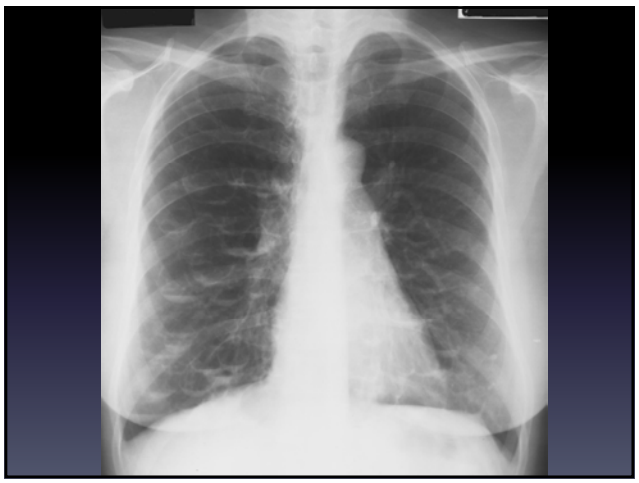
Idiopathic pulmonary fibrosis

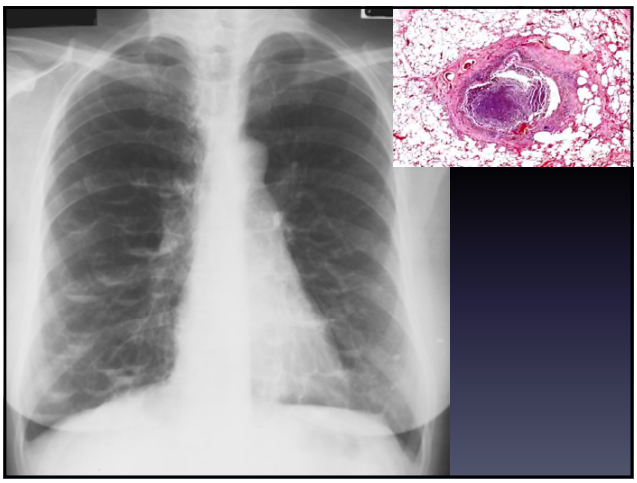


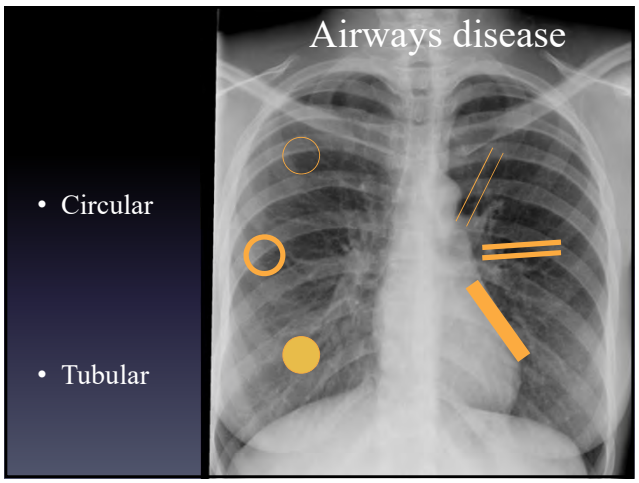
Hypersensitivity pneumonitis

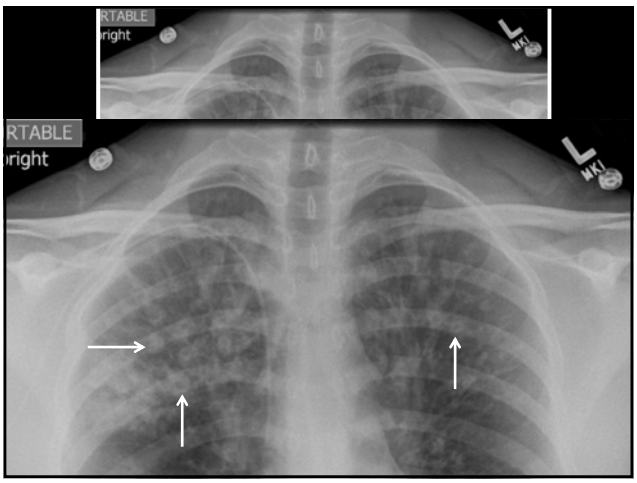








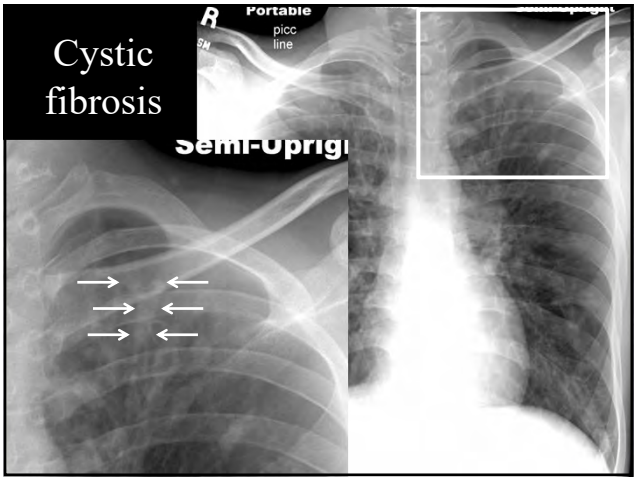

Airways disease
• Circular
• Tubular



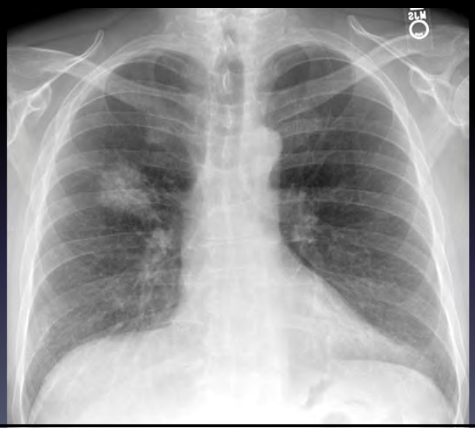
Differential diagnosis of airways disease

- Mild:
  - Asthma
  - Viral infection
  - Chronic bronchitis
  - Etc.
- Severe:
  - Bronchiolitis obliterans
  - Immunodeficiency
  - Ciliary dyskinesia
  - Cystic fibrosis
  - ABPA
  - Tuberculosis
  - Cartilage diseases

Cystic fibrosis

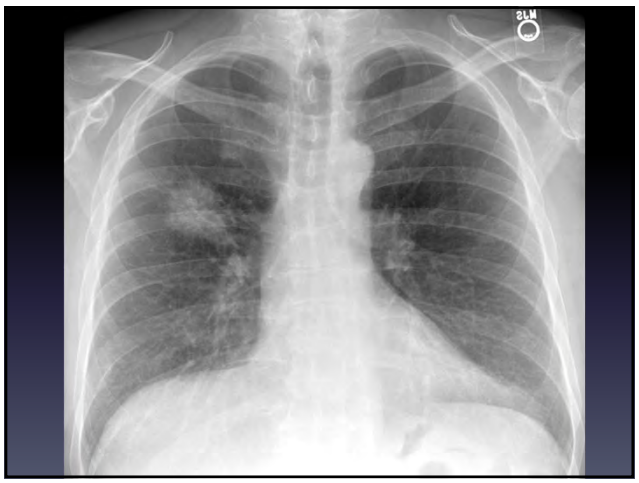


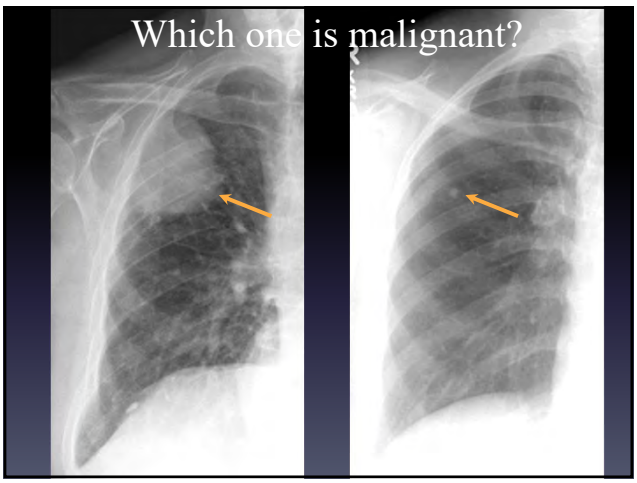
Which compartment of lung is affected?



Solitary pulmonary nodule: differential diagnosis

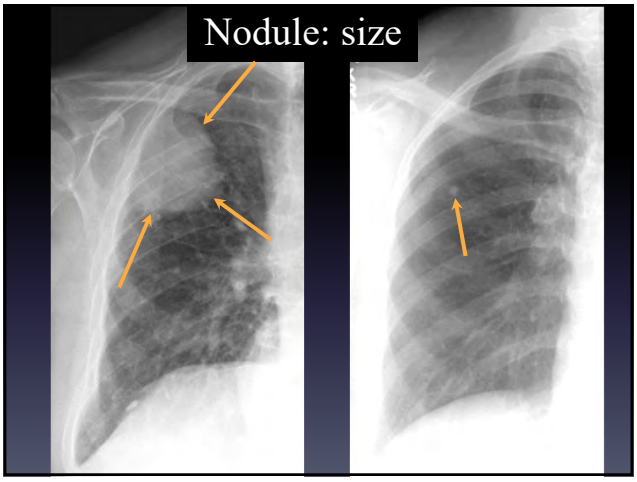
- Granuloma
- Hamartoma
- Primary bronchogenic carcinoma
- Metastasis
- Lots of others

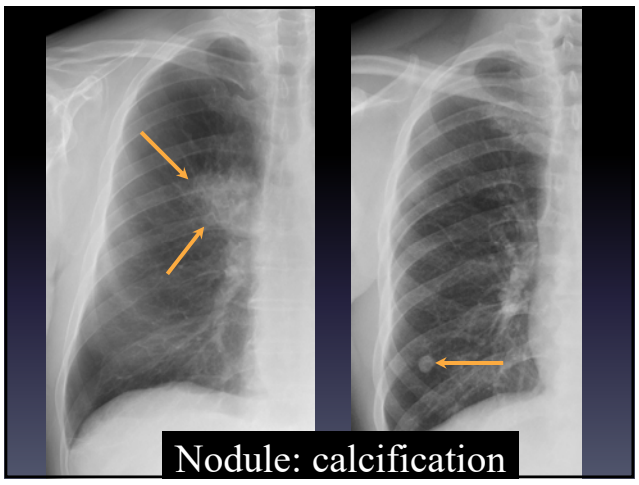


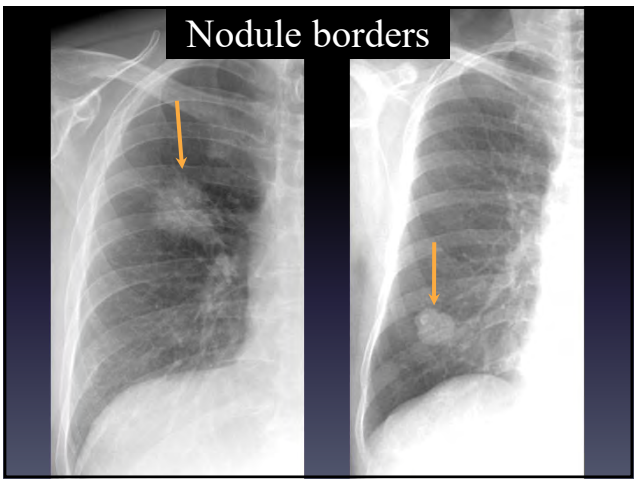


Nodules: benign vs. malignant

Benign	Malignant
Small size	Large size
Smooth border	Spiculated border
Diffuse calcification	No or irregular calcification
Stability over time	Growth over time

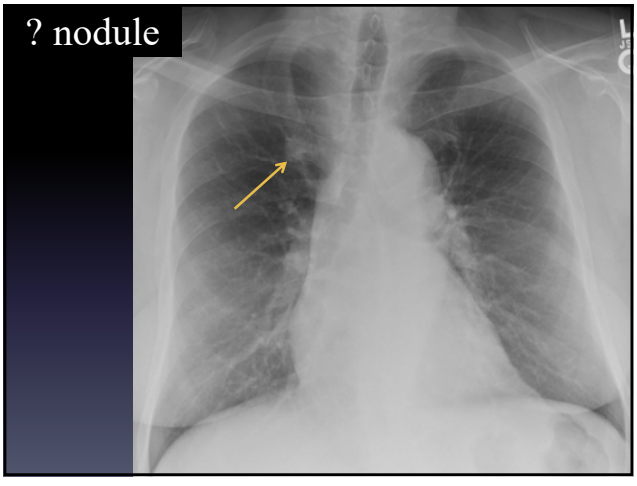




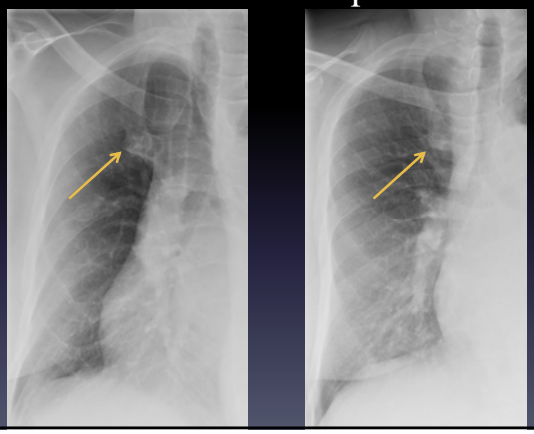


So you see a nodule on CXR…

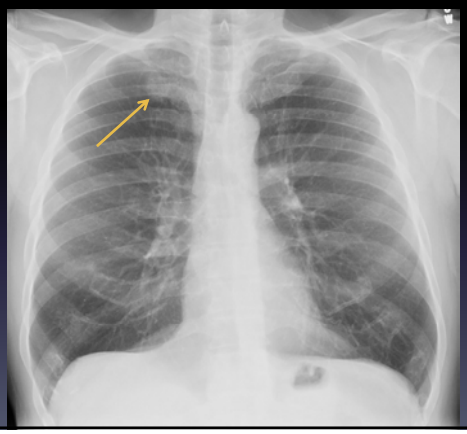
- 1. Is it actually a nodule?



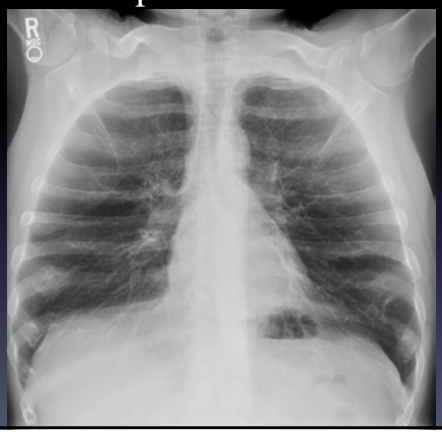
Shallow obliques



? nodule



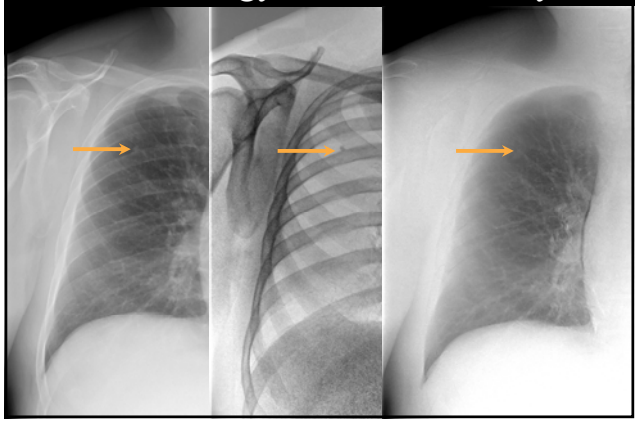
Apical lordotic



So you see a nodule on CXR…

- 1. Is it actually a nodule?
- 2. Look for prior films?
- 3. Is diffuse calcification present?

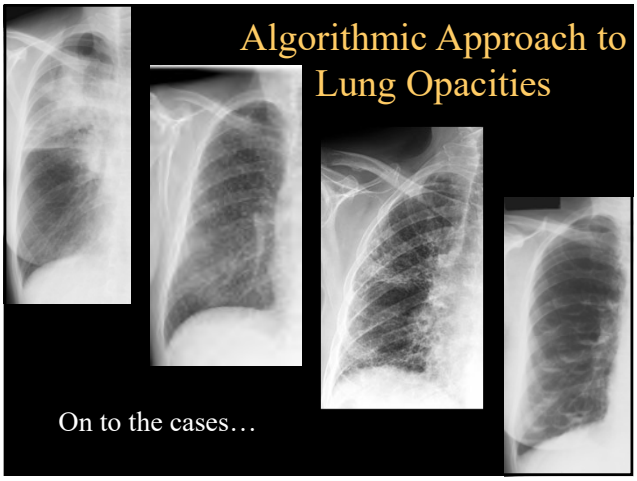
Dual energy subtraction x-ray



So you see a nodule on CXR…

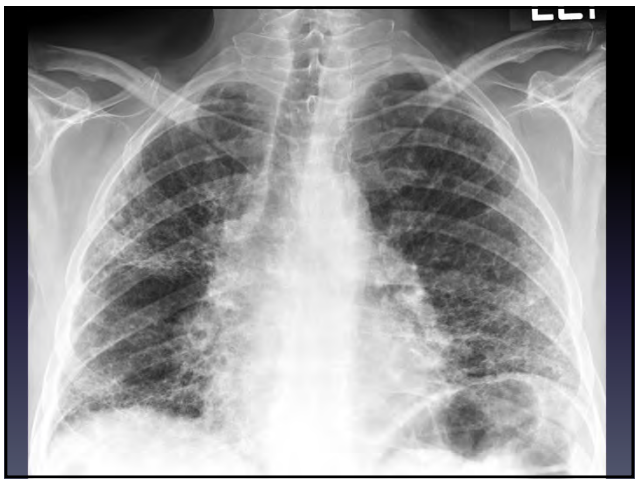
- 1. Is it actually a nodule?
- 2. Look for prior films?
- 3. Is diffuse calcification present?
- 4. Get a CT scan or a follow-up CXR

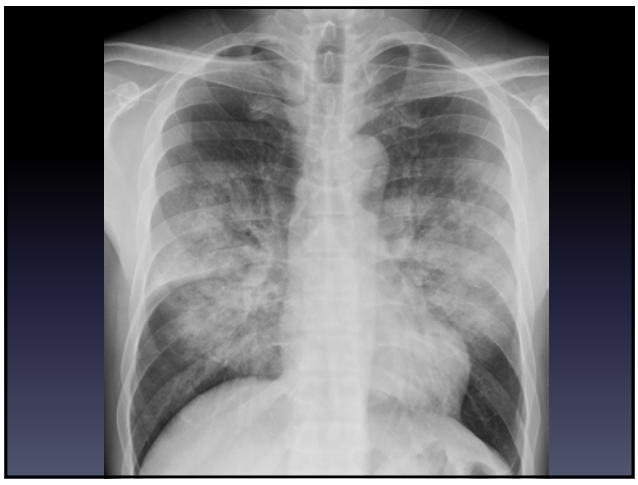
Category	Subcategory	CXR features	Common causes
Alveolar		•Confluent opacities •Air bronchograms •Fluffy edges	•Edema •Acute lung injury •Infection
Interstitial	Nodules	•Small, well-defined nodules •Opacities not confluent •Normal lung between nodules	•Tuberculosis •Fungal infection •Metastases •Sarcoidosis
	Lines (kerley-b)	•Thin, fine, delicate lines •Lines at periphery of lung (kerley-b)	•Pulmonary edema •Cancer
	Lines (reticular)	•Thick, wavy, irregular lines	•Fibrotic lung disease
Airways		•Circular or tubular •Thin or thick walled	•Numerous causes
Not in a single compartment		•One or a few nodules (≤3 cm) or masses (>3 cm)	•Lung cancer •Metastasis •Granuloma •Hamartoma

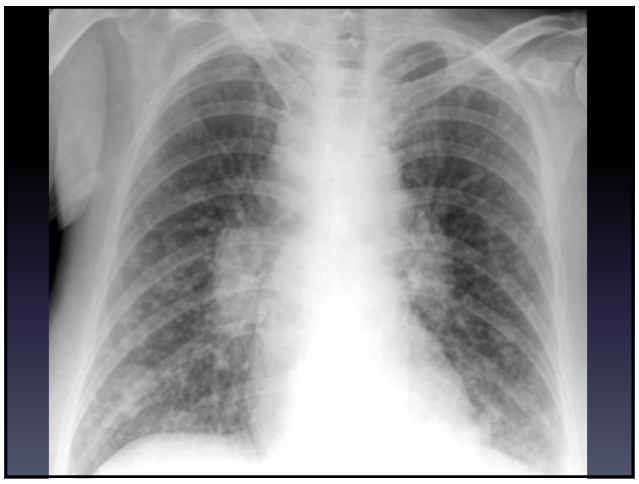


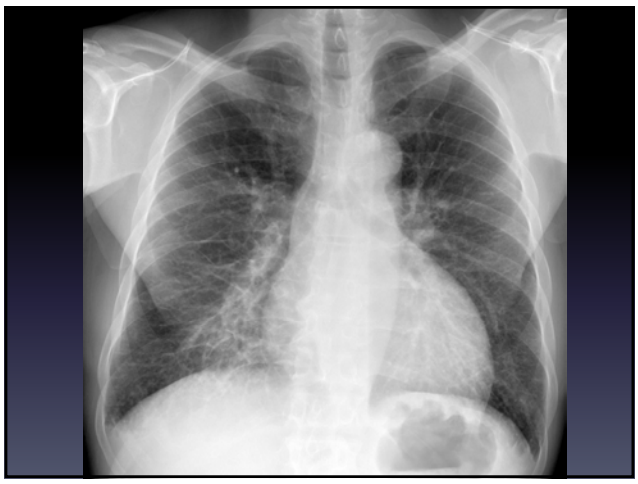
Algorithmic Approach to Lung Opacities

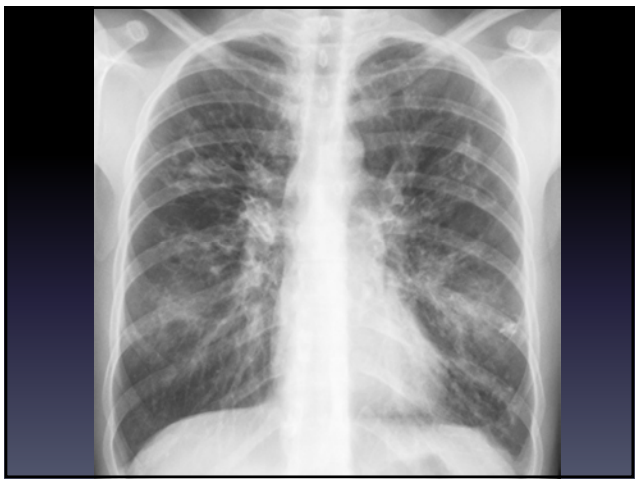
On to the cases…

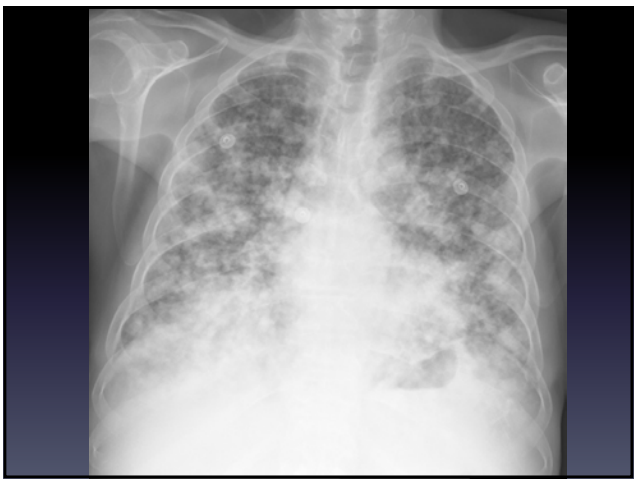












THROMBOEMBOLISM Q & A 2021

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Objectives

- Lingering questions from this mornings presentations
- Duration of anticoagulation for VTE
- Approach to subsegmental PE, calf vein DVT and superficial vein thrombosis
- Role of thrombophilia work up
- Resuming anticoagulation after a bleed

Resources

- AC Forum clinical guidance-VTE, splancnic vein, reversal etc. https://acforum.org/web/education-guidance.php
- University of Washington Anticoagulation http://depts.washington.edu/anticoag/home

Case

51 year old man with no PMHX presents with acute CP and SOB, BP stable, HR 120s O2 sat 92%, d-dimer 1500, CT PE with bilateral PE in all lobes with RV/LV ratio > 1.0. BNP 370, trop 1.5. He is started on rivaroxaban. He has no identifiable provoking factors. How long should he remain on anticoagulation?

1) At least 3 months
2) One year
3) Forever

ESC PE Guidelines-Duration of Therapy

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[c]	DURATION OF AC
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures	≥ 3 months
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight	ESC: Suggest indefinite CHEST 2021 Recommend AGAINST indefinite Weak rec/mod evid
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease	
	No identifiable risk factor		
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome	Recommend indefinite

Konstantinedes et al. Eur Heart J. 2019;

Table 4 Estimated risk of venous thromboembolic disease recurrence after anticoagulants discontinuation in proximal deep vein thrombosis

Estimated risk of recurrence	Risk factor category for index DVT	Examples
Low (<3%/year)	Major transient/ reversible risk factors	• Surgery with general anaesthesia for longer than 30 min • Confined to bed in hospital (only "bathroom privileges") for at least 3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8%/year)	Minor transient/ reversible risk factors	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Obesity (high body mass index) • Ongoing oestrogen therapy • Pregnancy or puerperium • Confined to bed out of hospital for at least 3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for at least 3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel and active autoimmune diseases (risk may change depending on activity and treatment)[a]
High (>8%/year)	Major persistent risk factors	• One or more previous episodes of VTE in absence of a major transient or reversible factor • Active cancer • Antiphospholipid antibody syndrome • Major hereditary thrombophilia[b] • Strong family history[c]
Variable	First episode with no identifiable risk factors	Higher recurrency risk: men, proximal DVT, concomitant PE, high D-dimers at anticoagulation discontinuation, age

Mazzolai et al European Journal of Preventative Cardiology

Duration of Anticoagulation for VTE: 2016 CHEST and AC Forum Guidelines/Guidance

Indication	CHEST 2021[1]	AC Forum 2016[2]
1st provoked VTE	3 mo	3 mo (surgical)[a] ≥3 mo (medical)
1st unprovoked VTE	Extended[b]	Extended
2nd unprovoked VTE	Extended[b]	Extended
VTE + cancer	Extended[b]	Extended

[a]Unless risk factors for recurrence persist
[b]No scheduled stop date, unless high bleeding risk.
Kearon C et al. *Chest*. 2016;149(2):315-352. Streiff MB et al. *J Thromb Thrombolysis*. 2016;41:32-67

VTE and Bleeding Risk: 2016 CHEST Guideline

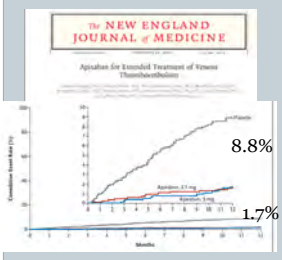
Risk of Major Bleeding After 3 Mo of Anticoagulation, %/y	Low (*0 risk factors*)	Moderate (*1 risk factor*)	High (*≥2 risk factors*)
Baseline risk	0.3	0.6	≥2.5
Increased risk	0.5	1.0	≥4.0
Total risk	0.8	1.6	≥6.5

Risk Factors for Bleeding with Anticoagulation

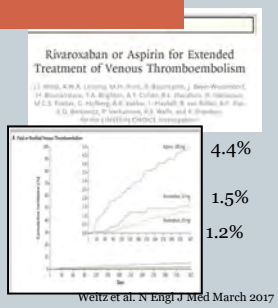
- **Age >65 y**
- **Age >75 y**
- **Previous bleeding**
- **Cancer**
- **Renal or hepatic failure**
- **Thrombocytopenia**
- **Previous stroke**
- **Diabetes**
- **Anemia**
- **Antiplatelet therapy**
- **Poor anticoagulation control**
- **Recent surgery**
- **Frequent falls**
- **Alcohol abuse**
- **NSAID use**

Reprinted from Ch.F. Dunn et al, Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report, 315-352, with permission from the American College of Chest Physicians.

CHEST 2021-suggest reduced dose DOAC over full dose for extended phase anticoagulation



Agnelli etal NEJM 2013



Weitz et al. N Engl J Med March 2017

UNPROVOKED VTE

- All - 3-6 months of FULL intensity anticoagulation
  - At 3-6 months determine candidacy for secondary prevention
- ~50% will develop recurrent VTE in 10 years off anticoagulation; Case fatality rate of VTE is ~4% in all comers but closer to 9% in PE
- Case fatality rate of bleeding is ~10%
- Case by case decision…consider continuation if not high bleeding risk. Most compelling in low bleed risk patients and in those with PE

Secondary Prevention Options
Low dose DOAC***
Full dose anticoagulation
ASA

Do not use dose reduced DOAC:
Cancer
Recurrent VTE on AC
Obesity

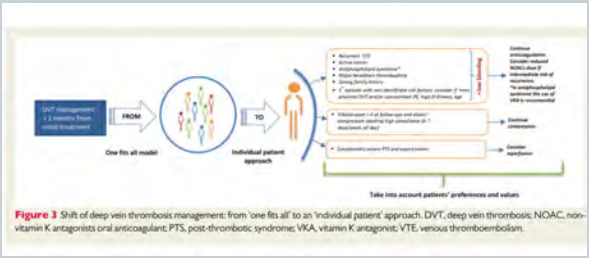


Figure 3 Shift of deep vein thrombosis management: from 'one fits all' to an 'individual patient' approach. DVT, deep vein thrombosis; NOAC, non-vitamin K antagonists oral anticoagulant; PTS, post-thrombotic syndrome; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Mazzolai et al European Journal of Preventative Cardiology

Case

51 year old man with no PMHX presents with acute CP and SOB, BP stable, HR 120s O2 sat 92%, d-dimer 1500, CT PE with bilateral PE in all lobes with RV/LV ratio > 1.0. BNP 370, trop 1.5. He is started on rivaroxaban. He has no identifiable provoking factors. How long should he remain on anticoagulation?

1) At least 3 months
2) One year
3) Forever

After 6 months you:
1. Continue full dose rivaroxaban
2. Reduce dose of rivaroxaban to prophylactic intensity
3. Transition to ASA

Subsegmental PE

A 77 yo man had undergoes colectomy for recurrent bleeding from diverticulosis. On POD # 3 he becomes tachycardic to the 110s. WBC is elevated.The surgical team orders an abdominal CT which shows a fluid collection concerning for early abscess. It also shows an isolated RLL subsegmental PE. A dedicated CTa shows a single isolated RLL subsegmenral PE. Do you anticoagulate this patient?

a) Sure, it is a PE.
b) No this is incidental. Let's pretend we don't know it is there

Isolated Subsegmental PE

Definition: PE shown on CT angiography that occurred in a subsegmental branch but no larger order of vessels. The subsegmental PE may involve one or more than one subsegmental branch

Identification of ISSPE has tripled over past decade

Isolated Subsegmental PE

Anticoagulant treatment for subsegmental pulmonary embolism

Hugo HB Yoo[1], Thaís HAT Queluz[2], Regina El Dib[2]

[1]Department of Internal Medicine, Botucatu Medical School, UNESP - Univ Estadual Paulista, Botucatu, Brazil. [2]Department of Anaesthesiology, Botucatu Medical School, UNESP - Univ Estadual Paulista, Botucatu, Brazil

Contact address: Hugo HB Yoo, Department of Internal Medicine, Botucatu Medical School, UNESP - Univ Estadual Paulista, Distrito de Rubiao Junior, s/n, Campus de Botucatu, Botucatu, Sao Paulo, 18618-970, Brazil. hugo@ibnb.unesp.br.

Editorial group: Cochrane Vascular Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2016.
Review content assessed as up-to-date: 15 December 2015.

Citation: Yoo HHB, Queluz THAT, El Dib R. Anticoagulant treatment for subsegmental pulmonary embolism. *Cochrane Database of Systematic Reviews* 2016, Issue 1. Art. No.: CD010222. DOI: 10.1002/14651858.CD010222.pub3.

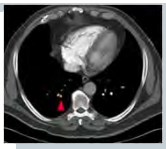
Summary of main results

There is currently no evidence from randomised controlled trials to assess the effectiveness and safety of anticoagulation therapy versus no intervention in patients with isolated subsegmental pulmonary embolism (SSPE) or incidental SSPE.

Isolated Subsegmental PE

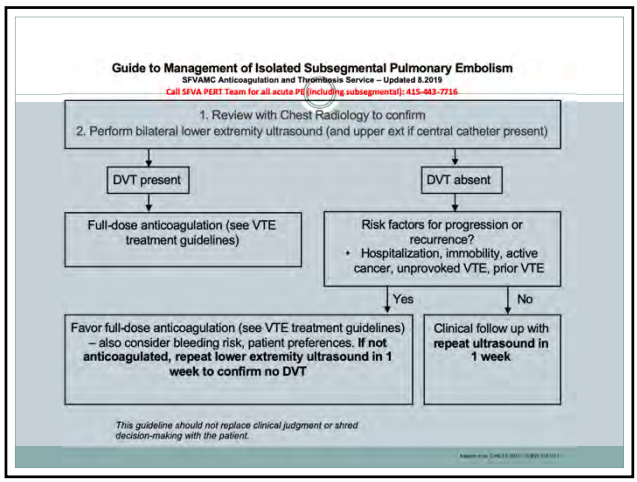
Whether to Anticoagulate Subsegmental PE

***19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation** (Grade 2C) **or (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C).



IS IT REAL?
ISSPE is more likely to be TRUE if....good quality scan, mult defects, centrally located, d-dimer elevated, seen on mult cuts, patient symptomatic vs incidental;high pretest prob of PE
Get u/s of bilateral lower extrem (upper if CVC)
Consider risk of recurrence-higher if not post op; immobile; active cancer
IF high bleed risk –don't AC: get serial u/s

Kearon et al. Chest. 2016;149(2):315-352.



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Superficial Vein Thrombosis

A 67 year old man with cirrhosis, new diagnosis of HCC is admitted with diarrhea, lowish BP and AKI. On exam he has bilateral lower extremity swelling, R> L. In the ED he has an ultrasound which shows thrombosis of the greater saphenous vein extending from the calf proximally and terminating 6 cm from the deep femoral vein. What do you recommend?

a. Prophylactic fondaparinux
b. Prophylactic rivaroxaban
c. Full dose DOAC or warfarin
d. Full dose LMWH
e. Warm compresses, no anticoagulation

Superficial Vein Thrombosis –CHEST Guidelines

- Factors that favor the use of AC : extensive SVT; above the knee, close to saphenofemoral junction; severe symptoms; involvement of the greater saphenous vein; history of VTE or SVT; active cancer; recent surgery
- In patients with superficial vein thrombosis of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B).

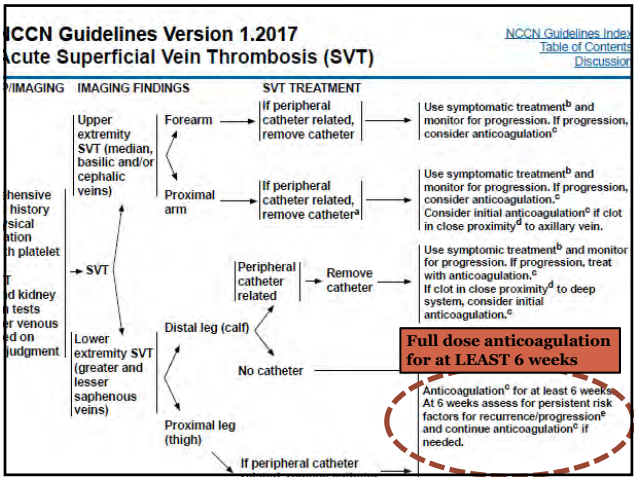
CALISTO TRIAL- fonda vs placebo
Primary outcome 1% vs 6%

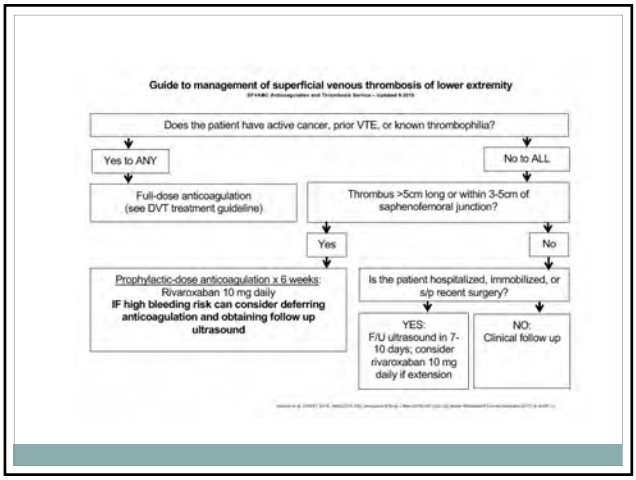
Kearon C et al. *Chest*. 2012

Superficial Vein Thrombosis

Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 2b trial

- >400 pts symptomatic SVT riva 10 mg v fonda 2.5mg
- Symptomatic above the knee SVT of at least ≥ 5 cm length + other risk factor (>65 , male,hx VTE , cancer, autoimmune disease, non-varicose veins)
- No difference in primary efficacy outcome
- After 6 weeks 7% recurrence risk in high risk patients (v 1.2% in CALISTO)





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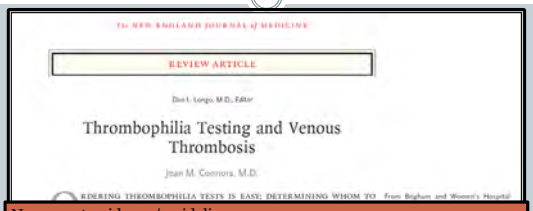
a. Prophylactic fondaparinux
b. Prophylactic rivaroxaban
c. Full dose DOAC or warfarin
d. Warm compresses, no anticoagulation

Thrombophilia Testing

50 year old man presents with unprovoked PE. He is hemodynamically stable but CT PE shows elevated RV/LV ratio. ECHO is ordered. He is admitted and started on rivaroxaban. Should you send a work up for thrombophilia?

- Yes-why not, he is here.
- No-then I am going to have interpret it and who needs that

Thrombophilia Testing


REVIEW ARTICLE

Thrombophilia Testing and Venous Thrombosis

Jean M. Connors, M.D.

No current guidance/.guidelines
EXCEPT ASH Choosing Wisely Campaign-"do not test in provoked VTE"
Results of thrombophilia testing should RARELY affect clinical decisions about VTE treatment-no strong influence on recurrence risk beyond stratification based on clinical presentation
Can help explain "why"
Can be of interest to family members
Current tests are insufficient for identifying inherited VTE risk

Who should we suspect harbors thrombophilia?

Table 1. Clinical Characteristics Suggestive of Inherited Thrombophilia in Patients with Venous Thromboembolism (VTE).

Thrombosis at a young age (<50 yr), especially in association with weak provoking factors (minor surgery, combination oral contraceptives, or immobility) or unprovoked VTE
Strong family history of VTE (first-degree family members affected at a young age)
Recurrent VTE events, especially at a young age*
VTE in unusual sites such as splanchnic or cerebral veins†

* The antiphospholipid syndrome must also be considered, but it is not inherited.
† Patients with splanchnic-vein VTE should be assessed for myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria.

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UNPROVOKED THROMBOSIS IN YOUNG PATIENT THINK ABOUT:

- PROTEIN C, S, ANTITHROMBIN DEFICIENCY→OFTEN POSITIVE FAMILY HISTORY
- FACTORV LEIDEN MUTATION AND PROTHROMBIN GENE MUTATION -Northern European descent
- APLS-PRIMARY OR SECONDARY (lupus)
- MAY THURNERS SYNDROME- ILIAC VEIN COMPRESSIOJN SYNDROME…LEFT LOWER EXTREM VENOUS COMPRESSION-LEFT ILIAC VEIN COMPRESSED BY RIGHT ILIAC ARTERY
- UPPER EXTREMITY DVT-PAGET SCHROEDERS SYNDROME-THORACIC OUTLET SYNDROME WITH VENOUS COMPRESSION
- NEPHROTIC SYNDROME/IBD/PNH
- PREGNANCY, IVF
- CANCER (less likely < 50 yo)

VENOUS AND ARTERIAL THROMBOSIS

- APLS
- PFO-with paradoxical embolism
- HYPERHOMOCYSTIENEMIA
- SICKLE CELL
- P VERA
- PNH
- HIT
- CANCER
- DIC
- Beurgers disease
- Hyperviscosity-MGUS, MM

Thrombophilia Tests

Table 1. Thrombophilia Tests and Prevalence of Risk Factors.*

Thrombophilia Type	Assay	Prevalence
Inherited		
Increased procoagulant activity (common)		
Factor V Leiden	APCR and PCR	White, 5.0% Hispanic, 2.2% Black, 1.2% Native American, 1.2% Asian, 0.4%
Prothrombin gene mutation	PCR	White, 3%
Decreased anticoagulant activity (uncommon)		
Protein C	Activity assay	<0.5%
Protein S	Activity assay	<0.5%
Antithrombin	Activity assay	<0.5%
Acquired		
Lupus anticoagulants†	In vitro clotting assay: PTT-LA, dRVVT, silica clotting time ELISA: ACL IgG and IgM, beta-2 glycoprotein I IgG and IgM	Overall, 0–5% Patients with VTE, 10–12% Patients with SLE, 35%

The NEW ENGLAND JOURNAL of MEDICINE

Summary of Recommendations Regarding Testing for Thrombophilia.

Table 2. Summary of Recommendations Regarding Testing for Thrombophilia.*

Recommendation	Explanation
Do not test at time of VTE event	Test at completion of anticoagulant therapy for provoked VTE; for unprovoked VTE, test after treatment for acute event if cessation of anticoagulant therapy is contemplated and test results might change management strategy
Do not test while patient is receiving anticoagulant therapy	Test when VKA has been stopped for at least 2 wk, DOAC has been stopped for at least 2 days (preferably longer), and UFH or LMWH for antithrombin levels has been stopped for more than 24 hr
Do not test if VTE is provoked by strong risk factors	Strong risk factors are major trauma, major surgery, immobility, major illness
Consider testing	Consider testing in patients in whom VTE occurs at a young age in association with weak provoking factors or a strong family history of VTE or in patients who have recurrent VTE
Identify goals of testing	Identify goals in order to aid decision-making regarding future VTE prophylaxis, to guide testing of family members (especially regarding risk associated with COC or pregnancy in female family members), and to determine cause (especially for severe VTE, fatal VTE in family members, or VTE in an unusual location); test results alone should not be used for decision making regarding duration of anticoagulant therapy

* COC denotes combination oral contraceptives, DOAC direct oral anticoagulant, LMWH low-molecular-weight heparin, UFH unfractionated heparin, and VKA vitamin K antagonist.

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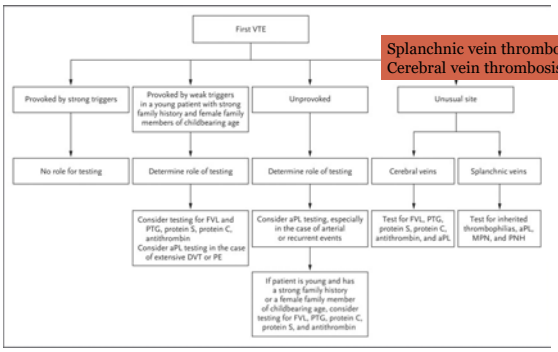
Algorithm for Selecting Patients with a First Venous Thromboembolism (VTE) for Thrombophilia Testing.



Splanchnic vein thrombosis
Cerebral vein thrombosis

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IMPACT OF ANTICOAGULATION & THROMBOSIS ON THROMBOPHILIA LABS

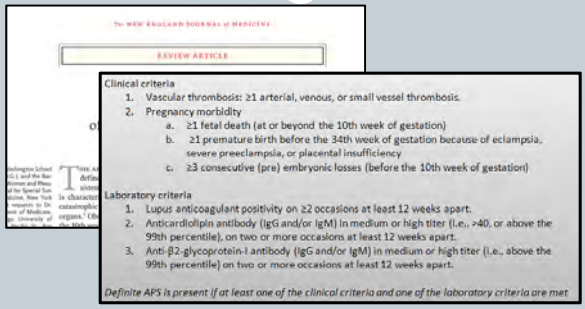
	ACUTE THROMBOSIS	WARFARIN	HEPARIN	DOAC
PROTEIN C,PROTEIN S	↓ (FALSE POSITIVE)	↓(FALSE POSITIVE)	NO EFFECT	FALSE NORAML
ANTITHROMBIN	↓ (FALSE POSITIVE)	↑(FASLE NEGATIVE)	↓(FALSE POSITIVE)	FALSE NORMAL
LUPUS ANTICOAGULANT	NO EFFECT	FALSE POSITVE	FALSE POSITIVE	FASLE POSITIVE
B2GP1, Acl ABS	NO EFFECT	NO EFFECT	NO EFFECT	NO EFFECT
FACTOR V LEIDEN	NO EFFECT	NO EFFECT	NO EFFECT	NO EFFECT
PROTHROMBIN GENE MUTATION	NO EFFECT	NO EFFECT	NO EFFECT	NO EFFECT

DEFER TESTING (3-6 MOS)

RARELY WE SEND APLS ACUTELYIF STRONG SUSPICION

CAN SEND FLV/PTG BUT IN HETEROZYGOUS FORM NOT IMPORTANT

Antiphospholipid Antibody Syndrome



Antiphospholipid Antibody Syndrome

- WHY- risk of recurrence off AC much higher; at risk for arterial disease, bridge therapy; DOACs generally avoided
- WHO- arterial and venous events, unexpected arterial events, recurrent thrombosis ON anticoagulation, underlying autoimmune d/o, prolonged aPTT
- WHAT-send Lupus anticoagulant, Beta 2 glycoprotein antibodies and anticardiolipin antibodies (IgG & Ig M)
- WHEN-LAC-don't do it on anticoagulation; antibodies you can send anytime
- IF POSITIVE-
  - must repeat in 12 weeks-high rate of transient positivity
  - LAC most predicative of 1st and recurrent VTE, triple positives at highest risk

Thrombophilia Testing

50 year old man presents with unprovoked PE. He is hemodynamically stable but CT PE shows elevated RV/LV ratio. ECHO is ordered. He is admitted and started on rivaroxaban. Should you send a work up for thrombophilia?

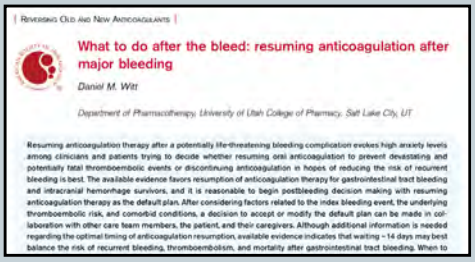
- Yes-why not, he is here.
- No-then I am going to have interpret it and who needs that

What To Do After the Bleed

76 y/o man with CAD (NSTEMI 2006), AFIB CHADS-Vasc=4 on warfarin and ASA is admitted with UGIB. INR is 3.0. He requires 3u PRBCs, vit K and FFP. EGD shows peptic ulcer disease. He is started on high dose PPI therapy, bx for H Pylori done. When should his anticoagulation be restarted?

a) Never
b) In two weeks
c) In three months
d) Let the primary provider deal with this one

What To Do After the Bleed



Reversing Old and New Anticoagulants

What to do after the bleed: resuming anticoagulation after major bleeding

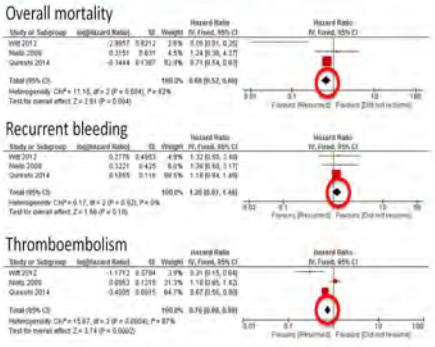
Daniel M. Witt

Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, UT

Resuming anticoagulation therapy after a potentially life-threatening bleeding complication evokes high anxiety levels among clinicians and patients trying to decide whether resuming oral anticoagulation to prevent devastating and potentially fatal thromboembolic events or discontinuing anticoagulation in hopes of reducing the risk of recurrent bleeding is best. The available evidence favors resumption of anticoagulation therapy for gastrointestinal tract bleeding and intracranial hemorrhage survivors, and it is reasonable to begin postbleeding decision making with resuming anticoagulation therapy as the default plan. After considering factors related to the index bleeding event, the underlying thromboembolic risk, and comorbid conditions, a decision to accept or modify the default plan can be made in collaboration with other care team members, the patient, and their caregivers. Although additional information is needed regarding the optimal timing of anticoagulation resumption, available evidence indicates that waiting ~14 days may best balance the risk of recurrent bleeding, thromboembolism, and mortality after gastrointestinal tract bleeding. When to

Witt Hematology 2016

Gastrointestinal Tract Bleeding

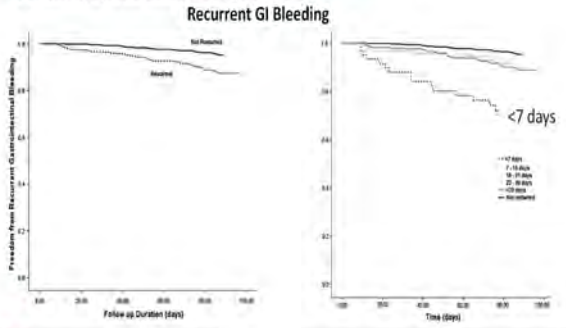


American Society of Hematology

Thromb Haemost 114:819

Gastrointestinal Tract Bleeding

Time-to-event adjusted analyses performed to find an association of restarting warfarin and recurrent GIB, arterial thromboembolism, and mortality.



American Society of Hematology

Am J Card 113:662

AC FORUM Clinical Guidance Antithrombotic Therapy for VTE

"IN THE EVENT OF GI BLEED WE SUGGEST WAITING AT LEAST 7 DAYS WITHOUT EVIDENCE OF ACTIVE BLEEDING AND AFTER ENDOSCOPIC TX BEFORE REINITIATING AC"

GIBs: DOACs vs Warfarin

Table 2
GIBs in studies on patients with AF : DOACs vs warfarin.
Data from: Connolly et al. N Engl J Med 2009;361:1139–1151; Patel et al. N Engl J Med 2011;365:883–891; Granger et al. N Engl J Med 2011;365:981–992; Giugliano et al. N Engl J Med 2013;369(22):2093–104.

	DOAC			Warfarin			DOAC/W (years-pts %)	RR (95% CI) GIB DOAC/W
	GI events (n)	Life-threatening GI events (n)	Total pts. (n)	GI events (n)	Life-threatening GI events (n)	Total pts. (n)		
Dabigatran 110 mg twice daily arm	133	67	6015	120	57	6022	1.12/1.02	1.10 (0.86–1.41) p: 0.43
Dabigatran 150 mg twice daily arm	182	94	6076	120	57	6022	1.51/1.02	1.50 (1.19–1.89) p < 0.001
Rivaroxaban 20 mg once daily arm	224	52 (1 fatal event)	7111	154	47 (5 fatal events)	7125	2.00/1.24	1.46 (1.117–1.902) p < 0.001
Apixaban 5 mg twice daily arm	105	ND	9088	119	ND	9052	0.76/0.86	0.879 (0.624–1.238) p = 0.33
Edoxaban 30 mg once daily arm	129	ND	7002	190	ND	7012	0.82/1.23	0.67 (0.53–0.83) p < 0.001
Edoxaban 60 mg once daily arm	232	ND	7012	190	ND	7012	1.23/1.51	1.23 (1.02–1.50) p = 0.03

ND: not determined.

Di Minno et al. Blood Reviews 2015.

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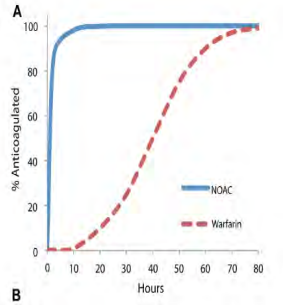
ND: not determined.

Di Minno et al. Blood Reviews 2015.

Resumption of DOACs



Anticoagulation **FULLY** therapeutic within *1-2 hours*

Only dabigatran has a reversal agent

Considerations After GIB on AC

- Reassess risk benefit of anticoagulation
  secondary prevention of VTE therapy, low CHADS-vasc
- Assess risk of rebleeding from source
  identifiable source, treatable lesion?
- Take steps to decrease risk of bleeding related to AC regimen
- Reconsider need for antiplatelet therapy
  if warfarin-was INR in range, is control good?
  spurious elevation in INR or poor TTR →DOAC
  increase INR monitoring->home POC INR?
- If ongoing strong indication for AC determine best time to restart therapy in multidisciplinary meeting with proceduralist -
  Remember DOAC immediately active

What To Do After the Bleed

76 y/o man with CAD (NSTEMI 2006), AFIB CHADS-Vasc=4 on warfarin and ASA is admitted with UGIB. INR is 3.0. He requires 3u PRBC[illegible] peptic ulcer disease. He[illegible] therapy, bx for H P[illegible] anticoagulation be r[illegible]

"Two weeks may provide the best balance among GI bleed recurrence , thromboembolism and mortality""

a) Never
b) In two weeks
c) In three months
d) Let the primary provider deal with this one

Questions?

Tough Cases & FAQs in Perioperative Medicine

Hugo Quinny Cheng, MD
Division of Hospital Medicine
University of California, San Francisco

FAQ in Perioperative Medicine

1. Postoperative Delirium
2. Screening for Postoperative MI
3. Delaying Surgery after MI & Stroke
4. Transfusion Threshold
5. Surgical Risk with Cirrhosis
6. Obstructive Sleep Apnea
7. Curbside Consultation

Postoperative Delirium

An 80-year-old woman falls and sustains a hip fracture at her assisted living facility. She has a history of stroke and uses a walker. She has mild dementia. She is alert, oriented to self & place but not date (baseline).

1. How likely is this patient to develop delirium?
2. What can be done to prevent delirium?
3. What should you do if she becomes delirious?

Postoperative Delirium Guideline

American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults:

Clinical Practice Guideline for Postoperative Delirium in Older Adults
http://archcare.org/static/files/pdf/ags-2014-clinical-practice-guideline-for-postop-delirium-in-older-adults.pdf

Postoperative Delirium in Older Adults: Best Practice Statement from the American Geriatrics Society
http://dx.doi.org/10.1016/j.jamcollsurg.2014.10.019

Postoperative Delirium

Clinical Features:

- Acute, fluctuating disturbance of consciousness
- Reduced ability to focus & attend
- Accompanied by cognitive and perceptual disturbances
- Postop delirium has onset peak 1-3 days after surgery

Usually self-limited but associated with bad outcomes:

- Increased mortality (10-20% rise per 48 hours of delirium)
- Increased LOS, higher risk of institutionalization

Incidence of Delirium

Population	Incidence	Author
Post-hip fracture	44 - 61% (up to one-third delirious on admission)	Berggren et al. Dolan et al.
Elective orthopedic	18%	Fisher et al.
Major elective surgery	9% (46% in aortic surgery)	Marcantonio et al.

Risk Factors (a partial list)

Patient (Chronic) Factors

- Advanced age
- Cognitive impairment
- Functional impairment
- Severe chronic illness
- Substance abuse
- Sensory deficits
- Malnutrition

Acute Factors

- Hip fracture
- Aortic or thoracic surgery
- Fluid / electrolyte disorder
- Sepsis
- Uncontrolled pain
- Polypharmacy
- Anemia
- Kidney injury
- Sleep deprivation

Assessing the Risk of Delirium

AGS guideline recommends preoperative assessment of risk of delirium:

- Consider age > 65, cognitive impairment, sensory deficit, severe illness, and infection
- Validated prediction tools available, but less practical
- For increased risk, would counsel patient & family and consider applying multi-component delirium prevention interventions (if available at your hospital)

Prevention: Care Packages

Multi-component intervention packages:

- e.g., Acute Care for Elderly (ACE) units, Comprehensive Geriatric Assessment (CGA), delirium prevention order sets
- Reorientation, non-drug sleep hygiene, bowel/bladder care, early PT/OT, nutrition, pain assessment, delirium screening
- Moderate evidence for benefit from numerous trials but requires institutional support & group effort

Prevention: Pharmacology

Avoid high-risk medications:

- Anticholinergics, meperidine, BZD & other sedatives
- Minimize opiates by using non-opiate analgesics

Role for prophylactic neuroleptics?

- Several trials of neuroleptics *to prevent* delirium
- Inconsistent findings, poor study quality
- Bottom line: insufficient evidence for or against

Screening & Diagnosis

- AGS doesn't take position on whether to screen
- Hyperactive (agitated) delirium usually obvious but hypoactive (sedated) delirium often missed

Confusion Assessment Method (CAM):

1. Acute change or fluctuation in mental status

AND

2. Inattention (trouble focusing or distractable)

AND

3. Disorganized thinking or altered level of consciousness

Evaluating the Delirious Patient

Specific, reversible etiology seldom identified

Approach to working up postoperative delirium:

- CBC, basic chemistry, urinalysis, EKG
- Other studies only if indicated by clinical findings
- Brain imaging rarely useful
- Low yield for thyroid tests, vitamin levels, RPR, LP, etc.

Review medications closely:

- Anticholinergic, BZD, opiate, antiemetic, antispasmodic

Treating Postoperative Delirium

Identify & treat reversible causes:

- Recommended but beware of excessive work-up

Multidisciplinary teams & multicomponent interventions:

- Similar to delirium prevention packages
- Weak & inconclusive evidence for benefit (vs. prevention)

Physical restraints:

- Not recommended unless no other option to prevent harm

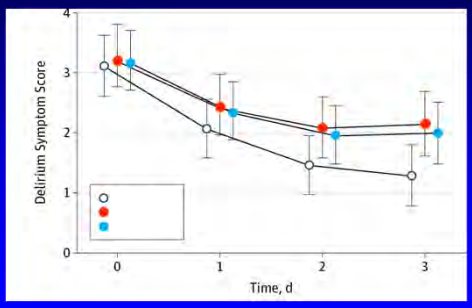
Treating Postoperative Delirium

Recommendations are based largely on expert opinion:

- Treat specific causes
- Adequate pain control
- Eliminate unnecessary medications, lines, catheters
- Mobilization during daytime
- Quiet, uninterrupted sleep at night
- Frequent re-orientation and reassurance
- Reserve sedation for patients at high risk for self-harm

Morrison RS, et al. AIM, 1998

Red Pill, White Pill, Blue Pill



JAMA Intern Med. 2017;177(1):34-42.

Antipsychotics for Management of Postoperative Delirium

Commonly used but poorly studied

- Lack of placebo-controlled trials in postop patients
- Are we changing natural history or just sedating patients?

Indications & Recommendations:

- Only for severe agitation or distress, if threatening substantial harm to self and/or others
- Try behavioral interventions first
- Use lowest effective dose for the shortest possible duration
- Don't treat hypoactive delirium with antipsychotics

Antipsychotic Regimens for Delirium

Haloperidol:
- Start 0.5 – 1 mg (PO, IV, IM); can repeat in 30-60 min

Risperidal
- Start at 0.5 – 1 mg (PO) BID; peak 1 hr; renal dose

Quetiapine
- Start 25 mg (PO) QHS or BID; peak 1.5 hr
- Preferred for patients with Parkinsonism

Olanzapine
- Start 2.5 mg (PO – also available IV/IM) QHS; peak 6 hr

IV Haldol & Long QTc

- Haldol not approved for IV use, but commonly done
- Risk of QTc prolongation and torsades de pointes
- Risk mainly if ≥ 2 mg single dose or ≥ 20 mg / 24 hrs
- Watch for other drugs that prolong QTc (e.g., methadone)
- UCSF policy:

  -- Tele or daily ECG needed if exceeding above doses

  -- IV haldol held if QTc > 440 ms

Screening for Postoperative MI

Findings from POISE (2008 beta-blocker trial):
- 5% of these "elevated risk" patients had postop MI, defined as elevated biomarker + ECG changes
- Most MI occurred by POD #3 (74% within 48 hr)
- Postoperative MI predicted 5-fold mortality
- Majority of postoperative MI were asymptomatic
- Silent MI had similar mortality as symptomatic MI

Postop Troponin Predicts Mortality

Study	Biomarker	Outcome
POISE (2011)	Troponin or CK-MB	2.5x mortality with isolated biomarker elevation
VISION (2012)	Troponin-T	4x mortality with any Tn-T elevation
Meta-analysis of 14 earlier studies (2011)	Troponin	3x mortality with elevation

1. Ann Intern Med. 2011;154(8):523-528.
2. JAMA. 2012; 307(21):2295-2304.
3. Anesthesiology 2011; 114(4): 796-806.

Arguments Against Screening

Too late to do anything:

- Nearly 2/3 of deaths in patients with MI occurred by POD 3
- Many deaths in MI patients are not cardiac-related
- Elevated troponin just identifies obviously crashing patients

No known effective intervention:

- Don't order the test unless it will change management

MANAGE Trial

Question: Does the direct thrombin inhibitor dabigatran improve outcomes in patients with elevated postop troponin?

Patients: 1754 patients who evidence of myocardial injury after noncardiac surgery (MINS), defined as elevated postop troponin either with clinical, ECG or imaging evidence of new ischemia or no other explanation (e.g., PE, sepsis, atrial fib)

Intervention: Dabigatran 110 mg bid *vs.* placebo for *up to 2 yrs*

Outcome: CV mortality, nonfatal MI, stroke, peripheral arterial thrombosis, and symptomatic PE

Amputation and symptomatic proximal DVT added *post hoc*

MANAGE Trial Outcomes

Outcome	Dabigatran	Placebo	NNT
Primary cardiac or vascular outcome	11%	15%	25 (p = .012)
Mortality – CV Mortality – All cause	6% 11%	7% 13%	NS
Myocardial Infarction	4%	5%	NS
Bleeding complications	3%	4%	NS

https://doi.org/10.1016/S0140-6736(18)30832-8

Screening for Myocardial Injury

Limitations of MANAGE trial:

- Design problems (changing sample size & outcomes)
- Outcomes too broad and individually no significant effect
- Comparison group was placebo
- Just too weird -- very different from usual practice

So now what?

Statin & ASA: Association between their use and lower mortality in patients with MINS or postop MI (retrospective study only)

Biomarkers in Clinical Practice

Canadian Cardiovascular Society (CCS)

- Measure BNP or NT-proBNP before major noncardiac surgery in all patients with CV disease, over age 65, or RCRI score ≥ 1
- Use biomarker instead of stress test for risk stratification
- BNP > 92 or NT-proBNP > 300 indicate increased risk
- Measure troponin daily for 48-72 hours after surgery if preoperative biomarker level elevated
- Patients with elevated postoperative troponin should receive long-term aspirin & statin therapy

Delaying Surgery After MI

A 63-year-old man suffers an acute myocardial infarction, treated without PCI. He was already scheduled for prostate cancer surgery in one month.

Because of his recent MI, surgery should be delayed for:

A. 1 month

B. 2 months

C. 3 months

D. 6 months

E. At least a year

Delaying Surgery After Acute MI

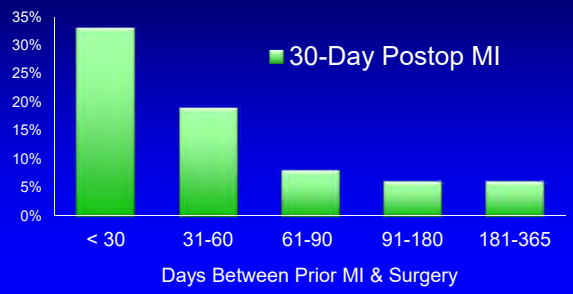
Question: How does time between acute MI and surgery affect the risk of postoperative MI?

563,842 patients (1999-2004) discharged after hip surgery, colectomy, cholecystectomy, AAA repair, or lower extremity amputation:

- 2.9% of cohort had experienced acute MI in prior year
- Outcome: 30-day postoperative MI

Livhits M et al. Annals of Surgery 2011; 253:857-63

Delaying Surgery after Acute MI



How Long to Wait after MI?

Conclusions:

- Surgery within one year of acute MI associated with high risk of postoperative MI
- Risk falls over time; most of the reduction within 2 months
- Trend is similar when only elective surgery considered

Caveats:

- Nonrandomized, observational study

ACC/AHA Guidelines:

- Delay elective surgery for at least 2 months after MI

Delaying Surgery After Stroke

A 63-year-old man suffers an acute stroke that is managed without thrombolysis. Brain MRI incidentally detects a large meningioma. The neurosurgeon wants to do a craniotomy to resect the tumor in 2 weeks.

Because of his stroke, you recommend delaying surgery for:

A. 1 month
B. 3 months
C. 6 months
D. 9 months
E. At least a year

Delaying Surgery After Stroke

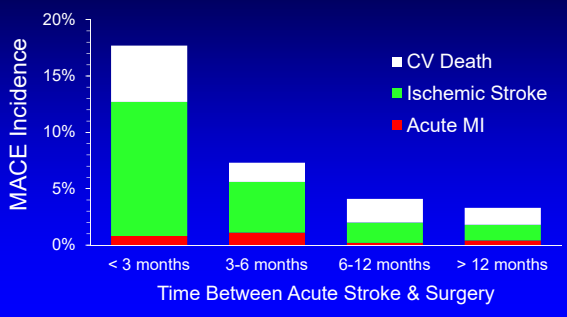
Question: How does time between stroke and surgery affect the risk of cardiovascular complications?

Danish cohort study of all adults undergoing elective noncardiac surgery from 2005-2011:

- 7137 patients had prior stroke (1.5% of total cohort)
- Outcome: 30-d postop Major Adverse Cardiac Events (MACE): cardiovascular death, nonfatal MI, ischemic stroke
- Looked at effect of time since stroke on MACE rate

Jorgenson ME et al. JAMA 2014; 312:269-277

Delaying Surgery After Stroke



How Long to Wait after CVA?

Conclusions:

- Surgery after CVA associated with high CV risk
- Risk falls over 9 months, biggest drop after first 3 months

Caveats:

- Nonrandomized, observational study

My take-away:

- Delay elective surgery for at least 3 months (up to 9 months) if possible

Perioperative Transfusion Threshold

82 y.o. woman has undergone repair of a femoral neck fracture. She denies heart disease, but has old pathologic Q-waves on her ECG. On post-op day # 2, she only complains of hip pain.

Exam: BP 140/80 HR 75
Heart, Lung, Abdomen exams normal

Labs: Hemoglobin = 8.3 (Hct = 25%)

When should she receive a blood transfusion?

Perioperative Transfusion Threshold

1. Transfuse to keep Hgb > 10
2. Transfuse to keep Hgb > 9
3. Transfuse to keep Hgb > 8
4. Transfuse to keep Hgb > 7
5. Only if symptomatic

FOCUS* Trial

(*Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair)

Patients: 2016 patients undergoing hip fracture repair. All patients had either diagnosis of or risk factors for cardiovascular disease.

- Mean age = 82
- HTN (82%); CAD (40%); DM (25%); CVA (24%); CHF(17%)

Treatment: Randomized to 2 transfusion strategies:

1. Hemoglobin < 10 g/dL
2. Symptoms of anemia (also permitted for hgb < 8)

Carson JL et al. *NEJM* 2011; 365:2453-62

FOCUS Trial Results

	PRBC Units Transfused Median (IQR)	Total Units Transfused
10 g/dL Trigger	2 (1,2)	1866
Symptomatic Trigger (or 8 g/dL)	0 (0,1)	652

Carson JL et al. *NEJM* 2011; 365:2453-62

FOCUS Trial Results

	In-hospital mortality	In-hospital mortality, cardiac complication	60-day mortality	60-day mortality + disability
10 g/dL Trigger	2.0%	4.3%	7.6%	35%
Symptom Triggered	1.4%	5.2%	6.5%	35%

Conclusion: No increased mortality or morbidity with a restrictive transfusion protocol.

Carson JL et al. *NEJM* 2011; 365:2453-62

Caveats to FOCUS Trial

- Small difference in hemoglobin levels may not be clinically significant
- Inadequate power to determine if presence of CV disease affects outcome
- Restrictive transfusion strategy leads to more symptomatic anemia (mostly ↑HR or ↓BP)

AABB Transfusion Guidelines

The society formerly known as the American Association of Blood Banks:

- "In postoperative surgical patients, transfusion should be considered at a hemoglobin concentration of 8 g/dL or less or for symptoms (chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure)." *Strong recommendation*
- Same recommendation if patient has pre-existing CV disease *Weak recommendation*

Carson JL et al. Ann Intern Med, 2012;E-429

Surgical Risk in Cirrhotic Patients

A 65-y.o. man with cirrhosis from HCV desires a hip arthroplasty. He feels well and has no current signs of ascites or encephalopathy on examination.

Labs: Creatinine = 1.6
Total Bilirubin = 1.9
Albumin = 3.5
INR = 1.6

How would you advise this patient about his postoperative mortality risk?

65-y.o. man with cirrhosis from HCV desires a hip arthroplasty. He's asymptomatic and has no signs of encephalopathy or ascites.

1. Patients with cirrhosis are not candidates for elective surgery
2. Your mild cirrhosis (Childs-Pugh class A) makes you an acceptable surgical candidate
3. Perioperative risk is acceptable, but long-term mortality risk makes surgery unappealing

Surgical Risk in Cirrhotic Patients

Question: How does his cirrhosis affect mortality risk?

Background:

- Risk traditionally assessed by Childs-Pugh classification (http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality)
- Mortality after GI surgery: Class A = 10%
  Class B = 30%
  Class C = 70%
- Limitations: single time point, less known about non-GI surgery; sensitive to minor laboratory result differences

MELD Score as Risk Predictor

MELD Score (Model for Endstage Liver Disease):

- Main use in organ allocation
- Variables: INR, bilirubin, creatinine

Retrospective multivariate analysis of 772 cirrhotic patients undergoing GI, orthopedic, and CV surgery

- Independent predictors of mortality: Age & MELD Score
- Predicts mortality @ 1 wk, 1 mo, 3 mo, 1 yr, 5 yr

www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/post-operative-mortality-risk-patients-cirrhosis

Teh et al. Gastroenterology, 2007

65 y.o. man with stable HCV-related cirrhosis. He has no current signs of encephalopathy or ascites.

Labs: Creatinine = 1.6
Total Bilirubin = 1.9
Albumin = 3.5
INR = 1.6

Childs-Pugh Class A
MELD Score = 19

Mortality Prediction:

- Childs-Pugh: 10% in-hospital mortality
- MELD Score: 6.5% 1 week mortality
  24% 1 month mortality
  36% 3 month mortality
  50% 1 year mortality

OSA & The Surgical Patient

Obstructive Sleep Apnea in Surgical Patients

A 55-y.o. morbidly obese man is scheduled to undergo knee arthroplasty. He has hypertension but no other medical history. He reports occasional fatigue and somnolence. He doesn't know if he snores or has apneic spells. Exam and recent lab tests are unremarkable.

What should be done?

1. Notify surgical team of suspected OSA
2. Notify surgical team & recommend empiric CPAP postop
3. Delay surgery for formal polysomnography

OSA and the Surgical Patient

OSA probably increases postoperative complications:

- Pulmonary complications (11 of 17 studies)
- Postop atrial fibrillation (5 of 6 studies)

Previously undiagnosed OSA may be associated with more complications than known OSA

Clinical screening tools have high + predictive value

Benefits of positive airway pressure (CPAP, BiPAP) for surgical patients with OSA uncertain

Chung F et al. Anesth Analg. 2016;123(2):452-73

Society of Anesthesia and Sleep Medicine Guidelines for Preoperative Evaluation

1. Screen patients clinically for OSA risk
   - Snoring
   - Tired or sleepy
   - Observe apnea
   - Pressure (HTN)
   - BMI > 35 kg/m^2
   - Age > 50 years
   - Neck > 17" (M)/16" (F)
   - Gender is male

STOP-BANG

High risk for OSA if either

- 5 or more total points

or

- 2 STOP points + B, N, or G

Chung F et al. Anesth Analg. 2016;123(2):452-73
http://www.stopbang.ca/osa/screening.php

Society of Anesthesia and Sleep Medicine Guidelines for Preoperative Evaluation

2. Patient and care team should be informed about known or suspected OSA
3. Insufficient evidence to recommend delaying surgery to perform advanced testing (polysomnography)

   Exception: patients with evidence of severe or uncontrolled systemic complications of OSA or impaired gas exchange (e.g., severe pulm HTN, hypoventilation, resting hypoxia)
4. Continue PAP after surgery

   Insufficient evidence to recommend empiric PAP

Are Curbside Consults Safe?

You're happily about to leave the hospital…

…when the orthopedic surgeon calls to say, "My patient's glucose levels are elevated. She's otherwise stable. Maybe you could give curbside advice?"

Are Curbside Consults Safe?

What's your personal approach to requests for informal "curbside" advice?

1. I never do curbside consults
2. I ask questions to determine whether curbside is appropriate
3. I'm pretty open to giving curbside advice

Curbside Consults

Studied 47 requests for curbside advice to hospitalist

- Curbside consultant could ask questions ad lib
- Made recommendations without seeing patient or chart
- Different hospitalist performed formal, in-person evaluation

Questions:

- Did curbside consultant obtain accurate information?
- Did advice and management differ?

Burden, M et al. *J Hosp Med*, 2013; 8:31–3

Curbside vs. Formal Medicine Consult

Compared to formal consultation, how often did curbside evaluation lead to:	
Incomplete clinical information	34%
Inaccurate clinical information	28%
Any difference in management	60%
Major difference in management	36%

Burden, M et al. *J Hosp Med*, 2013; 8:31–3

Curbside with Caution

Be wary when giving (or requesting) informal advice:

- Only for basic, generic questions
- If you're asking a lot of questions, do a formal consult
- Avoid in unstable or critically ill patients
- Offer to perform formal consultation; insist on it if "curbsided" again on same patient
- Don't visit patient, write orders, review chart, or submit bill

Thank You

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UCSF School of Medicine

Point-of-Care Ultrasound for Hospitalists

Trevor Jensen, MD MS
Associate Professor of Medicine

October 2021

Disclosures

- Consultant for Caption Health

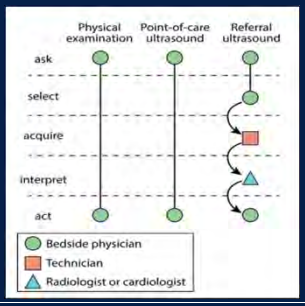
Session Outline

Point-of-Care Ultrasound (POCUS) is the future of the physical exam

- Questions we'll address around this topic:
  - What is POCUS for hospitalized patients?
  - Why learn POCUS?
  - How POCUS is used (cases + demo)?
  - How to get started with POCUS (for you & your institution)?

What is POCUS?

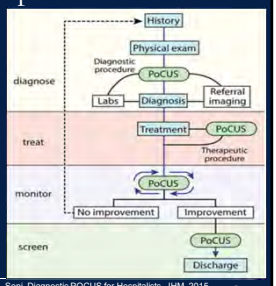
- Performed *and interpreted* by primary provider…
- …at the bedside…
- …to help answer a specific clinical question…
- …quickly



Soni, Diagnostic POCUS for Hospitalists. JHM, 2015

How we use POCUS in Hospital Medicine?

- Diagnostic
- Therapeutic (procedural guidance)
- Treatment monitoring
- Disease screening



Soni, Diagnostic POCUS for Hospitalists. JHM, 2015

Why learn POCUS?

Reason 1: It makes you a better doctor…

↓ Procedural complications

↑ Efficiency and accuracy of diagnosis

↑ Patient satisfaction

Why learn POCUS?

Reason 2: Most IM/HM doctors don't know much….

(Especially if you trained awhile ago)

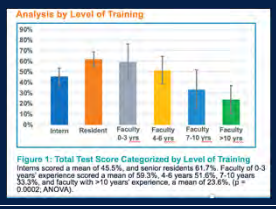


Figure 1: Total Test Score Categorized by Level of Training

Interns scored a mean of 45.5%, and senior residents 61.7%. Faculty of 0-3 years' experience scored a mean of 59.3%, 4-6 years 51.6%, 7-10 years 53.3%, and faculty with >10 years' experience, a mean of 23.6%. ($p = 0.0002$; ANOVA).

Anstey et al, SHM abstract, 2018

Why learn POCUS?

Reason 3: Despite lack of knowledge, people think its important….

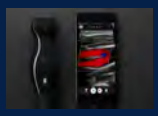
2017 Needs Assessment of UCSF Hospitalists

93%	I believe POCUS is important for diagnostic purposes in internal medicine.
88%	I believe POCUS should be a formal part of residency training.
93%	I believe faculty would benefit from faculty development in POCUS.

Conner et al, POCUS Journal

Why learn POCUS?

Its coming whether you like it or not…




AMA | ACP American College of Physicians | shm Society of Hospital Medicine | ALLIANCE for ACADEMIC INTERNAL MEDICINE

Cases: Inpatient Care as a POCUS Hospitalist

- Four common inpatient scenarios
  - Brief HPI and exam
  - Demo image acquisition and review normal anatomy/findings
  - Review abnormal images from the case
  - Discuss how POCUS impacted care delivery

Case 1: Mr. Seth is short of breath

- **HPI**: 61 M with HFrEF, COPD admitted for COPD exacerbation & CAP.
  - → nebulizers, prednisone, and antibiotics
- HD #3: increasing respiratory distress and anxiety
- **Vitals:** AF, HR 102, BP 192/97, RR 26, O2 sat 82% on RA → 93% on 6L NC
- **Exam:**
  - General: moderate distress.
  - CV: Tachycardic, no MRG. Unable to assess JVP. 1+ pitting edema of b/l LEs.
  - Lung: tachypneic, increased WOB, scattered wheeze with bilateral lower lobe rales.
- **Labs:** normal CBC and BMP, BNP 421, TnI pending, EKG non-ischemic. CXR ordered.

Case 1: Mr. Seth is short of breath + POCUS!

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On admission, >3 b-lines in R anterior lung, otherwise normal. IVC 1.8cm and collapsible

Now, diffuse b-lines in bilateral lung fields, bilateral pleural effusions. IVC 2.4cm and minimally collapsible.

(You were done with your POCUS assessment by the time the CXR was ordered ☺)

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Demo: Lung Ultrasound (LZ 1-3)

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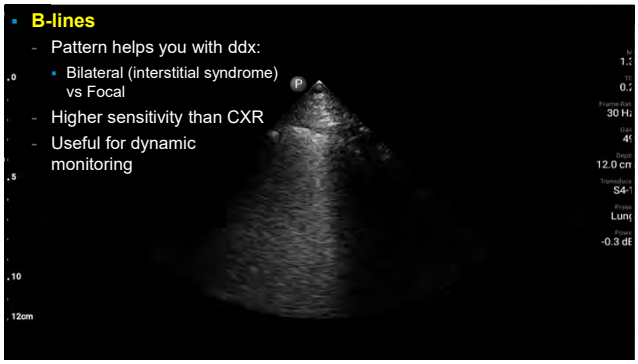
Demo: Lung Ultrasound (LZ 4)

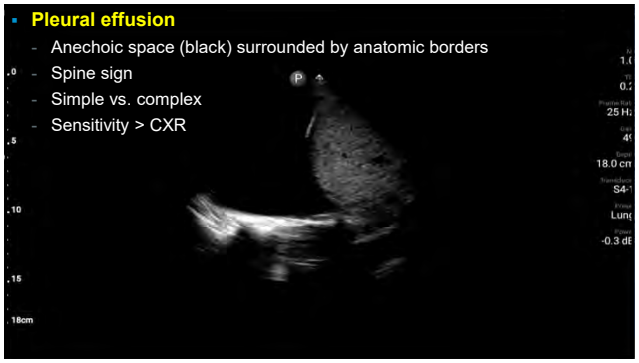
UCSF School of Medicine

Demo: IVC Ultrasound

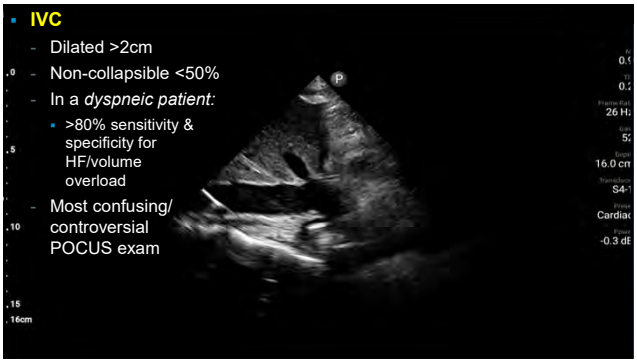
- **B-lines**
  - Pattern helps you with ddx:
    - Bilateral (interstitial syndrome) vs Focal
  - Higher sensitivity than CXR
  - Useful for dynamic monitoring



- **Pleural effusion**
  - Anechoic space (black) surrounded by anatomic borders
  - Spine sign
  - Simple vs. complex
  - Sensitivity > CXR



- **IVC**
  - Dilated >2cm
  - Non-collapsible <50%
  - In a *dyspneic patient:*
    - >80% sensitivity & specificity for HF/volume overload
  - Most confusing/ controversial POCUS exam

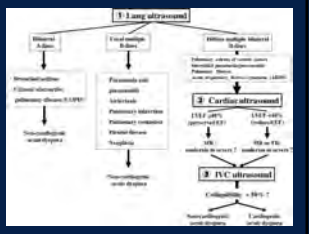


Case 1 Resolution

- POCUS diagnosis: interstitial syndrome, pleural effusions, volume overload
- You give him IV Lasix and treat his blood pressure → BP normalized and hypoxia improving
- You make a mental note to check his lung and IVC US again tomorrow to decide about thoracentesis and further need for diuretics

Case 1 Take Home Points

- POCUS
  - improved the quality of your index exam
  - helped you *quickly* identify why his condition acutely changed
- When possible:
  - Have an algorithmic approach
  - Combine multiple pcus exams and integrate with other data



Kajimoto et al, Cardiovascular Ultrasound, 2012.

Case 2: Mrs. Essig is hypotensive

- **HPI**: 52W with metastatic breast cancer c/b L malignant pleural effusion on chemotherapy p/w generalized weakness, dyspnea, lethargy, HR 123 BP 82/40
  - → given 2L IVF with improvement.
- **Vitals:** AF, HR 112, BP 90/47, RR 16, O2 sat 96% on RA
- **Exam:**
  - General: arousable but somnolent, comfortable
  - CV: Tachycardic, regular, no MRG. JVP 6cm. Chronic lymphedema of the b/l LEs
  - Lung: breathing comfortably on RA, diminished breath sounds LLB but otherwise CTA bilaterally
- **Labs:** CBC and BMP normal. Tbili 1.6, normal AST/ALT. BNP 235 (unknown baseline). TnI negative.

Case 2: Mrs. Essig is hypotensive + POCUS!

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- **Labs:** CBC and BMP normal. Tbili 1.6, normal AST/ALT. BNP 235 (unknown baseline). TnI negative.

Lungs with a-lines throughout, moderate L pleural effusion

IVC 1.8cm with ~50% collapse with inspiration

Cardiac US with mildly reduced LVEF, pericardial effusion

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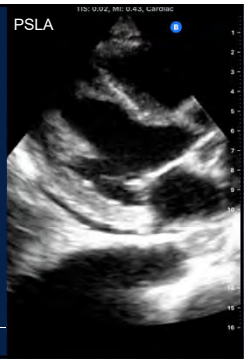
Demo: Cardiac US (Parasternal Long Axis)

UCSF School of Medicine

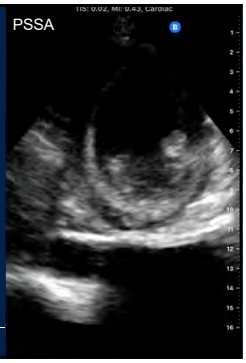
Demo: Cardiac US (Parasternal Short Axis)

- **LV Ejection Fraction**
  - Evaluation
    - End-point Septal Separation (EPSS)
    - Fractional Shortening
    - Myocardial Thickening
  - Qualitative assessment
    - Hyperdynamic
    - Normal
    - Mild-moderately reduced
    - Severely reduced
  - LV dysfunction by hospitalists: 91% sensitivity; 88% specificity



25

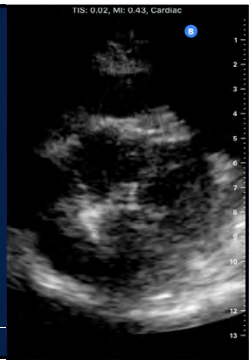
- **Pericardial Effusion**
  - Qualitative assessment:
    - Small
    - Moderate
    - Large
  - Pericardial effusion by hospitalists: 100% sensitivity; 87% specificity
  - Apical 4 chamber, sub-xiphoid best for evaluating signs of chamber collapse (tamponade)



26

Case 2 Resolution

- POCUS diagnosis: new mild-moderate LVEF reduction, new small pericardial effusion
- Repeat TTE on HD#1 confirms new EF 40%, pericardial effusion enlarging
- HD#3 she develops tamponade, undergoes pericardial drain placement. Patient and family opt for hospice referral.



27

Case 2 Take Home Points

- POCUS led you to a faster, new diagnosis of HFrEF.
  - Clinical management: more cautious with IVF
  - Further diagnostic testing: ordered TTE from admission
  - Monitoring evolution of pericardial effusion
  - Assist with prognostication & GOC

Table 4 Diagnostic Test Characteristics of Hand-Carried Echocardiography Using Standard Echocardiography as the Reference Standard in 210 Participants*

Cardiac Abnormality	Prevalence n/total n	Sensitivity* % (95% CI)	Specificity* % (95% CI)	$LR_{positive}$* (95% CI)	$LR_{negative}$* (95% CI)
LV systolic dysfunction	67/210	84 (73-92)	85 (78-90)	5.4 (3.7-8.1)	0.2 (0.1-0.3)
Pericardial effusion, moderate or large	3/210	100 (29-100)	87 (82-91)	7.7 (2.6-10.1)	0 (0-0.6)

Adapted from Lucas et al, Am J Med 2011

28

Case 3: Dr. Nye has an AKI

- **HPI**: 84M with BPH, HTN, DM2 presents with AMS, lower abdominal pain, decreased urination, K 6.4. ED POCUS shows hydronephrosis and a distended bladder
  - → foley with 400cc urine output. hyperK treatment.
- **Vitals:** within normal limits
- **Exam:**
  - General: mildly agitated but redirectable, no distress
  - Abd: soft, +suprapubic tenderness, no CVA tenderness, no distension, NABS
  - GU: foley in place draining cloudy yellow urine
- **Labs:** WBC 11.7, BUN 48, Cr 2.6, K 6.1, otherwise normal. UA +WBC, +nitrite, +LE, +blood. Urine culture pending. CTAP pending.

Case 3: Dr. Nye has an AKI

+ POCUS!

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Renal US: Bilateral hydronephrosis

Bladder still distended with foley balloon visible

FAST negative for free fluid

IVC 1.4cm, collapsible with inspiration

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Demo: Renal Ultrasound (RUQ)

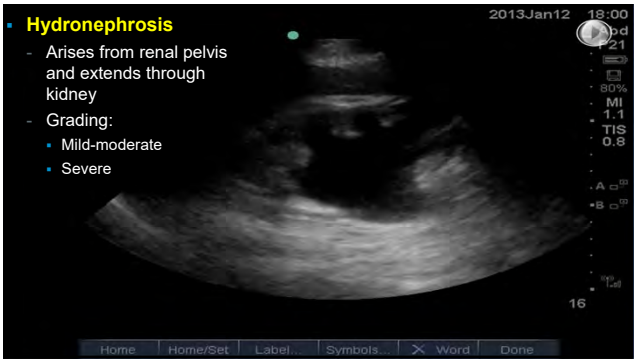
UCSF School of Medicine

Demo: Renal Ultrasound (LUQ)

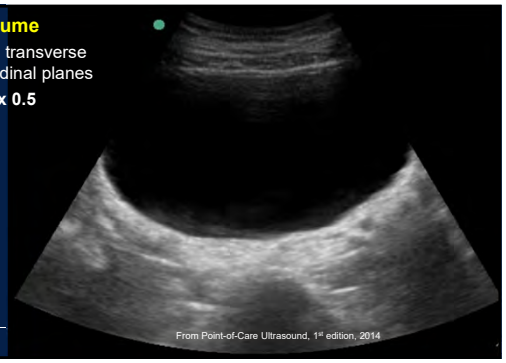
UCSF School of Medicine

Demo: Bladder Ultrasound

- **Hydronephrosis**
  - Arises from renal pelvis and extends through kidney
  - Grading:
    - Mild-moderate
    - Severe



- **Bladder Volume**
  - Measure in transverse and longitudinal planes
  - **L x W x H x 0.5**



Case 3 Resolution

- POCUS diagnosis: severe hydronephrosis, foley dysfunction with urinary retention
- Foley is flushed and repositioned → additional 800cc urine output. He is started on ceftriaxone for UTI and Tamsulosin for BPH. His abdominal pain resolves; you cancel the CT scan.
- HD #2: urine culture + for pan-sensitive E Coli → abx narrowed to cephalexin. K, Cr improved. Foley is removed and he passes a trial of void prior to discharge.

Case 3 Take Home Points

- POCUS helped you quickly identify a complication in your treatment plan
  - → avoided a potential bad outcome & unnecessary CT scan.
- Accuracy of bladder volume by POCUS > bladder scan
- Detecting hydronephrosis is a readily attainable skill
  - IM residents x5 hrs of renal US practice = 94% sensitivity; 93% specificity for moderate-severe hydronephrosis

Case 4: Ms. Nidus has cellulitis

- **HPI**: 36W with IVDU, DVT not on anticoagulation presents Saturday night with a red, swollen, and painful RLE. No fevers or chills.
  - → IVF, empiric antibiotics for cellulitis and orders a RLE Doppler
- **Vitals:** Afebrile, HR 98, BP 108/55, RR 16, O2 sat 98% RA
- **Exam:**
  - General: awake, alert, cooperative. In mild distress 2/2 pain.
  - CV: RRR, no MRG.
  - MSK: RLE tender, erythematous, warm to touch distally. No fluctuance or purulence. She is diffusely TTP overlying the area. Mild pitting edema of R>LLE. Intact pulses.
- **Labs:** WBC 12.3, CBC otherwise normal. CMP normal. Lactate 2.1. D-dimer 785. Doppler RLE is ordered, but won't be performed until the techs arrive on Monday morning.

How many people would anticoagulate her?

Case 4: Ms. Nidus has cellulitis + POCUS!

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- **Labs:** WBC 12.3, CBC otherwise normal. CMP normal. Lactate 2.1. D-dimer 785. Doppler RLE is ordered, but won't be performed until the techs arrive on Monday morning.

IVC 0.9cm diameter with almost 100% collapsibility with inspiration

Normal LVEF

Soft tissue US +cobblestoning, no deep fluid pockets

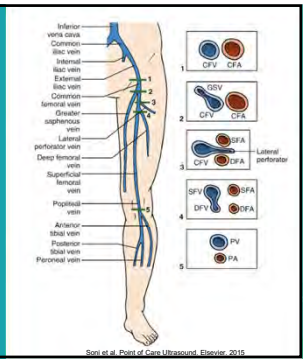
DVT US non-collapsible at level of common femoral vein

UCSF School of Medicine

Demo: Soft Tissue Ultrasound

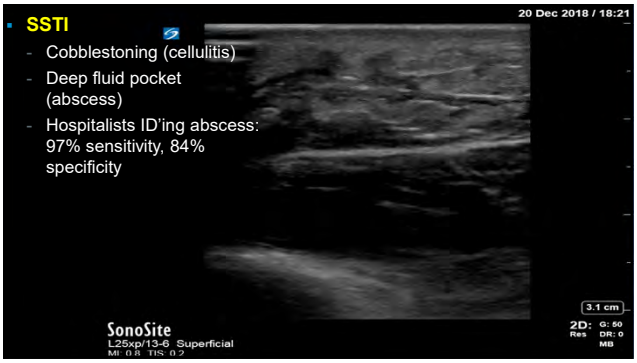
UCSF School of Medicine

Demo: DVT US

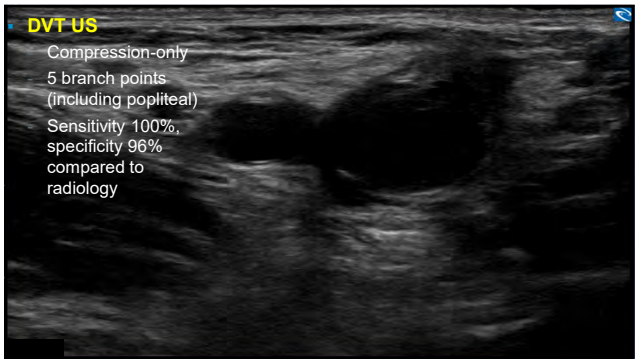


Soni et al. Point of Care Ultrasound. Elsevier, 2015

- **SSTI**
  - Cobblestoning (cellulitis)
  - Deep fluid pocket (abscess)
  - Hospitalists ID'ing abscess: 97% sensitivity, 84% specificity



- **DVT US**
  - Compression-only
  - 5 branch points (including popliteal)
  - Sensitivity 100%, specificity 96% compared to radiology



Case 4 Resolution

- POCUS diagnosis: cellulitis, no abscess, +DVT. Safe for further fluid resuscitation.
- You give an additional 1L IVF → lactate, BP normalizes
- You start her on therapeutic lovenox for DVT seen on POCUS; confirmed by radiology DVT study 36 hours later.
- She tolerates oral antibiotics well, cellulitis improves. Prior to discharge, switch to oral DOAC with plans to follow up with a community PCP

UCSF

Case 4 Take Home Points

- In a resource-limited environment (overnights, weekends) POCUS can lead to faster initiation of appropriate therapy
- POCUS can help guide fluid resuscitation in the setting of hypotension or tachycardia.
- Just because you POCUS, doesn't mean you can't order the formal study!

So why do we POCUS?

- Earlier diagnosis and treatment
- Avoids additional tests and reduces radiation exposure
- Safe treatment monitoring, prognostication
- Skills are attainable and lead to better quality care delivery than exam alone

POCUS doesn't replace the physical exam; it enhances the physical exam.

It IS the physical exam

Data for the POCUS we covered

Exam	Statistical Performance
IVC	Correlation coefficient 0.7-0.9
LVEF	LR +5.4; LR -0.2
Pericardial Effusion	LR +7.7; LR -0.0
Pulmonary Edema	Sensitivity 94%; Specificity 92%
Pleural Effusion	Sensitivity 93%; Specificity 96%
Hydronephrosis	Sensitivity 94%; Specificity 93%
DVT	Sensitivity 100%; Specificity 96%
Abscess	Sensitivity 97%; Specificity 84%

Data for POCUS Algorithms

- Rapid Ultrasound in Shock and Hypotension (RUSH)

	Shock Type Based on Final Diagnosis				
	Hypovolemic (n = 16)	Cardiogenic (n = 20)	Obstructive (n = 11)	Distributive (n = 11)	Mixed (n = 11)
Sensitivity	100%	90%	90.9%	72.7%	63.6%
Specificity	96.2%	98%	98.2%	100%	98.2%
PPV[†]	88.9%	94.7%	90.9%	100%	87.5%
NPV	100%	97%	98.3%	95.1%	93.3%
Kappa (P Value)	0.92 (0.000)	0.89 (0.000)	0.89 (0.000)	0.81 (0.000)	0.70 (0.000)

- BLUE protocol for dyspnea/hypoxia

Findings	Diagnosis	Sensitivity (%)	Specificity (%)
A lines (normal)	Asthma/COPD	89	97
Diffuse B lines (>2 lung zones)	Pulmonary edema	97	95
Loss of pleural line, consolidation, patchy B lines	Pneumonia	89	94
A lines without pleural sliding, lung point	Pneumothorax	81	100

What is the scope of POCUS in HM?

TABLE 1. Common POCUS applications for hospitalists

Cardiac	Pulmonary	Abdominal	Vascular	MSK	Procedural
LV assessment	Pleural effusion	Free fluid	DVT	Cellulitis	Paracentesis
RV assessment	Interstitial syndromes	Kidney size	AAA	Abscess	Thoracentesis
Atrial size	Alveolar syndromes	Hydronephrosis		Joint effusions	CVC placement
Right atrial pressure (IVC/JJ)	Pneumothorax	Bladder volume		Fractures	PIV placement
Pericardial effusion		Gallbladder			Arterial line placement
Chamber hypertrophy		Spleen size			Arthrocentesis
Gross valvular abnormalities		Liver size			Abscess drainage
					Lumbar puncture

Multisystem

Hypotension and shock: cardiac, RAP, pulmonary, DVT, abdominal free fluid
Resuscitation: cardiac, RAP, pulmonary
Dyspnea: pulmonary, Cardiac, RAP, DVT
Acute renal failure: renal, bladder, IVC, pulmonary

LV, left ventricle; RV, right ventricle; IVC, inferior vena cava; IJ, internal jugular vein; DVT, deep venous thrombosis; AAA, abdominal aortic aneurysm; CVC, central venous catheter; PIV, peripheral intravenous catheter; RAP, right atrial pressure.

Soni et al, "Point-of-Care Ultrasound for Hospitalists: A Position Statement of the Society of Hospital Medicine." JHM 2019

How should you integrate POCUS into your practice?

- Many factors to think through:
  - Context
  - Frequency
  - Difficulty
  - Data

Scope of POCUS in HM at UCSF

TABLE 1. Common POCUS applications for hospitalists

Cardiac	Pulmonary	Abdominal	Vascular	MSK	Procedural
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Hypotension and shock: cardiac, RAP, pulmonary, DVT, abdominal free fluid
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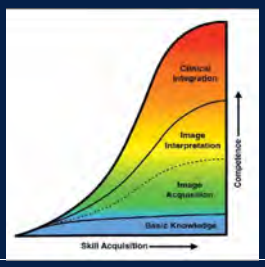
Soni et al, "Point-of-Care Ultrasound for Hospitalists: A Position Statement of the Society of Hospital Medicine." JHM 2019

Addressing Barriers

- Hardware
- Training
- Time and money constraints
- Credentialing and privileging

https://www.krestonreeves.com/news-and-events/12/07/2019/address-business-growth-barriers

POCUS Learning Pathways



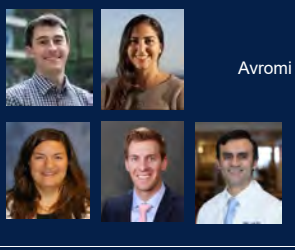
- Pursue a certificate program (SHM, CHEST)
- Attend workshops (SHM, ACP, AIUM, UCSF)
- Learn from local experts (EM, critical care colleagues)
- Self-learning, ad hoc (FOAMed)

 Soni et al. Cert of POCUS. JHM 2017 UCSF

Our institution's experience

Getting started…

- Champion(s)
- Leadership buy-in
  - Education
  - Research
  - Cost savings
  - Clinical outcomes



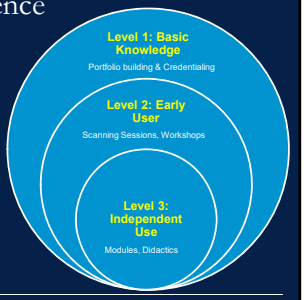
Avromi

 UCSF

Our institution's experience

Building momentum…

- Training program development
- Equipment investment



 Conner et al, POCUS Journal, in press. UCSF

Making it official

1. Privileging and Credentialing
2. Quality assurance
3. Integration into EMR and billing

IMAGE HERE:
Notary stamp?

 UCSF

"The larger issue now is to decide whether we believe that – in this case hospitalists – building competency in ultrasound among generalist physicians will enhance patient safety, quality, and value. **Personally, I do."**

- Bob Wachter, 2012

UCSF

Review of Session Goals

- What is POCUS for hospitalized patients?
- Why learn POCUS?
- How POCUS is used (cases + demo)?
- How to get started with POCUS (for you & your institution)?

POCUS is the future of the physical exam.

UCSF

Questions?

- **Trevor.Jensen@ucsf.edu**

Credit: University of South Carolina Point of Care US

NOTES

UCSF
University of California
San Francisco

Diagnosis and Management of Acute Kidney Injury

25th Annual Management of the Hospitalized Patient

Lowell Lo, MD
Associate Clinical Professor
Renal Ambulatory Service and Practice Chief
Mount Zion Dialysis Unit Medical Director
Division of Nephrology
University of California San Francisco

10/15/2021

Disclosure

There are no conflicts of interest to disclose.

UCSF

My Boss's Boss Instruction

Thou shalt "have a good sense of what the audience need to know about diagnosing and managing inpatients with rising creatinine"

UCSF

Objectives

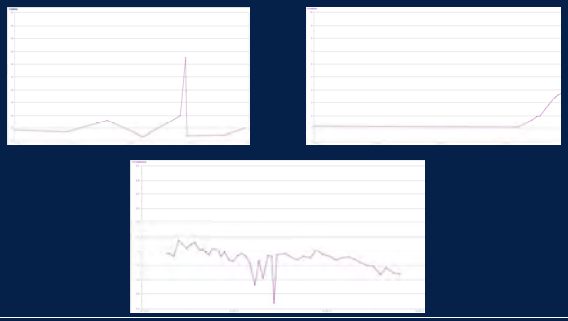
- Differentiate scenarios that may not be JUST acute tubular necrosis (ATN)
- Explain the limitation of common lab tests
- Devise a treatment plan for non-oligouric ATN

Overview

- **The pre, post, and "intrinsic" (15 mins)**
- The patient's Cr bumped (45 mins)
- Will the patient need dialysis (5 mins)
- Will the patient recover (5 mins)
- Covid-19 and kidney injury (5 mins)

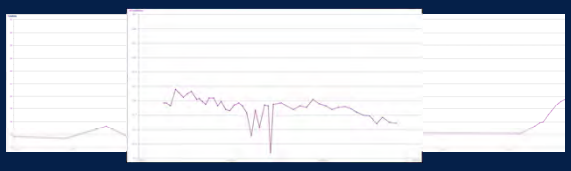
UCSF

Cr Bump – 3 Variations



UCSF

A Word about ARF to AKI



"The diagnosis of 'injury', by contrast, does not presuppose a reduction in glomerular filtration...The analogy to cardiology may be instructive: clinicians diagnosing acute myocardial infarction do not wait until a reduction in cardiac output, but rather make the diagnosis of myocardial injury on the basis of elevations of tissue-specific biomarkers in the serum."

Waikar Curr Opin Nephrol Hypertens 2007

UCSF

Objectives

- **Differentiate scenarios that may not be JUST acute tubular necrosis (ATN)**
- Explain the limitation of common lab tests
- Devise treatment plan for non-oligouric ATN

UCSF

Case 1 (ARS)

- 52 y/o male with PMH of poorly controlled T2DM over 10 years, HTN over 15 years, ongoing tobacco use, PVD, and CKD stage 3b with baseline ~Cr 1.9 admitted for non-healing foot ulcer and possible osteomyelitis of the toes. He was started on IV vanc and PO cipro. On day 4 of admission, he became altered and his SBP dropped to 80s (baseline 130s on Losartan, Amlodipine, and Carvedilol). He received 2L of LR and was urgently operated with toe amputation. On day 5, his Cr increased to 2.5 and received 2 more liter of LR. On day 6, his Cr increased to 2.8 and surgical bone Cx grew mixed GPC and GNR. On day 7, his Cr increased to 3.6 and nephrology was consulted. What's the cause of his AKI?

A: Pre-renal

B: Acute tubular necrosis

C: Acute interstitial nephritis

D: Post-renal

A Wise Nephrologist Once Told Me:

"If you fell asleep during Nephrology Clerkship and woke up by the dreaded question of why did this patient have renal failure, just say ATN"

Case 1 (ARS with answer)

- 52 y/o male with PMH of poorly controlled T2DM over 10 years, HTN over 15 years, ongoing tobacco use, PVD, and CKD stage 3b with baseline ~Cr 1.9 admitted for non-healing foot ulcer and possible osteomyelitis of the toes. He was started on IV vanc and PO cipro. On day 4 of admission, he became altered and his SBP dropped to 80s (baseline 130s on Losartan, Amlodipine, and Carvedilol). He received 2L of LR and was urgently operated with toe amputation. On day 5, his Cr increased to 2.5 and received 2 more liter of LR. On day 6, his Cr increased to 2.8 and surgical bone Cx grew mixed GPC and GNR. On day 7, his Cr increased to 3.6 and nephrology was consulted. What's the cause of his AKI?

A: Pre-renal

B: Acute tubular necrosis

C: Acute interstitial nephritis

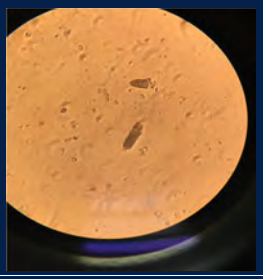
D: Post-renal

A Wise Nephrologist Once Told Me:

"A Nephrologist is an Internist who spins the urine."

Case 1

- 52 y/o male with PMH of poorly controlled T2DM over 10 years, HTN over 15 years, ongoing tobacco use, PVD, and CKD stage 3b with baseline ~Cr 1.9 consulted for AKI with Cr increased to 3.6. Urine microscopy showed:



Case 1 - "Intrinsic"

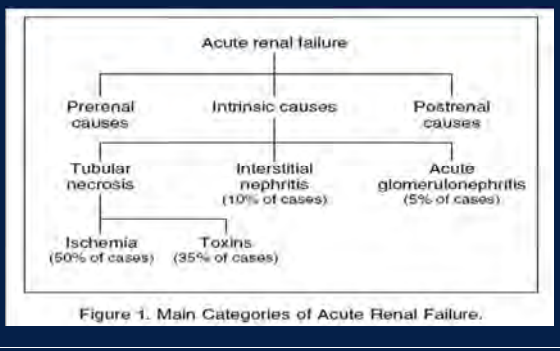
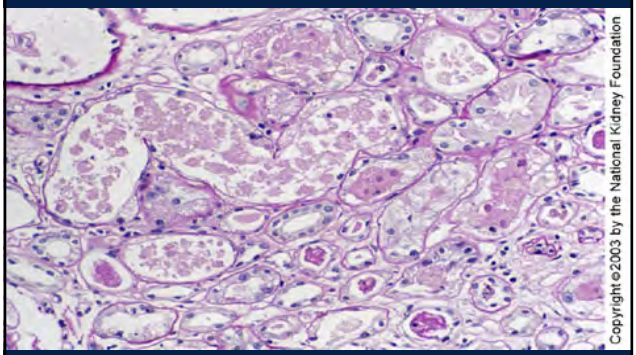


Figure 1. Main Categories of Acute Renal Failure.

Thadhani NEJM 1996 UCSF

Case 1 – What is ATN



UCSF

Case 1 – Continue (ARS)

- 52 y/o male with PMH T2DM, HTN, tobacco use, PVD, and CKD stage 3b with baseline ~Cr 1.9 consulted for AKI. Cr increased to 3.6 on day 7 with urine microscopy showed + muddy brown casts. A diagnosis of ATN secondary to osteomyelitis from mixed GPC and GNR was made. Vancomycin and cipro was continued. His Cr peaked on day 9 at 4.3. On day 10, his Cr down trended to 3.9 and his Cx grew MSSA (vanc changed to nafcillin) and GNR grew pseudomonas sensitive to cipro (continued). On day 11, his Cr further improved to 3.2 (renal team signed off). As the team was planning to discharge the patient on day 13 to SNF, his AM lab showed Cr increased from 2.5 back to 3.5. What's the cause of the new AKI?

A: Pre-renal

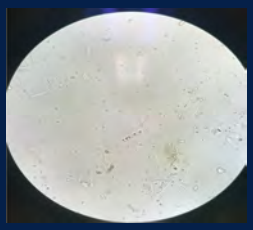
B: Acute tubular necrosis

C: Acute interstitial nephritis

D: Post-renal

Case 1 – Continue

- New urinary sediment reviewed:



Case 1 – Continue (ARS with answer)

- 52 y/o male with PMH T2DM, HTN, tobacco use, PVD, and CKD stage 3b with baseline ~Cr 1.9 consulted for AKI. Cr increased to 3.6 on day 7 with urine microscopy showed + muddy brown casts. A diagnosis of ATN secondary to osteomyelitis from mixed GPC and GNR was made. Vancomycin and cipro was continued. His Cr peaked on day 9 at 4.3. On day 10, his Cr down trended to 3.9 and his Cx grew MSSA (vanc changed to nafcillin) and GNR grew pseudomonas sensitive to cipro (continued). On day 11, his Cr further improved to 3.2 (renal team signed off). As the team was planning to discharge the patient on day 13 to SNF, his AM lab showed Cr increased from 2.5 back to 3.5. What's the cause of the new AKI?

A: Pre-renal

B: Acute tubular necrosis

C: Acute interstitial nephritis

D: Post-renal

Case 1 – AIN

- Clinical suspicion
- Onset s/p potential culprit meds (1-2 weeks with new exposure or few days with repeated exposure)
- Pyuria (50-90%), tubular proteinuria
- Fever, rash (15-50%)
- Eosinophilia

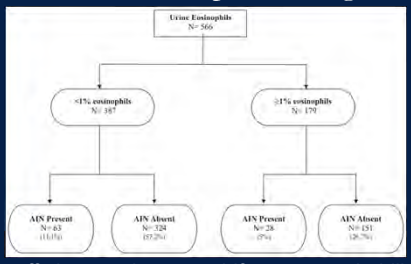
Table 1. Selected drugs associated with acute interstitial nephritis (AIN).

Antibiotics	β-lactam drugs*
	Fluoroquinolones*
	Rifampin*
	Sulfa-based drugs*
	Vancomycin
	Minocycline
	Ethambutol
	Erythromycin
	Chloramphenicol
Antiviral medications	Acyclovir
	Abacavir
	Indinavir
	Atazanavir
GI medications	Proton pump inhibitors*
	Histamine-2 receptor blockers
Analgesics	Nonsteroidal anti-inflammatory drugs*
	Selective COX-2 inhibitors
Anti-seizure drugs	Phenobarbital
	Phenytoin*
	Carbamazepine
Other drugs	Allopurinol*
	5-Aminosalicylates*
	Captopril
	Interferon
	Cyclosporine
	Anti-angiogenesis drugs (tyrosine kinase inhibitors)
	Diuretics

*Most common offending agents.

Perazella Clinical Nephrology 2014 UCSF

Case 1 - Urine Eosinophil Testing?



"At 1% cutoff, the test does not shift pretest probability of AIN in any direction."

"Even at 5% cutoff, UEs performed poorly in distinguishing AIN from ATN or other kidney diseases."

Muriithi CJASN 2013 UCSF

Case 1 – End

The patient was diagnosed with presumptive AIN secondary to Cipro (The patient had multiple exposures to penicillin like Augmentin prior). Despite stopping cipro, his creatinine continued to increase. He received a renal biopsy which confirmed AIN. Then he was treated with prednisone for a month with Cr eventually settled in the high 2s after 6 months.

Case 1 – My Pearls for AKI NOT? ATN

- No major medical events – unexplained Cr rise
- Patients appear well with great/graduate Cr rise
- Positive hematuria and proteinuria (always get an UA before renal consult if possible)
- Pyuria with negative Culture
- Inpatient de novo GN (except for infectious GN) is very rare

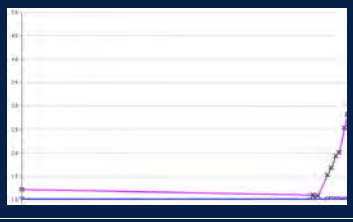
- No muddy brown cast ≠ no ATN
- Patients can have AIN without urinary WBCs

Overview

- The pre, post, and "intrinsic" (15 mins)
- **The patient's Cr bumped (45 mins)**
- Will the patient need dialysis (5 mins)
- Will the patient recover (5 mins)
- Covid-19 and kidney injury (5 mins)

Case 2

- 85 y/o female with PMH of aflutter, T2DM and HTN presenting with Afib RVR and shortness of breath. On DOA, the patient had CT PE protocol which ruled out PE and PNA. On day 2, she had RHC which showed elevated right- (Mean RA ~31 mmHg) and left-sided (PCWP ~33 mmHg) filling pressures with low CO. She was diagnosed with decompensated heart failure and started on IV Lasix but did not make much urine. Her Cr trend:



Case 2 (ARS)

- 85 y/o female with PMH of aflutter, T2DM and HTN presenting with Afib RVR and shortness of breath. On DOA, the patient had CT PE protocol which ruled out PE and PNA. On day 2, she had RHC which showed elevated right- (Mean RA ~31 mmHg) and left-sided (PCWP ~33 mmHg) filling pressures with low CO. She was diagnosed with decompensated CHF and started on IV Lasix but only made about 1L of urine. Cr increased from 1.1 to 1.5 to 2 to 2.9. Nephrology was consulted for whether to continue diuresis. What was the cause of the patient's AKI?

A: Pre-renal
B: Acute tubular necrosis
C: Acute interstitial nephritis
D: Post-renal

Case 2 (ARS with answer)

- 85 y/o female with PMH of aflutter, T2DM and HTN presenting with Afib RVR and shortness of breath. The patient was s/p CT PE protocol on DOA which ruled out PE and PNA. On day 2, she had RHC which showed elevated right- (Mean RA ~31 mmHg) and left-sided (PCWP ~33 mmHg) filling pressures with low CO. She was diagnosed with decompensated CHF and started on IV Lasix but only made about 1L of urine. Cr increased from 1.1 to 1.5 to 2 to 2.9. Nephrology was consulted for whether to continue diuresis. What was the cause of the patient's AKI?

A: Pre-renal
B: Acute tubular necrosis 2/2 contrast nephropathy
C: Acute interstitial nephritis
D: Post-renal

Case 2 (ARS)

- 85 y/o female with PMH of aflutter, T2DM and HTN presenting with Afib RVR and decompensated heart failure exacerbation. Her hospital course was complicated by contrast nephropathy. Assuming her baseline GFR was normal at 100mL/min and her creatinine peaked at close to 4 and level off. What was her GFR at the arrow point?

A: ~100mL/min
B: ~80mL/min
C: ~50mL/min
D: ~20mL/min

Objectives

- Differentiate scenarios that may not be JUST acute tubular necrosis (ATN)
- **Explain the limitation of common lab tests**
- Devise a treatment plan for non-oliguric ATN

Case 2 – Assessing Kidney Fx in AKI

- Limitations of serum [Cr]
  - Not helpful when not in steady state

The patient's kidney function has been the same since day 1 of injury. Clinical implication would be dosing medications with GFR < 10-30mL/min and avoid meds that will accumulate in patients with advanced kidney disease.

UCSF

Case 2 (ARS with answer)

- 85 y/o female with PMH of aflutter, T2DM and HTN presenting with Afib RVR and decompensated heart failure exacerbation. Her hospital course was complicated by contrast nephropathy. Assuming her baseline GFR was normal at 100mL/min and her creatinine peaked at close to 4 and level off. What was her GFR at the arrow point?

A: ~100mL/min
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C: ~50mL/min
D: ~20mL/min

UCSF

Case 2 – Assessing Kidney Fx in AKI

- Limitations of serum [Cr]
  - Need to take into account volume of distribution

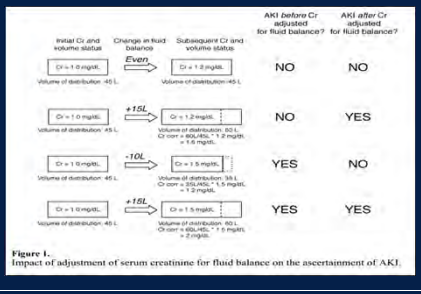
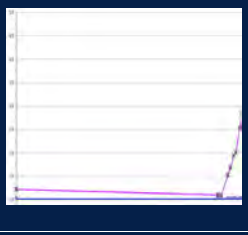


Figure 1.
Impact of adjustment of serum creatinine for fluid balance on the ascertainment of AKI.

Liu Crit Care Med 2011
UCSF

Case 2 (ARS)

- 85 y/o female with PMH of aflutter, T2DM and HTN presenting with Afib RVR and decompensated heart failure exacerbation. The patient developed contrast nephropathy. Her RHC showed elevated right- (Mean RA ~31 mmHg) and left-sided (PCWP ~33 mmHg) filling pressures with low CO. However, creatinine continued to increase with diuresis. Should we continue diuresis?



A: Yes
B: No, waitful watching
C: No, check FeNa
D: No, check FeUrea
E: No, give IVF

UCSF

Case 2 – Lasix vs IVF

- Limitations of FeNa
  - Not helpful when not Oligouric
- Purpose of FeNa: Explain why a patient is oliguric
- If a patient is not oliguric, what does FE_{Na} represent?
- Assuming normal renal function, what would your FE_{Na} be?

UCSF

Case 2 – Origin of FeNa

Fractional Excretion of Sodium

Exceptions to Its Diagnostic Value

Stuart Zarich, MD; Leslie S. T. Fang, MD, PhD; Jonathan R. Diamond, MD

- Low FE_{Na} reported in:
  - Oliguric ATN
  - CIN
  - Acute glomerulonephritis
  - Myoglobin-induced AKI
  - HRS
  - Renal allograft rejection
  - AIN
- FE_{urea} better if diuretics involved
  - Unclear whether studies included CKD

Zarich Arch Int Med 1985

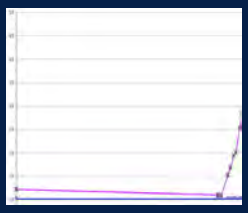
UCSF

A Wise Nephrologist Once Told Me:

"Acute tubular necrosis is a solute retention state."

Case 2 (ARS with answer)

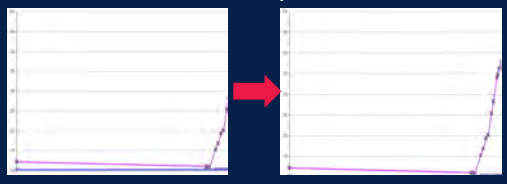
- 85 y/o female with PMH of aflutter, T2DM and HTN presenting with Afib RVR and decompensated heart failure exacerbation. The patient developed contrast nephropathy. Her RHC showed elevated right- (Mean RA ~31 mmHg) and left-sided (PCWP ~33 mmHg) filling pressures with low CO. However, creatinine continued to increase with diuresis. Should we continue diuresis?



A:	**Yes**
B:	No, waitful watching
C:	No, check FeNa
D:	No, check FeUrea
E:	No, give IVF

Case 2 – Assessment and Plan

- 85 y/o female with PMH of aflutter, T2DM and HTN presenting with Afib RVR and decompensated heart failure exacerbation. The patient developed contrast nephropathy. Her RHC showed volume overload. She was managed with IV Lasix with minimal response and transitioned to inotrope infusion and IV bumex gtt. Her creatinine continued to worsen daily:



- What can a nephrologist do that an internist can't do now?

Case 2 – Nephrologist = Internist PLUS

- Intensive Insulin Thera
- Loop Diuretics
- Erythropoietin
- Insulin-like growth fact
- Thyroxine
- Dopamine
- Fenoldopam

Objectives

- Differentiate scenarios that may not be JUST acute tubular necrosis (ATN)
- Explain the limitation of common lab tests
- **Devise a treatment plan for non-oligouric ATN**

Case 2 – Assessment and Plan

- 85 y/o female with PMH of aflutter, T2DM and HTN presenting with Afib RVR and decompensated heart failure exacerbation. The patient developed contrast nephropathy with RHC showing volume overload. She was managed with IV Lasix with minimal response and transitioned to inotrope infusion and IV bumex gtt without signs of renal recovery.

Plan: FEN

- 1) Solute/Fluid
- 2) Na
- 3) K
- 4) HCO3/AG
- 5) Ca/Mg/Phos
- 6) BUN/Nutrition/Uremia

Case 2 – Assessment and Plan

S: + SOB, fatigue, poor appetite, +N and small amount of V

O: AF, HR 80s, RR 16, BP 90/50, O2 Sat 97% on 4LNC, Wt 72.6 (Adm 71.6), Intake 430mL UOP 800mL

PE: JVD to mandible, irregularly irregular, bibasilar crackles, Bilateral 1+ thigh edema, +asterixis

Plan: FEN

- 1) Solute/Fluid
- 2) Na
- 3) K
- 4) HCO3/AG
- 5) Ca/Mg/Phos
- 6) BUN/Nutrition/Uremia

Case 2 – Assessment and Plan

1) Solute/Fluid (Wt ~5Kg + up) – Total solute overload, perfusion pressure OK

Increase bumex gtt and low sodium diet

2) Na (122) – Total water overload

Fluid restriction to < 1L per day

3) K (4.9) – Total body K adequate

Monitor for hypokalemia especially if UOP increases

4) HCO3/AG (18/12) – likely NAGMA due to decreased ammoniagenesis and dilutional

May improve with diuresis

Case 2 – Assessment and Plan

5) Ca/Mg/Phos (7.8/2.5/5.2) – Mild hypoCa from resistance to PTH and decreased 1,25-OH vitamin D and hyperMg/hyperPhos from decreased excretion

Renal diet to decrease phos intake (not too concerned right now given poor PO intake)

6) BUN/Nutrition/Uremia (79) – Concerning with decreased PO intake, +N/V, +asterixis

Patient is needing dialysis soon if renal function doesn't start to recover (hoping for renal recovery by 7-10 days with CIN). Dialysis indication – uremia *don't let BUN level lead you around by the nose

Case 2 – My Pearls for BUN level

- [C] = m/K, concentration = mass production rate/clearance

(in medicine, you can substitute clearance with renal function)

- **Elevated BUN states without uremia**

-- Excessive protein feeding (ex: transitioning off CVVHD to IHD)

-- GI Bleed

-- High catabolic state (ex: high dose steroid)

- **Low BUN states with uremia**

-- Malnourished state

Case 2 – One more word about BUN

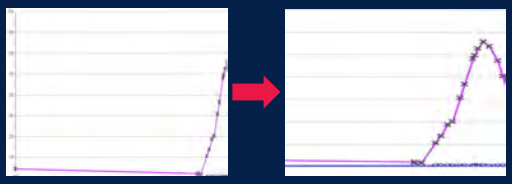
- BUN is not a true uremic toxin – it is a SURROGATE

Solute Group	Example	Source	Characteristics
Peptides and small proteins	Beta$_2$-microglobulin	Shed from MHC	Poorly dialyzed because of large size
Guanidines	Guanidinosuccinic acid	Arginine	Increased production in uremia
Phenols	p-Cresol sulfate	Phenylalanine, tyrosine	Protein bound, produced by gut bacteria
Indoles	Indican	Tryptophan	Protein bound, produced by gut bacteria
Aliphatic amines	Dimethylamine	Choline	Large volume of distribution, produced by gut bacteria
Furans	CMPF	Unknown	Tightly protein bound
Polyols	Myoinositol	Dietary intake, cell synthesis from glucose	Normally degraded by the kidney rather than excreted
Nucleosides	Pseudouridine	tRNA	Most prominent of several altered RNA species
Dicarboxylic acids	Oxalate	Ascorbic acid	Formation of crystal deposits
Carbonyls	Glyoxal	Glycolytic intermediates	Reaction with proteins to form advanced glycation end products

Meyer NEJM 2007

Case 2 – End

- 85 y/o female with PMH of aflutter, T2DM and HTN presenting with Afib RVR and decompensated heart failure exacerbation. The patient developed contrast nephropathy. After 2 days of high dose bumex gtt and inotrope, the patient's UOP increased to 3L per day with Cr slightly down trending. The next day, despite reducing bumex gtt to spot dosing, she made 5L UOP with Cr down to low 3s with resolution of N/V and asterixis.



Case 2 – Reflection

- Did I do anything to help with this case?

#AKI on CKD
-Hold diuresis for now pending RHC numbers
-RHC today to assess hemodynamics and volume status, and further determine diuretic needs
-Holding home ARB for now

-- I diagnosed the patient with contrast nephropathy

#AKI on CKD, concern for cardiorenal vs ATN vs both
- Holding home ARB for now
- Avoid nephrotoxic agents
- Monitor BMP BID
- Appreciate Nephrology recs

-- I reassured the team that despite Cr going up, it was ok to continue diuresis

-- I helped keeping an eye on FEN and got ready to perform dialysis while being hopeful for the potential renal recovery around 7-10 days

Case 2 – My Pearls for CIN Prophylaxis

- IV saline, IV saline, IV saline
- How much?

- Enough that pt doesn't develop shortness of breath
- 100cc/hr x3-6hrs pre and 6-12hrs post

- NO pre-emptive dialysis
- NO IV NaHCO3
- NO mucomyst

Weisbord NEJM 2018, Brar Lancet 2014

Case 3

- 90 y/o male with PMH of HFpEF, afib s/p pacemaker, COPD, CKD baseline Cr ~2, T2DM and BPH admitted for worsening cough, shortness of breath and orthopnea. He was diagnosed with CHF exacerbation and diuresed ~2L the first 2 days. Cr on admission was close to baseline, worsened initially and improved back to baseline after diuresis. The AM prior to consultation he went into Afib RVR. The day of consultation his Cr rose from 2 --> 2.46. The team consulted us to assist with AKI management specifically regarding whether to give Lasix or IVF.

Case 3 (ARS)

- After his episode of Afib with RVR s/p amiodarone load, the patient developed hypercapnic respiratory failure with pH 7.15, CO2 78, O2 66 → ICU and intubated. Post intubation, the patient developed shock requiring 1L NS bolus followed by initiation of norepi gtt. On exam, the patient's SBP was 110s and HR 70s. Pertinent exam: Afib, rate controlled, + JVD without peripheral edema, decreased BS at bases, and extremities are warm. His TTE showed severe tricuspid regurgitation. LV ejection fraction was estimated to be 45 to 50%. Mechanical ventilation precluded the accurate estimation of right atrial pressure. CXR showed worsening of perihilar opacity which may reflect edema, infection, or acute lung injury, with moderate layering effusions. CT chest non-con showed dependent consolidation throughout the mid to lower lungs suspicious for aspiration, infection, or dependent edema and esophageal pathology that predisposed to aspiration. The patient became +1.5L with only 190mL UOP through the day. Renal was consulted for management of AKI and volume status. We should recommend:

A: Bolus IVF for septic shock

B: Give IV loop diuretics for ATN

C: Start patient on CVVHD

A Wise Nephrologist Once Told Me:

"If you don't know what to do with the fluid status, consult nephrology."

Case 3 – My Pearl for ATN Fluid Management

Lasix vs IVF?

- The patient's total solute is UP (from ATN) and renal injury already occurred (from aspiration + Afib c RVR)
- The million-dollar question is: Will perfusing pressure improve with off-loading vs additional loading solute during mixed shock?

My Approach:

- Give liters of base containing IVF during frank septic/hemorrhagic shock, sepsis (especially abdominal), and hepatorenal (give albumin)
- It is much easier to put solute in than taking out during ATN
- **When not so certain, give diuretic aiming even to slightly negative fluid balance (ATN is a solute retention state)**
- ARDS net trial – aggressive diuresis after initial IVF reduces ICU length of stay
- Need to be even more careful with IVF when patient is oligoanuric despite high dose loop diuretic (should involve renal in these cases)

Case 3 (ARS with answer)

- After his episode of Afib with RVR s/p amiodarone load, the patient developed hypercapnic respiratory failure with pH 7.15, CO2 78, O2 66 → ICU and intubated. Post intubation, the patient developed shock requiring 1L NS bolus followed by initiation of norepi gtt. On exam, the patient's SBP was 110s and HR 70s. Pertinent exam: Afib, rate controlled, + JVD without peripheral edema, decreased BS at bases, and extremities are warm. His TTE showed severe tricuspid regurgitation. LV ejection fraction was estimated to be 45 to 50%. Mechanical ventilation precluded the accurate estimation of right atrial pressure. CXR showed worsening of perihilar opacity which may reflect edema, infection, or acute lung injury, with moderate layering effusions. CT chest non-con showed dependent consolidation throughout the mid to lower lungs suspicious for aspiration, infection, or dependent edema and esophageal pathology that predisposed to aspiration. The patient became +1.5L with only 190mL UOP through the day. Renal was consulted for management of AKI and volume status. We should recommend:

A: Bolus IVF for septic shock

B: Give IV loop diuretics for ATN

C: Start patient on CVVHD

Case 3 – Assessment and Plan

Events: s/p IV diuril+bumex, IV Abx and off pressor with improved oxygenation

S: intubated

O: AF, HR 70s, RR 16, BP 154/76, O2 Sat 98% on 40%FiO2, Wt 73.5 (Adm 81.6), Intake 1.3L UOP 1.7L

PE: JVD elevated, +crackle at bases, no dependent edema, alert following command

Sodium	149
Potassium	4.0
Chloride	107
CO2	22
Urea Nitrogen, Ser...	124
Creatinine	3.36
Glucose	262 *
Anion Gap	20 *
eGFR - high estimate	18 *
eGFR - low estimate	15 *
Calcium	9.0
Magnesium, Serum /...	2.3
Phosphorus, Serum ...	6.2

Plan: FEN

- 1) Solute/Fluid
- 2) Na
- 3) K
- 4) HCO3/AG
- 5) Ca/Mg/Phos
- 6) BUN/Nutrition/Uremia

Case 3 – Assessment and Plan

1) Solute/Fluid – Total solute still up with pulm edema, perfusion pressure fine

Continue IV diuril and bumex

2) Na (149) – Water deficient (WHAT? Should I give diuretics?)

What to do???

3) K (4) – Total body K adequate for now, monitor for hypoK

4) HCO3/AG (22/20) – Met Alkalosis (from diuretics) and Gap acidosis (from ATN)

5) Ca/Mg/Phos (9/2.3/6.2) – HyperPhos from decreased excretion

Renal diet +/- phos binder pending on trend

6) BUN/Nutrition/Uremia (132) – Uremia? Dialysis?

Case 3 (ARS)

- Patient is hypertensive, + pulm edema and + hypernatremia. How to manage the patient?

A: Continue IV diuril and bumex for volume overload

B: Waitful watching

C: Only give diuril and stop IV bumex to generate hyponatremia

D: Continue IV diuril and bumex and give NGT water 500cc q4hr

E: Stop IV diuril and bumex and give NGT water 500cc q4hr

Case 3 – Volume Expansion And Dehydration

Events	"Euvolemic"	"CHF"	Diuresis	Diuresis	Intubation	Diuresis	Auto-Diuresis
	Baseline	Admission	Day 1	Day 2	Day 3	Day 4	Day 5
Total Na (meq)	5600	6020	5920	5820	5820	5770	5670
Total Body Water (L)	40	43	42.2	41.4	40.1	39.6	37.6
[Na] (meq/L)	140	140	140	142	145	146	151
Na PO Intake (meq)			50	50	150	50	50
Water PO Intake (L)			1.2	1.2	1	1	1
Urinary Na Output (meq)			150	150	150	100	150
Urinary Water Output (L)			2	2	2	1.5	3
Net Na Balance (meq)		420 +	100 -	100 -	0	50 -	100 -
Net Water Balance (L)		3 +	0.8 -	0.8 -	1 -	0.5 -	2 -

Case 3 (ARS with answer)

- Patient is hypertensive, + pulm edema and + hypernatremia. How to manage the patient?

A: Continue IV diuril and bumex for volume overload

B: Waitful watching

C: Only give diuril and stop IV bumex to generate hyponatremia

D: Continue IV diuril and bumex and give NGT water 500cc q4hr

E: Stop IV diuril and bumex and give NGT water 500cc q4hr

Overview

- The pre, post, and "intrinsic" (15 mins)
- The patient's Cr bumped, what now (45 mins)
- **Will the patient need dialysis (5 mins)**
- Will the patient recover (5 mins)
- Covid-19 and kidney injury (5 mins)

A Wise Nephrologist Once Told Me:

"The rules of A, E, I, O, U are not helpful to a Nephrologist."

Case 3 – My Pearls for Dialysis Need

- BUN/Nutrition/Uremia (132) – Uremia? Dialysis?

1) Acidosis, Electrolytes, Overload

-- oligo-anuria without hope of renal recovery soon

2) Ingestion

-- depends on renal function, level, and type of toxin

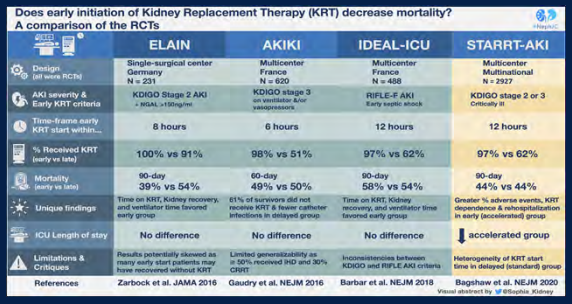
3) Uremia

-- AMS (diagnosis of exclusion)

-- cardiac rub

-- poor nutritional intake, N/V

Case 3 – Any Outcome Diff with early HD



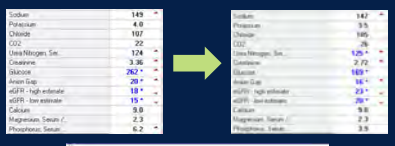
Does early initiation of Kidney Replacement Therapy (KRT) decrease mortality?
A comparison of the RCTs

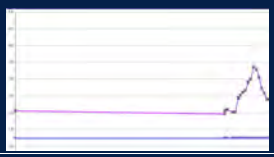
	ELAIN	AKIKI	IDEAL-ICU	STARRT-AKI
Design (all were RCTs)	Single-surgical center Germany N = 231	Multicenter France N = 620	Multicenter France N = 488	Multicenter Multinational N = 2927
AKI severity & Early KRT criteria	KDIGO Stage 2 AKI + NGAL >150ng/ml	KDIGO stage 3 on ventilator &/or vasopressors	RIFLE-F AKI Early septic shock	KDIGO stage 2 or 3 Critically ill
Time-frame early KRT start within...	8 hours	6 hours	12 hours	12 hours
% Received KRT (early vs late)	100% vs 91%	98% vs 51%	97% vs 62%	97% vs 62%
Mortality (early vs late)	90-day 39% vs 54%	60-day 49% vs 50%	90-day 58% vs 54%	90-day 44% vs 44%
Unique findings	Time on KRT, Kidney recovery, and ventilator time favored early group	61% of survivors did not receive KRT & fewer catheter infections in delayed group	Time on KRT, Kidney recovery, and ventilator time favored early group	Greater % adverse events, KRT dependence & rehospitalization in early (accelerated) group
ICU Length of stay	No difference	No difference	No difference	↓ accelerated group
Limitations & Critiques	Results potentially skewed as many early start patients may have recovered without KRT	Limited generalizability as ≥ 50% received IHD and 30% CRRT	Inconsistencies between KDIGO and RIFLE AKI criteria	Heterogeneity of KRT start time in delayed (standard) group
References	Zarbock et al. JAMA 2016	Gaudry et al. NEJM 2016	Barbar et al. NEJM 2018	Bagshaw et al. NEJM 2020

Visual abstract by @Sophia_Kidney

Case 3 – End

The patient received IV bumex and 2.5L FW via NGT. His respiratory status improved leading to successful extubation the next day. The patient's FEN parameters all started to improve:





Case 3 – AKI Significance

- Up to 20% of all admissions
- Independently associated with increased:
  - Inpatient mortality
  - Length of stay
  - Hospital costs
- Rise in serum Cr of ≥0.5 mg/dL:
  - 6.5-fold increase in odds of death
  - 3.5-day increase in LOS
  - $7,500 in excess hospital costs

Zeng JASN 2014; Chertow JASN 2005 UCSF

Overview

- The pre, post, and "intrinsic" (15 mins)
- The patient's Cr bumped, what now (45 mins)
- Will the patient need dialysis (5 mins)
- **Will the patient recover (5 mins)**
- Covid-19 and kidney injury (5 mins)

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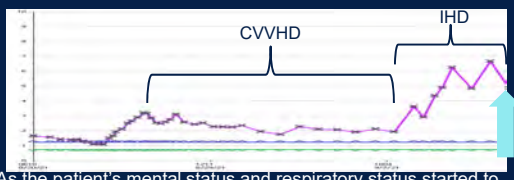
Case 4

- 42 y/o male with PMH of HTN and obesity admitted for progressive encephalopathy, weakness, and fevers diagnosed with West Nile virus-meningoencephalitis. His hospital course was complicated by hypercapnic respiratory failure and septic shock leading to oligo-anuric ATN initiated on continuous veno-venous hemodialysis for acidosis and volume overload. His Cr trend:



- As the patient's mental status and respiratory status started to improve, his wife asked: "Will he need dialysis for the rest of his life?"

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Case 4 -- AKI-D Significance

- 6-7% of ICU patients
- Independently associated with short-term mortality

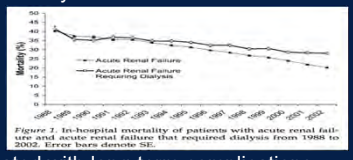

Figure 1. In-hospital mortality of patients with acute renal failure and acute renal failure that required dialysis from 1988 to 2002. Error bars denote SE.

- Associated with long-term complications:
  - CKD, ESRD
  - CVD: HTN, CHF, CHD
  - Stroke

Cerda Lancet 2015; Lo KI 2009; Odutayo JASN 2017; Waikar JASN 2006 UCSF

Case 4 – AKI-D Recovery Probabilities

Pre-admission eGFR (mL/min/1.73m²)		**Renal Recovery (among survivors)**
>90	(inpt death 53%)	**100%** (Schiffl NDT 2006)
≥45	(inpt death 41%)	**84%** (Lo KI 2009)
30-44	(inpt death 35%)	**58%** (Hsu CJASN 2009)
15-29	(inpt death 28%)	**37%** (Hsu CJASN 2009)

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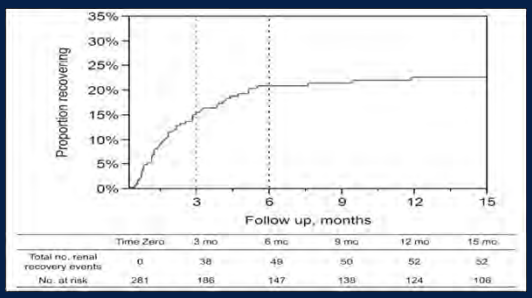
Case 4 – AKI-D Recovery Timing



	Time Zero	3 mo	6 mo	9 mo	12 mo	15 mo
Total no. renal recovery events	0	38	49	50	52	52
No. at risk	281	186	147	139	124	106

Hickson AJKD 2015

UCSF

Case 4 – AKI-D Better Outcome?

Table 2 | **RRT characteristics that might affect recovery from AKI**

RRT characteristic	Effect on renal recovery	Effect on patient recovery
Modality (intermittent, prolonged intermittent, continuous, peritoneal)[a]	Intermittent RRT might delay recovery	No effect
Fluid purity and quality standards	Dialysate purity might affect recovery	No effect
Membrane type[a]	Bioincompatible membranes might delay recovery	Bioincompatible membranes might affect recovery
Anticoagulation	No reported effect on recovery	Uncertain effect
Haemodynamic stability[a]	Hypotension might delay recovery	Uncertain effect
Mode of solute clearance (diffusion or convection)[a]	No evidence of effect	No evidence of effect
Ultrafiltration rate	Rapid fluid removal might delay recovery by causing hypotension	No data
Fluid Balance[a]	A positive fluid balance during RRT might delay recovery	A positive fluid balance during RRT might delay recovery
Dialysate temperature	A cooler dialysate temperature might minimize hypotension and promote recovery	No data
Dialysate composition	Higher dialysate sodium concentrations might minimize hypotension and thereby promote recovery	No data
Effect of RRT on other care parameters	RRT might affect drug dosing, nutritional support and nephrotoxin accumulation, which might affect recovery	RRT might affect drug dosing, nutritional support and nephrotoxin accumulation, which might affect recovery
RRT components (for example, access, circuit, fluid composition)	Possible adverse effect	Unknown
Dose/intensity (that is, small solute, clearance)[a]	Level 1 evidence that intensity of solute control does not affect recovery	Level 1 evidence that intensity of solute control does not affect recovery

[a]Only association studies; one randomized controlled trial (RCT). [b]Bioincompatible membranes are no longer in use. [c]Based on association. [d]Small underpowered RCTs. [e]Independent association. [f]No effect of small solute control in two large RCTs. AKI, acute kidney injury; RRT, renal replacement therapy.

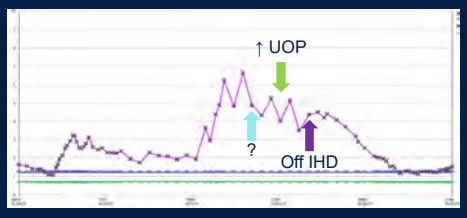
Chawla Nature Review: Nephrology 2017

10/15/2021

UCSF

Case 4 – Renal Recovery

- 42 y/o male with PMH of HTN and obesity admitted for progressive encephalopathy, weakness, and fevers diagnosed with West Nile virus-meningoencephalitis → AKI-D. I told the patient's wife that he has ~80% chance coming off dialysis by 3-6 months after discharged from the hospital.



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Overview

- The pre, post, and "intrinsic" (15 mins)
- The patient's Cr bumped, what now (45 mins)
- Will the patient need dialysis (5 mins)
- Will the patient recover (5 mins)
- **Covid-19 and kidney injury (5 mins)**

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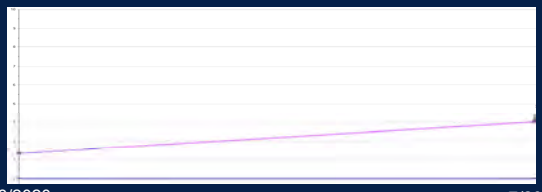
Case 5 – A Case of Covid-19

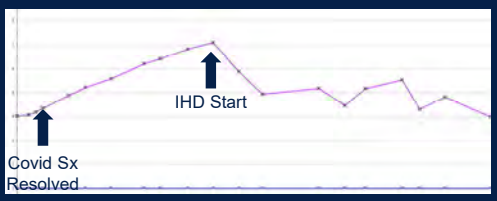
- 50 y/o female with PMH of HTN, DM, CKD 4 with nephrotic range proteinuria (last creatinine check 2020 was 2.3) admitted for mechanical fall due to weakness and found to have febrile illness with Covid (+ vaccinated with Janssen). No NSAID or other nephro-toxin exposure. We are consulted for elevated creatinine:



8/2020 7/2021

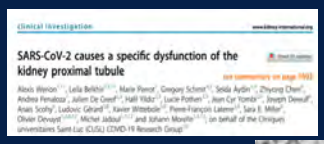
Case 5 – A Case of Covid-19

- 50 y/o female with PMH of HTN, DM, CKD 4 admitted for mechanical fall and Covid with ATN. The patient's creatinine continued to trend up despite supportive care (pt declined remdesivir due to fever and URI symptoms improved by day 2):



Case 5 – A Case of Covid-19

- What caused the ATN? Febrile illness? Pulmonary sepsis? Mechanical Fall? Or Covid-19?

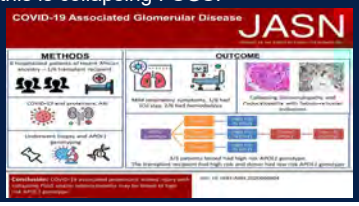

clinical investigation

SARS-CoV-2 causes a specific dysfunction of the kidney proximal tubule

Werion KI 2020 10/15/2021 UCSF

Case 5 – A Case of Covid-19

- Maybe this is collapsing FSGS:



Shetty JASN 2021 10/15/2021 UCSF

Summary

1) Be on the look out for non-ATN AKI
2) Don't be afraid to give loop diuretic with creatinine trending up to manage ATN
3) Absolute level of BUN ≠ yes/no uremia
4) Oligouria, ingestion, and uremia are the real indications for RRT
5) For AKI-D, ~80% for GFR >=45, ~40% for GFR <45 will come off dialysis 3-6 months after discharge
6) Covid-19 likely has some direct kidney injury effect

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References

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Questions or Comments?

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Updates & Controversies in Medical Consultation

Hugo Quinny Cheng, MD
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Updates in Perioperative Medicine

- Perioperative anticoagulation – increasing clarity
- Preoperative echo – useful or overused?
- Postoperative atrial fibrillation – anticoagulation?
- Surgery after COVID-19 – because of course
- Curbside consultation – risks for patient and provider

Managing Perioperative Anticoagulation

A head & neck surgeon asks how to manage anticoagulation in two patients on warfarin who will have major surgery next week.

- One patient has atrial fibrillation due to HTN
- The other has a mechanical aortic valve prosthesis
- Neither has any other relevant comorbidity

"Should we bridge with LMWH while their warfarin is held?"

1. Bridge for AVR only
2. Bridge for AF only
3. Bridge for both
4. Bridge for neither

BRIDGE Trial

Randomized trial of perioperative bridging for AF

- 1884 patients taking warfarin for atrial fibrillation or flutter
- Excluded: mechanical valve, stroke < 12 wks, cardiac & neurologic surgery
- Randomized to bridging with LMWH or placebo when warfarin interrupted for major or minor procedures
- Outcomes: 30-day arterial thromboembolism & bleeding

Douketis JD et al. NEJM, 2015; 373:823-33

BRIDGE Trial

	Bridged	No Bridge	
Embolic Event	0.3%	0.4%	Non-inferior
Major Bleeding	3.2%	1.3%	NNH = 53
Minor Bleeding	21%	12%	NNH = 12

Douketis JD et al. NEJM, 2015; 373:823-33

PERIOP 2 Trial

Randomized trial of bridging for AF or mechanical valve

- 1471 patients taking warfarin for atrial fib/flutter, mechanical valve, or both undergoing major or minor procedure
- Excluded mechanical valve patients with: prior stroke/TIA, multiple valves, or Starr-Edwards valve
- All patients received dalteparin prior to surgery
- Randomized to dalteparin or placebo after surgery
  - Therapeutic dose given after low-bleeding risk procedures
  - Prophylactic dose given after high-bleeding risk procedures
- Outcomes: 90-day thromboembolism & bleeding rates

Kovacs MJ et al. *BMJ* 2021;373:n1205

PERIOP 2 Trial

90-day Outcome	Bridge	No Bridge
Major thromboembolism	1.0%	1.2%
Major bleeding	1.3%	2.0%

- No significant difference in TE & bleeding risk in all comparisons
- Outcomes similar for patients with AF and mechanical valves
- Only 1 out of the 304 patients with mechanical valve had a TIA

Kovacs MJ et al. *BMJ* 2021;373:n1205

Conclusions from BRIDGE & PERIOP 2

Bridging does not reduce risk of thromboembolism:

- Strong evidence for atrial fibrillation
- Fair evidence for mechanical valves
- Baseline TE risk is low without bridging

Bridging likely increases the bleeding risk:

- Small effect on major bleeds, larger effect on minor bleeds

Caveat:

- Studies had relatively few patients with very high TE risk or bleeding risk

ACC Guideline for AF (2017)

	Normal Bleeding Risk*	Elevated Bleeding Risk*
High Thrombotic Risk CHA_2DS_2-VASc = 7+	Bridge	Clinical Judgment
Mod Thrombotic Risk CHA_2DS_2-VASc = 5-6	Clinical Judgment	No Bridge
Low Thrombotic Risk CHA_2DS_2-VASc = 1-4	No Bridge	

* Bleeding risk elevated if major bleed or ICH < 3 months, platelets low or abnormal, aspirin use, supratherapeutic INR, or prior bleeding with bridging or similar surgery

How to PAUSE a DOAC

Perioperative **A**nticoagulation **U**se for **S**urgery **E**valuation

- International study of 3007 elective surgery patients taking apixaban, rivaroxaban or dabigatran for atrial fibrillation
- Interrupted & resumed DOAC using standardized protocol
- Considers surgical bleeding risk and (for dabigatran) CrCl
- No bridging was permitted

Douketis et al. *JAMA Intern Med*. doi:10.1001/jamainternmed.2019.2431 Pub online August 5, 2019

PAUSE Trial Results

- Average CHADS2 = 2.1 (CHA_2DS_2VASc = 3.4)
- Patients having high bleeding risk surgery = 33%

	Dabigatran	Apixaban	Rivaroxaban
Major Bleeding	0.9%	1.35%	1.85%
Arterial Thrombo-embolism	0.6%	0.16%	0.37%

Douketis et al. *JAMA Intern Med*. doi:10.1001/jamainternmed.2019.2431 Pub online August 5, 2019

Dabigatran (CrCl ≥ 50), Apixaban, Rivaroxaban:

	Day - 3	Day - 2	Day - 1	OR	Day + 1	Day + 2	Day + 3
High Bleed Risk	💊	▨	▨		▨	? 💊	💊
Low Bleed Risk	💊	💊	▨		💊	💊	💊

Dabigatran with CrCl < 50:

	Day - 5	Day - 4	Day - 3	Day - 2	Day - 1	OR	Day + 1	Day + 2	Day + 3
High Bleed Risk	💊	▨	▨	▨	▨		▨	? 💊	💊
Low Bleed Risk	💊	💊	💊	▨	▨		💊	💊	💊

Preoperative Echocardiography

You perform an urgent preoperative evaluation on an 83-y.o. woman with a hip fracture. She has history of mild dementia, remote stroke, diabetes, and hypertension. She reports no dyspnea or angina. Functional capacity unknown, as she is sedentary. Cardiopulmonary exam is normal.

You wonder whether to obtain a transthoracic echo.

1. No, it's not indicated
2. Yes, it is indicated
3. Yes, because Anesthesia will insist

Preoperative TTE for Urgent Surgery

Japanese national database of 66,620 hip fracture surgery patients:

- 52% underwent preoperative TTE
- Patient having preop TTE were older & sicker
- Patients were matched using propensity score

	TTE	No TTE	
In-hospital Mortality	1.65%	1.74%	All N.S.
Cardiac Complications	0.39%	0.40%	
ICU Admission	0.46%	0.37%	

Yonekura H et al. Anesth Analg 2019;128:213–20

Guideline Indications for Preop Echo

- Suspect moderate or greater valvular stenosis or regurgitation if no echo in past year or significant clinical change since then

(Recommended)

- Heart failure with worsening dyspnea or other change in clinical status
- Dyspnea of unknown origin

(Reasonable)

- Reassessment of LV function in clinically stable patients with previous documented LV dysfunction may be considered if there has been no assessment within 1 year

(Not unreasonable)

ACC/AHA Guideline *Circulation.* 2014;130:2215–2245

Postoperative Atrial Fibrillation

You evaluate a 70-y.o. woman with h/o HTN who develops new postoperative (POAF) atrial fibrillation after total knee arthroplasty. You slow her rate with metoprolol, and she coverts back into NSR overnight. Echocardiogram shows normal LV function, normal valves, and mild LAE. Her $CHA_2DS_2VASc = 3$.

Would you recommend long-term anticoagulation?

1. No
2. Yes
3. Let the PCP decide

POAF Predicts Further AF & Stroke

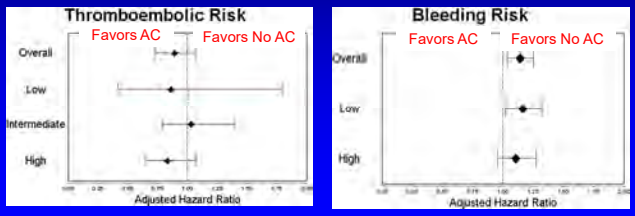
- Observational study of 452 patients with new POAF
- Matched by age, sex, year of surgery, and type of surgery with patient without POAF
- Followed out for 5 years after surgery

5-year Event Rate	POAF	No POAF	Adj. HR
Subsequent AF diagnosis	51%	12%	7.9 [4.8-13]
Stroke or TIA	10.7%	6.0%	2.7 [1.4-5.3]
All Cause Mortality	46.6%	37.2%	1.7 [1.3-2.1]

Siontis KC et al. JAMA. 2020;324(9):871-878

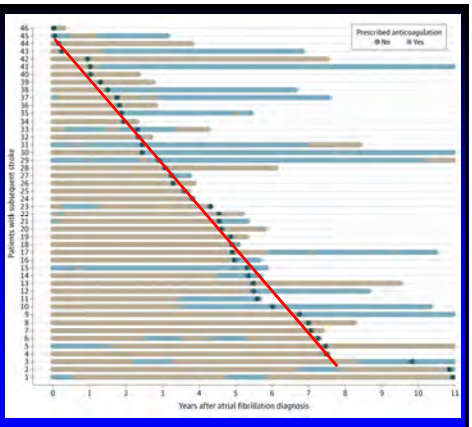
POAF: Does Anticoagulation Help?

- Retrospective study identified 22,007 patients with new POAF
- Looked at rates of stroke and bleeding based on whether they were prescribed anticoagulation
- Stratified based on CHA_2DS_2VASc & HAS-BLED



Can J Card, 2021. https://doi.org/10.1016/j.cjca.2020.08.023

Time Between POAF and Stroke



Siontis KC et al. JAMA. 2020;324(9):871-878

Stroke Risk Conclusions

Long-term stroke risk from POAF underappreciated:

- Patients with POAF have 2-fold (adjusted) risk of stroke compared to surgical patients who do not develop AF
- Stroke risk for POAF may be similar to patients with usual, non-surgical NVAF
- Benefits of anticoagulation are unproven

What to do?

- Guidelines recommend treating POAF as regular AF
- Evidence lacking for options: AC? Rhythm monitoring?

Surgery After COVID-19

You discharge a 50-y.o. obese woman after a 5-day admission for COVID-19 pneumonia. She is now oxygenating well, but still very tired and a little short of breath. On the way out, she says:

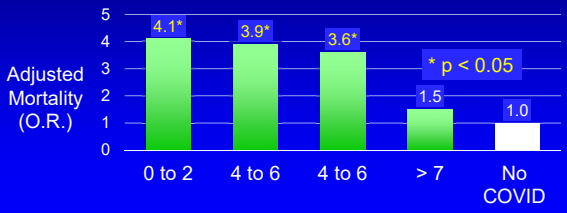
"I'm scheduled for a gastric bypass in 4 weeks. Can I still have surgery?"

1. Yes, that should be okay
2. Only if your symptoms resolve
3. No…really just don't

Surgery After COVID-19

Prospective cohort study of surgical cases in Oct 2020:

- 3127 patients (2.2%) had prior COVID-19 infection
- Adjusted mortality for non-infected patients = 1.5%



Weeks between COVID-19 infection and Surgery

Surgery After COVID-19

Higher mortality when surgery performed < 7 weeks after COVID-19 infection:

- Regardless of age, health, urgency/intensity of surgery
- Even if asymptomatic infection (though not as high)
- Even after 7 weeks, mortality higher in patients with ongoing or resolved symptoms compared with asymptomatic cases
- Same pattern observed for postop pulmonary complications

COVIDSurg Collaborative. *Anaesthesia* 2021, 76, 748–758

Surgery After COVID-19

UK Multidisciplinary Consensus Statement

- Surgical planning should consider: severity of infection; ongoing symptoms; comorbid & functional status, before and after SARS-CoV-2 infection; clinical priority and risk of disease progression; and complexity of surgery
- Avoid elective surgery within 10 days of mild/mod infection & 15-20 days of severe infection
- Elective surgery should not be scheduled within 7 weeks of diagnosis, unless outweighed by the risk of delaying
- Delaying surgery beyond 7 weeks should be considered in patients with persistent symptoms

El-Boghdadly K et al. *Anaesthesia* 2021, 76, 940–946

Are Curbside Consults Safe?

A surgeon calls you to discuss admission for patient with a suspected infection. Based on this conversation, it doesn't sound like admission is necessary.

However, you wonder whether you're liable if you give bad advice on a patient you're not treating.

1. You're safe; there's no duty to treat
2. Put your lawyer on speed-dial
3. What state am I practicing in?

Curbside Consults

Studied 47 requests for curbside advice to hospitalist

- Curbside consultant could ask questions ad lib
- Made recommendations without seeing patient or chart
- Different hospitalist performed formal, in-person evaluation

Questions:

- Did curbside consultant obtain accurate information?
- Did advice and management differ?

Burden, M et al. *J Hosp Med*, 2013; Jan;8(1):31-5

Curbside vs. Formal Medicine Consult

Compared to formal consultation, how often did curbside evaluation lead to:	
Incomplete clinical information	34%
Inaccurate clinical information	28%
Any difference in management	60%
Major difference in management	36%

Burden, M et al. *J Hosp Med*, 2013; Jan;8(1):31-5

Liability from Curbside Consults

Traditional view:

- Physician-patient relationship ("duty to care") required for malpractice liability
- Purely curbside consultation does not establish treatment relationship – but deeper involvement (chart review, visiting patient, documentation, care coordination) blurs the line

Minnesota & "reasonably foreseeable":

- Warren v. Dinter (2018)
- "duty arises…when the physician provides medical advice and it is foreseeable that the third party will rely on [it]"

Curbside with Caution

Be wary when giving (or requesting) informal advice:

- Only for basic, generic questions
- Avoid in unstable or critically ill patients
- If you're asking a lot of questions, do a formal consult
- Offer to perform formal consultation; insist on it if "curbsided" again on same patient
- Don't visit patient, write orders, review chart, or submit bill

Take Home Points

1. Most patients on anticoagulation of atrial fibrillation or mechanical valves don't require perioperative bridging
2. Echocardiography has a role in preoperative evaluation, but it's smaller than you might think
3. Postoperative atrial fibrillation predicts future stroke and mortality; benefit vs. risks of anticoagulation uncertain
4. Delay elective surgery at least 7 weeks after COVID-19 diagnosis if possible, even longer if still symptomatic
5. Exercise caution when providing curbside advice

Thank You

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Cardiology Pearls for the Hospitalist

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Management of the Hospitalized Patient
October 22, 2021

Disclosures

- No Conflicts of Interest
- No Financial Disclosures

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Outline

- **Coronary Artery Disease**
  - Aspirin and prevention of coronary artery disease (CAD)
  - Antiplatelet therapy for secondary prevention
  - Management of combined anticoagulation and antiplatelet agents
- **Heart Failure**
  - Updates in Medical Therapies: ARNI and SGLT2 Inhibitors
  - Treatment of Functional Mitral Regurgitation
  - Putting it all together: Rethinking the algorithm for $HF_{reduced}EF$

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Cardiology Pearls for the Hospitalist

- Major Society Guideline Updates 2016-2021
- Clinical Trials Published 2016-2021

Address common questions from
Internal Medicine / Hospitalist Community

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Acronyms

- **ACS**: Acute Coronary Syndrome
- **BMS:** Bare Metal Stent
- **CAD**: Coronary Artery Disease
- **CABG:** Coronary Artery Bypass Graft Surgery
- **DAPT**: Dual Antiplatelet Therapy
- **DES:** Drug Eluting Stent
- **DOAC:** Direct Oral Anticoagulant
- **HF:** Heart Failure
- **MR:** Mitral Regurgitation
- **PCI**: Percutaneous Coronary Intervention
- **SIHD**: Stable Ischemic Heart Disease
- **VKA**: Vitamin K Antagonist

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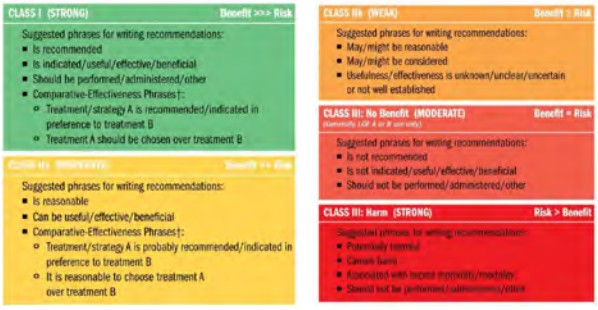
Strength of Guideline Recommendations



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- **Heart Failure**
  - Updates in Medical Therapies: ARNI and SGLT2 Inhibitors
  - Transcatheter Repair for Mitral Regurgitation
  - Putting it all together: Rethinking the algorithm for $HF_{reduced}EF$

7

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Primary Prevention: Aspirin

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Recent EMR Messages…

Dr. -

I just saw on the TV news tonight that for people over 65 years old that the daily dose of baby aspirin is not necessary and may even be counter productive. They are effective for people in their 40's.

Should I continue to take my daily dose of baby aspirin?
Please advise. Thank you

Hi Dr. -

I wanted to see if you think it would be reasonable to discontinue Mr. XX aspirin. His MI was remote in 1994 and he continues on rivaroxaban for afib. Would love to hear your thoughts.

Anticoagulation Pharmacist

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USPSTF 2021 DRAFT Guidance

U.S. Preventive Services TASK FORCE

Recommendation Summary

Population	Recommendation	Grade
Adults ages 40 to 59 years with a 10% or greater 10-year cardiovascular disease (CVD) risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD in adults ages 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit.	C
Adults age 60 years or older	The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults age 60 years or older.	D

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USPSTF 2016 Guidance

U.S. Preventive Services TASK FORCE

Recommendation Summary

Population	Recommendation	Grade
Adults aged 50 to 59 years with a 10% or greater 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years with a 10% or greater 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I

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Primary Prevention: Aspirin

ARRIVE Trial

Clinical Question:

What is the clinical benefit of 100 mg per day of aspirin in reducing the risk of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack in patients at moderate risk of cardiovascular events without diabetes?

Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial

J Michael Gaziano, Carlos Brotons, Rosa Coppolecchia, Claudio Cricelli, Harald Darius, Philip R Gorelick, George Howard, Thomas A Pearson, Peter M Rothwell, Luis Miguel Ruilope, Michal Tendera, Gianni Tognoni, the ARRIVE Executive Committee

Gaziano JM, Brotons C, Coppolecchia R, et al., on behalf of the ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018;Aug 26:

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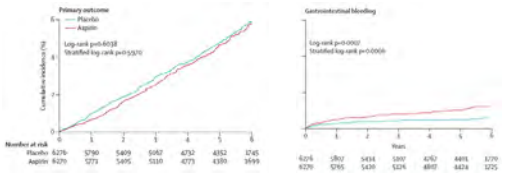
Primary Prevention: Aspirin
ARRIVE Trial

	Aspirin	Placebo	p Value
Composite Outcome of Cardiovascular Death, Myocardial Infarction, Unstable Angina, Stroke, or TIA	4.3%	4.5%	p = 0.60
Gastrointestinal Bleeding	0.97%	0.43%	p = 0.0007



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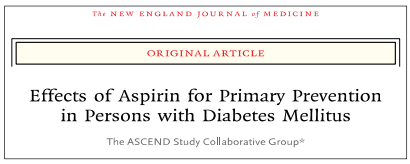
Primary Prevention: Aspirin
ASCEND Trial

Clinical Question:

What is the clinical benefit of 100 mg per day of aspirin in reducing the risk of vascular death, myocardial infarction, or stroke/transient ischemic attack in patients with known diabetes but no history of cardiovascular disease


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

The ASCEND Study Collaborative Group. Effects of Aspirin for Primary Prevention in Persons With Diabetes Mellitus. N Engl J Med 2018;379:1529-39.

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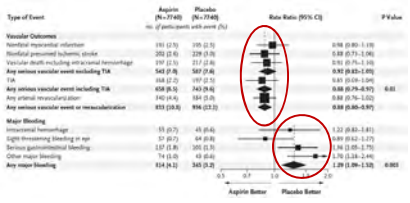
Primary Prevention: Aspirin
ASCEND Trial

	Aspirin	Placebo	p Value
Composite Outcome of Cardiovascular Death, Myocardial Infarction, Stroke, or TIA	8.5%	9.6%	p = 0.01
Major Bleeding	4.1%	3.2%	p = 0.003



Vascular Events Better

Bleeding worse

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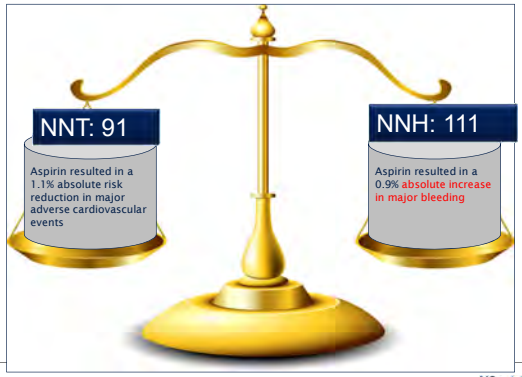
Primary Prevention: Aspirin
ASCEND Trial



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Primary Prevention: Aspirin

ASCEND Trial

What about cancer?...

	Aspirin	Placebo	p Value
Gastrointestinal Cancer	2.0%	2.0%	p = 1
All Cancer	11.6%	11.5%	p = 0.98

No Benefit in Reducing Fatal or Non-Fatal Cancer

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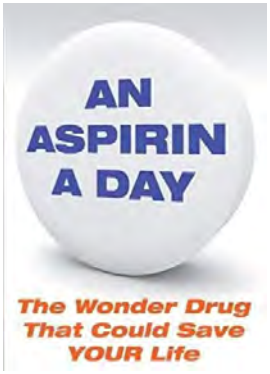
Primary Prevention: Aspirin



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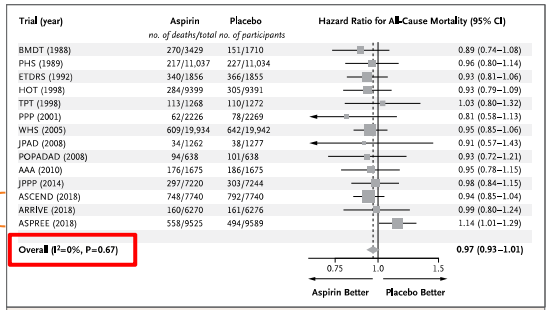
Primary Prevention: Aspirin

Aspirin and All Cause Mortality in
14 Primary Preventions Trials



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Primary Prevention: Aspirin

An aspirin a day...

Should not routinely be prescribed to patients without prior cardiovascular events due to a lack of clinical benefit and/or increased risk of bleeding that offsets the reduction in cardiovascular events

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Primary Prevention: Aspirin
2019 AHA/ACC Guidelines

4.6. Aspirin Use

Recommendations for Aspirin Use
Referenced studies that support recommendations are summarized in Online Data Supplements 17 and 18.

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (S4.6-1–S4.6-8).
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age (S4.6-9).
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding (S4.6-10).

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Outline

- **Coronary Artery Disease**
  - Aspirin and prevention of coronary artery disease (CAD)
  - Antiplatelet therapy for secondary prevention
  - Management of combined anticoagulation and antiplatelet agents
- **Heart Failure**
  - Updates in Medical Therapies: ARNI and SGLT2 Inhibitors
  - Transcatheter Repair for Mitral Regurgitation
  - Putting it all together: Rethinking the algorithm for $HF_{reduced}EF$

22

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Antiplatelet therapy in patients with known Coronary Artery Disease (CAD)

ACC/AHA FOCUSED UPDATE

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

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Oral Antiplatelet Agents

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Indication	ACS Post PCI Stroke PVD	ACS Post PCI Stroke PVD	Post PCI	ACS Post PCI
Dose Load Maintenance	 325 mg 81 mg DAILY	 300-600 mg 75 mg DAILY	 60 mg 10 mg DAILY	 180 mg 90 mg BID
Class	NSAID	2nd gen thienopyridine (PRODRUG)	2nd gen thienopyridine (PRODRUG)	CTPT
Mechanism	IRREVERSIBLE COX 1	IRREVERSIBLE $P2Y_{12}$	IRREVERSIBLE $P2Y_{12}$	REVERSIBLE $P2Y_{12}$
Peak Effect	1-3 hours	6 hours	4 hours	2 hours
CYP Metabolism	NA	2C19	3A4	3A4/5
FDA Approval		*1997*	*2009*	*2011*
Generic Approved	+	+	*2017*	*2018*

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Aspirin dosing in patients with Coronary Artery Disease

Aspirin Dosing in Patients Treated With DAPT

COR	LOE	Recommendation
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.

- Higher doses of aspirin are associated with bleeding and no increased anti-ischemic benefit
- When used with ticagrelor, aspirin doses of >100 mg are contraindicated

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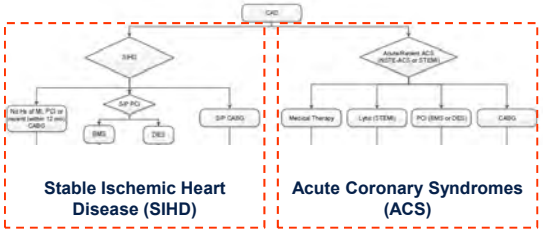
Duration of dual antiplatelet therapy (DAPT)

- Duration of DAPT depends on:
  - Underlying condition
  - Treatment provided



Stable Ischemic Heart Disease (SIHD)

Acute Coronary Syndromes (ACS)

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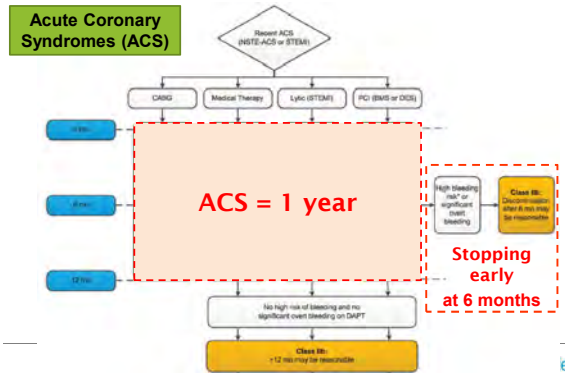
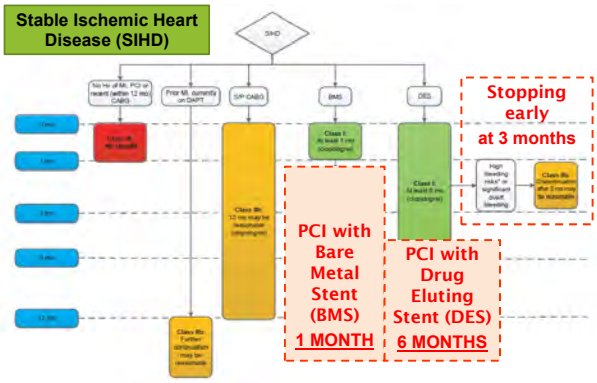
Duration of dual antiplatelet therapy (DAPT) in patients with ACS



Duration of dual antiplatelet therapy (DAPT) in patients with SIHD



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Duration of Antiplatelet Therapy
TWILIGHT Trial

Clinical Question:

Can ***aspirin be safely discontinued*** from the dual antiplatelet regimen ***after three months*** in patients undergoing PCI?


THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ticagrelor with or without Aspirin in High-Risk Patients after PCI

R. Mehran, U. Baber, S.K. Sharma, D.J. Cohen, D.J. Angiolillo, C. Briguori, J.Y. Cha, T. Collier, G. Dangas, O. Dudek, V. Džavík, J. Escaned, R. Gil, P. Gurbel, C.W. Hamm, T. Henry, K. Huber, A. Kastrati, U. Kaul, R. Kornowski, M. Krucoff, V. Kunadian, S.O. Marx, S.R. Mehta, D. Moliterno, E.M. Ohman, K. Oldroyd, G. Sardella, S. Sartori, R. Shlofmitz, P.G. Steg, G. Weisz, B. Witzenbichler, Y. Han, S. Pocock, and C.M. Gibson

Mehran R, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. NEJM 2019;Sep 26

Regimen:

Aspirin 81 + Ticagrelor x 12 months

OR

Aspirin 81+ ticagrelor x 3 months
then
ticagrelor + placebo x 9 months

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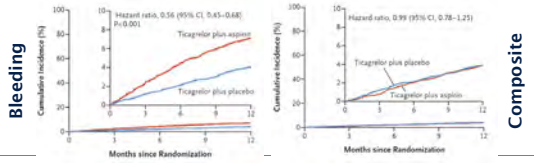
Duration of Antiplatelet Therapy
TWILIGHT Trial

	ASA + Ticagrelor (12 months)	ASA (3 mos) Ticagrelor (12 months)	HR P-value
Bleeding	7.1%	4.0%	0.56 P<0.001
Composite • Death (any cause) • Nonfatal MI • Nonfatal stroke	3.9%	3.9%	0.99 P <0.001 (non-inferiority)



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Antiplatelet Therapy Summary

- When used, dose of Aspirin for all patients with CAD is **81 mg daily**
- Duration of DAPT:
  - ACS Patients: **1 YEAR for ALL** (with/without stent)
  - SIHD (Stable Ischemic Heart Disease) Patients:
    - **Drug Eluting Stent (DES): 6 MONTHS**
    - **Bare Metal Stent (BMS): 1 MONTH**
- Stopping Early:
  - New trials show that shorter durations of aspirin therapy after stenting may be effective and result in lower bleeding risk

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Outline

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32

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Management of combined anticoagulant and antiplatelet therapy

EXPERT CONSENSUS DECISION PATHWAY

2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease

Triple Therapy: The conundrum

- Long-term treatment with oral anticoagulants is necessary in patients with:
  - Mechanical heart valves
  - Many with atrial fibrillation
- 20–30% of these patients have concomitant ischemic heart disease that requires PCI with stenting and subsequent antiplatelet therapy.
- The combination of oral anticoagulants and antiplatelets is associated with a high annual risk (4–16%) of fatal and non-fatal bleeding episodes.

Dewilde, Lancet 2013

What is the indication for triple therapy?

Dual Antiplatelet (DAPT)	Anticoagulation
Recent ACS (<1 year)	Atrial fibrillation
Recent PCI (< 6 months)	Mechanical heart valves
Chronic Ischemic heart disease	Deep venous thrombosis
Stroke	Pulmonary embolism
Peripheral vascular disease	Other indications

- Need to balance risk of thrombotic / ischemic events with bleeding
- Use risk scores to help assess:
  - $CHADS_2VASC$ for stroke risk in AF
  - HAS-BLED for bleeding risk

Multiple medical options for therapy

Dual Antiplatelet (DAPT)	Oral Anticoagulation
Aspirin	Coumadin
$P2Y_{12}$ Inhibitors	Dabigatran
Clopidogrel	Rivaroxaban
Ticagrelor	Apixaban
Prasugrel	Edoxaban

- What is the safety and efficacy of each medication?
- What combinations offer the greatest reduction in ischemic / thrombotic events?
- Which combinations have the lowest bleeding risk?

Four recent trials:
- WOEST (2013)
- PIONEER AF (2016)
- RE DUAL PCI (2017)
- AUGUSTUS (2019)

Triple therapy associated with higher bleeding without thrombotic protection

Preferred options in United States

			Bleeding	Thrombosis
WOEST				
Coumadin	+ Clopidogrel		19%	11%
Coumadin	+ Clopidogrel	+ Aspirin	44%	18%
PIONEER AF PCI				
Rivaroxaban 15 mg Daily	+ $P2Y_{12}$		17%	6.5%
Rivaroxaban 2.5 mg BID	+ $P2Y_{12}$	+ Aspirin	18%	5.6%
Coumadin	+ $P2Y_{12}$	+ Aspirin	27%	6.0%
RE DUAL PCI				
Dabigatran 110 mg BID	+ $P2Y_{12}$		15%	13%
Dabigatran 150 mg BID	+ $P2Y_{12}$		20%	13%
Coumadin	+ $P2Y_{12}$	+ Aspirin	26%	14%

Long Term Anticoag and Antiplatelet

AFIRE Trial

Clinical Question:

What is the safest and most effective medical regimen for patients with atrial fibrillation and chronic coronary artery disease (angiography with no intervention or PCI/CABG > 1 year prior)?


The NEW ENGLAND JOURNAL of MEDICINE

SEPTEMBER 19, 2019

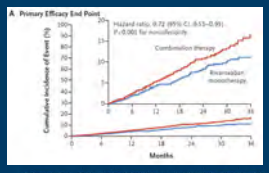
Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease

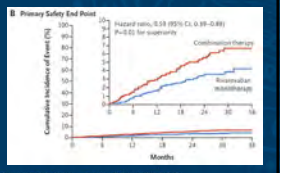
Yasuda, S, et al . Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. NEJM 2019;Sept 19: 1103.

Long Term Anticoag and Antiplatelet

AFIRE Trial

	Rivaroxaban + Placebo	Rivaroxaban + antiplatelet	p Value
Composite Outcome of Stroke, Embolism, Myocardial Infarction, Unstable Angina requiring revasc, or Death	4.14%	5.75%	p = <0.001
Major Bleeding	1.62%	2.76%	p = 0.01





Long Term Anticoag and Antiplatelet

AFIRE Trial

- Patients with atrial fibrillation and stable coronary artery disease more than 1 year after revascularization or in those with angiographically confirmed coronary artery disease not requiring revascularization
- Rivaroxaban monotherapy was **noninferior** to combination with respect to cardiovascular events and death from any cause
- Rivaroxaban monotherapy was **superior** with respect to major bleeding.

All this evidence now incorporated into the 2020 ACC Expert Consensus Pathway

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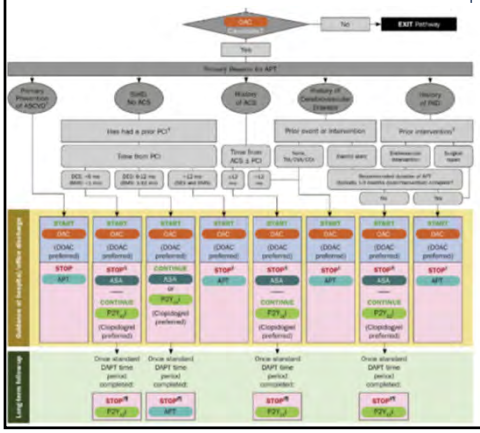
2021 ACC Expert Consensus

(For patients needing anticoagulant and antiplatelet therapy)



Key Themes

DOAC Preferred

Single antiplatelet agent only

Clopidogrel preferred

Long Term: DOAC ONLY (no aspirin!)

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Bottom Line regarding triple therapy

Anticoagulant

DOAC strongly preferred over Coumadin if the patient is a candidate

- DOACs should not be used for patients with:
  - Mechanical heart valves
  - Atrial fibrillation and mitral stenosis

P_2Y_{12}

Clopidogrel preferred over other P_2Y_{12} agents

Aspirin

Little need for triple therapy, can usually drop aspirin in favor of DOAC + P_2Y_{12} alone

Long Term

Drop BOTH antiplatelet agents (oral anticoagulation alone)

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The Role for Aspirin in 2021

	Primary Prevention	Recent PCI / Acute Coronary Syndrome	Chronic Coronary Disease
Not on Anticoagulation	No Antiplatelet	Dual Antiplatelet (P_2Y_{12} + Aspirin) 3-12 months	Single Antiplatelet (Aspirin)
Concurrent Anticoagulation	AC Alone (DOAC)	DOAC + Single Antiplatelet (P_2Y_{12}) 6-12 months	AC Alone (DOAC)

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Doc, Should I still take my aspirin?

	Aspirin?	Therapy in 2021
Primary Prevention	Not Routinely	Lifestyle
After Acute Coronary Syndrome (ACS) ▪ **Recent MI / PCI < 1 year**	As short as 3 months	P_2Y_{12} for 1 Year Aspirin 3-12 mos
ACS + Atrial fibrillation	NO	DOAC indefinitely P_2Y_{12} for one year
Chronic Coronary Disease ▪ **MI >1 year / PCI >6 mos**	YES	Aspirin Alone
Chronic Coronary Disease and Atrial Fibrillation	NO	DOAC Alone

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46

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Management of Heart Failure in 2021

47

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Standard of Care and State of the Art in 2021

Medical Therapy
- Beta Blockers
- ACE Inhibitors/ARBs
- Mineralocorticoid Receptor Antagonists
- **Angiotensin Receptor / Neprilysin Inhibitor (ARNI)**
- **Sodium Glucose co-transporter 2 Inhibitors (SGLT2i)**

Intracardiac Devices
- Implantable Cardiac Defibrillators
- Cardiac Resynchronization Therapy
- Pulmonary Artery Pressure sensors

Management of Valve Disease (particularly functional mitral regurgitation)
- Surgical Therapies
- **Percutaneous Interventional Therapies**

48

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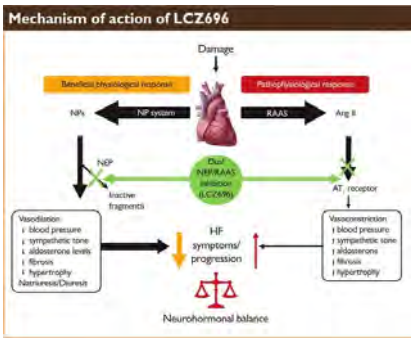
ARNI Mechanism

Angiotensin Receptor / Neprilysin Inhibitor (ARNI) = Sucabitril/Valsartan



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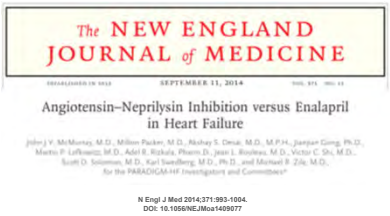
ARNI in heart failure with reduced EF

- **Clinical Question**: Does sucabitril/valsartan improve the risks of death or rehospitalization compared to enalapril in patients with heart failure?



N Engl J Med 2014;371:993-1004.
DOI: 10.1056/NEJMoa1409077

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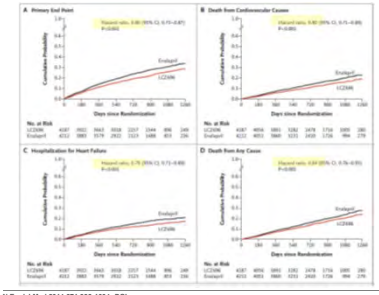
ARNI in heart failure with reduced EF

Patients on ARNI had significantly reduced rates of death and hospitalization for heart failure.



Double Blind, Randomized
- 8442 Patients
- Class II, III, IV HF
- EF <= 40%
- All on baseline therapy

Primary Outcome: composite of death or hospitalization for HF.

Stopped early at 27 months

ARNI group had more angioedema and hypotension.

N Engl J Med 2014;371:993-1004. DOI: 10.1056/NEJMoa1409077

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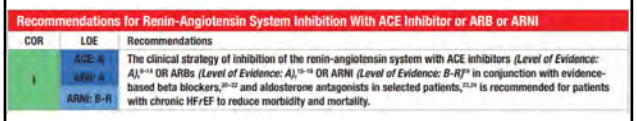
ARNI added to HF guidelines in 2016



N Engl J Med 2014;371:993-1004. DOI: 10.1056/NEJMoa1409077

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Current recommendation for ARNI use

Indications for Use of an ARNI

- HFrEF (EF ≤40%)
- NYHA class II–IV HF
- Administered in conjunction with a background of GDMT for HF in place of an ACEI or ARB

ARNIs	Starting Dose	Target Dose
Sacubitril/valsartan	24/26 mg-49/51 mg twice daily	97/103 mg twice daily

Maddox et al, 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment

53

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Current recommendation for ARNI use

A) Sacubitril/Valsartan

Contraindications

- Within 36 hours of ACEI use
- History of angioedema with or without an ACEI or ARB
- Pregnancy
- Lactation (no data)
- Severe hepatic impairment (Child-Pugh C)
- Concomitant aliskiren use in patients with diabetes
- Known hypersensitivity to either ARBs or ARNIs

Cautions

- Renal impairment:
  - Mild-to-moderate (eGFR 30-59 mL/ min/1.73 m²): no starting dose adjustment required
  - Severe* (eGFR <30 mL/min/ 1.73 m²): reduce starting dose to 24/26 mg twice daily; double the dose every 2–4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated
- Hepatic impairment:
  - Mild (Child-Pugh A): no starting dose adjustment required
  - Moderate (Child-Pugh B): reduce starting dose to 24/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated
- Renal artery stenosis
- Systolic blood pressure <100 mm Hg
- Volume depletion

Maddox et al, 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment

54

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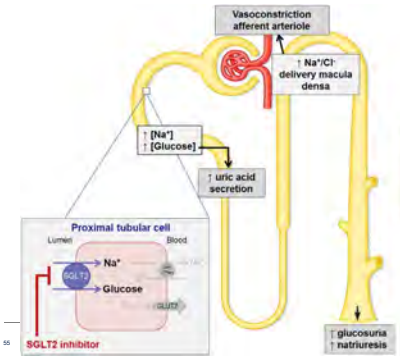
SGLT2 Mechanism

Sodium Glucose Co-Transporter 2 Inhibitor

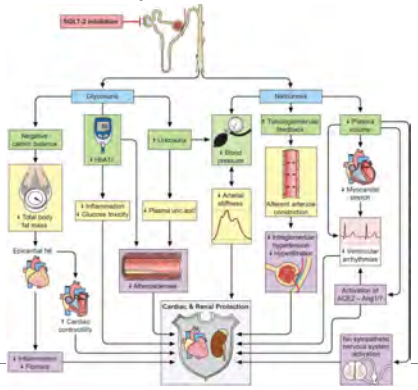


Clinical findings

- ↓ Plasma glucose
- ↓ Body weight
- ↓ Blood pressure
- ↓ Plasma uric acid
- ↓ Glomerular hyperfiltration

55

SGLT2 Pleotropic Effects



56

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SGLT2 in heart failure with reduced EF

- **Clinical Question**: Does empagliflozin (SGLT2i) improve the risks of death or rehospitalization compared in patients with heart failure with reduced EF?


The NEW ENGLAND JOURNAL of MEDICINE

OCTOBER 8, 2020

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

N Engl J Med 2020;383:1413-24.
DOI: 10.1056/NEJMoa2022190

57

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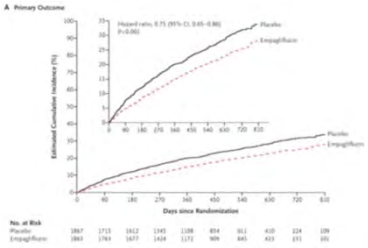
SGLT2 in heart failure with reduced EF

Patients on Empagliflozin had significantly reduced rates of death and hospitalization for heart failure.



Double Blind, Randomized
- 3730 Patients
- Class II, III, IV HF
- EF <= 40%
- All on baseline therapy

Primary Outcome: composite of death or hospitalization for HF.

Median follow up 16 months

Findings occurred in patients with and without diabetes

N Engl J Med 2020;383:1413-24. DOI: 10.1056/NEJMoa2022190

58

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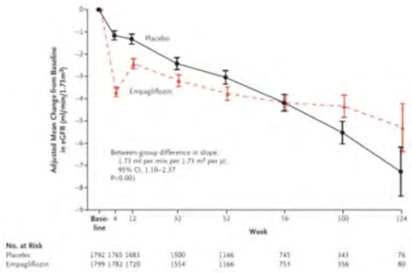
SGLT2 in heart failure with reduced EF

Patients also had a lower rate of decline in GFR



N Engl J Med 2020;383:1413-24. DOI: 10.1056/NEJMoa2022190

59

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Clinical Data for SGLT2i Heart failure with reduced EF

Table 2 Sodium glucose cotransporter 2 inhibitors in patients with heart failure and reduced ejection fraction

Study	Agent	Sample size (n)	Patients	Baseline HF medications	Follow-up (months)	Key findings
DAPA-HF[21]	Dapagliflozin 10 mg daily	Total: 4744 Drug: 2373 Placebo: 2371	Age 66 years, 76% male, 42% diabetes, LV EF 31%, eGFR 66 mL/min/1.73 m², NYHA class II 68%, class III 31%, class IV 1%.	ACEi 56%, ARB 28%, sacubitril-valsartan 11%, beta blocker 96%, MRA 71%.	18	CV death/HF hospitalisation: HR 0.74 (95% CI 0.65 to 0.85); worsening HF: HR 0.70 (95% CI 0.59 to 0.83); CV death: HR 0.82 (95% CI 0.69 to 0.98).
EMPEROR-Reduced[22]	Empagliflozin 10 mg daily	Total: 3730 Drug: 1863 Placebo: 1867	Age 67 years, 76% male, 50% diabetes, LV EF 27%, eGFR 62 mL/min/1.73 m², NYHA class II 75%, class III 24%, class IV 1%.	ACEi/ARB 70%, sacubitril-valsartan 19%, beta blocker 95%, MRA 71%.	16	CV death/HF hospitalisation: HR 0.75 (95% CI 0.65 to 0.86); HF hospitalisation: HR 0.70 (95% CI 0.58 to 0.85).

ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

Gulsin GS, et al. Heart 2021;0:1–6. doi:10.1136/heartjnl-2021-319185

60

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Current recommendation for SGLT2i

Indications for Use of an SGLT2 Inhibitor

- HFrEF (EF ≤40%) with or without diabetes
- NYHA class II–IV HF
- Administered in conjunction with a background of GDMT for HF

SGLT2 inhibitors	Starting Dose	Target Dose
Dapagliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 mg daily

Maddox et al, 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment

61

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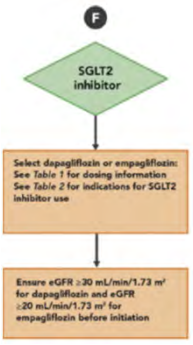
Current recommendation for SGLT2i



C) SGLT2 Inhibitors

Contraindications

- Not approved for use in patients with type I diabetes due to increased risk of diabetic ketoacidosis
- Known hypersensitivity to drug
- Lactation (no data)
- On dialysis

Cautions

- For HF care, dapagliflozin, eGFR <30 mL/min/1.73 m²
- For HF care, empagliflozin, eGFR <20 mL/min/1.73 m²
- Pregnancy
- Increased risk of mycotic genital infections
- May contribute to volume depletion. Consider altering diuretic dose if applicable
- Ketoacidosis in patients with diabetes:
  - Temporary discontinuation before scheduled surgery is recommended to avoid potential risk for ketoacidosis
  - Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level
- Acute kidney injury and impairment in renal function: consider temporarily discontinuing in settings of reduced oral intake or fluid losses
- Urosepsis and pyelonephritis: evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated
- Necrotizing fasciitis of the perineum (Fournier's gangrene): rare, serious, life-threatening cases have occurred in both female and male patients; assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise

Maddox et al, 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment

62

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Outline

- Coronary Artery Disease
  - Aspirin and prevention of coronary artery disease (CAD)
  - Antiplatelet therapy for secondary prevention
  - Management of combined anticoagulation and antiplatelet agents
- **Heart Failure**
  - Updates in Medical Therapies: ARNI and SGLT2 Inhibitors
  - Treatment of Functional Mitral Regurgitation
  - Putting it all together: Rethinking the algorithm for $HF_{reduced}EF$

63

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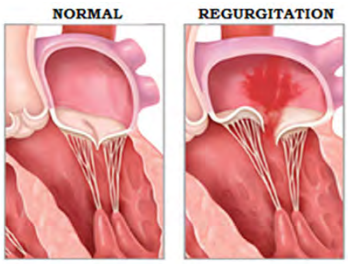
Functional mitral regurgitation



Dilation of a failing left ventricle can result in significant mitral regurgitation (MR).

MR increases left atrial pressures and can result in heart failure symptoms

If MR does not resolve with medical management of HF, additional therapies may be warranted

64

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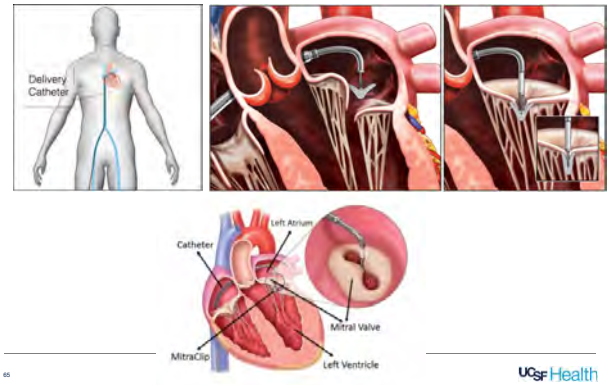
Percutaneous mitral valve repair



65

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Percutaneous mitral valve repair

- **Clinical Question**: Do patients who have heart failure with reduced EF and symptomatic moderate to severe mitral regurgitation benefit from transcatheter mitral valve repair in addition to guideline directed medical therapy?


ORIGINAL ARTICLE

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

N Engl J Med 2018;379:2307-18.
DOI: 10.1056/NEJMoa1806640

66

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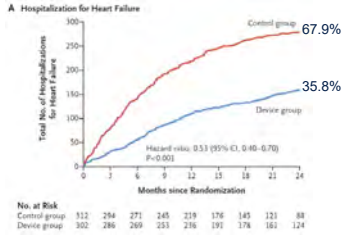
Percutaneous mitral valve repair

Patients who underwent mitral repair had a significant decline in hospitalization for heart failure.



Randomized controlled trial
- 614 patients
- 78 sites US and Canada
- HF symptomatic mod-sev MR
- All on maximum therapy

Primary Efficacy Outcome: Hospitalization for HF within 24 mos

Primary Safety Outcome: Freedom from complications at 12 mos

N Engl J Med 2018;379:2307-18. DOI: 10.1056/NEJMoa1806640

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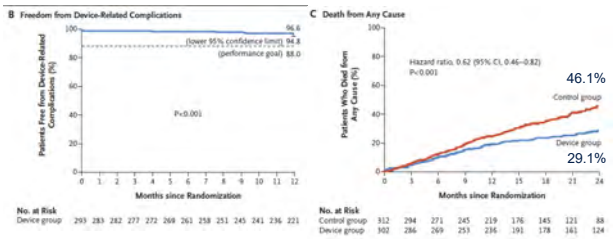
Percutaneous mitral valve repair

Patients who underwent mitral repair had a significant decline in death with low procedural complication rate.



N Engl J Med 2018;379:2307-18. DOI: 10.1056/NEJMoa1806640

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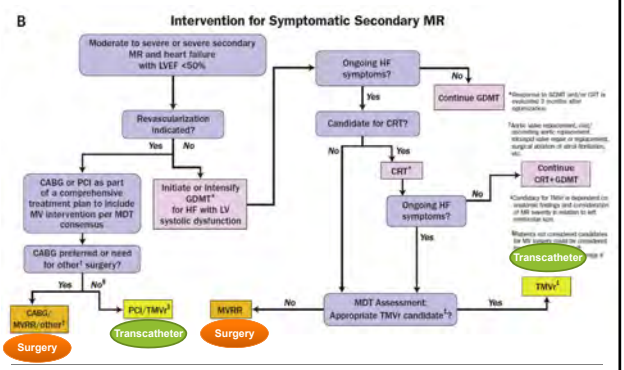
2020 ACC Focused Update

2020 Focused Update of the 2017 ACC Expert Consensus Decision Pathway on the Management of Mitral Regurgitation



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Treatment Algorithm

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

PUBLISHED BY ELSEVIER

EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

Maddox et al, 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment

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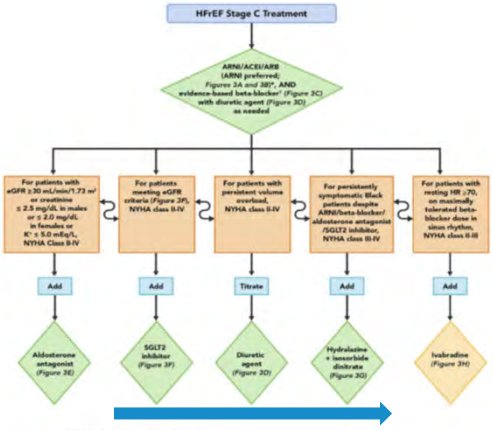

Maddox et al, 2021 Update to 2017 ECDP for Optimization of Heart Failure Treatment

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Steps in managing HF with reduced EF

(1) Start ACEi/ARB/**ARNI** (ARNI preferred)
(2) Start guideline directed beta blocker
(3) Use diuretic as needed for volume overload
(4) Uptitrate (1) and (2) as tolerated every 2 weeks with monitoring
(5) Start aldosterone antagonist if eGFR > 30 ml/min/1.73m and K < 5.0 meq/dL
(6) Start **SGLT2 inhibitor** if eGFR >20 ml/min/1.73m
(7) Repeat transthoracic echocardiogram in 2-3 months
(8) Refer for ICD/CRT therapies if EF remains low and patient qualifies
(9) Refer to valve center for consideration of valve therapy if significant mitral regurgitation

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Outline

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Take Home Points

- **Coronary Artery Disease**
  - Aspirin should not routinely be prescribed to patients without prior cardiovascular events
  - When used for treating CAD, dose of Aspirin is **81 mg daily**
  - Duration of DAPT:
    - ACS Patients: **1 YEAR for ALL** (with/without stent)
    - SIHD (Stable Ischemic Heart Disease) Patients:
      - **Drug Eluting Stent (DES): 6 MONTHS**
      - **Bare Metal Stent (BMS): 1 MONTH**
  - For patients requiring anticoagulation and antiplatelet therapies
    - Ensure there is an indication for both
    - DOACs are preferred over coumadin
    - Clopidogrel preferred over other P2Y12 agents
    - Aspirin can usually be omitted from the regimen

75
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Take Home Points

- **Heart Failure**
  - For your patients with heart failure and reduced EF:
    - ARNI confer a benefit for mortality and reduced hospitalizations
    - SGLT2 Inhibitors benefit patients with and without DM
    - Severe functional mitral regurgitation that has not responded to optimal medical therapy can be treated with transcatheter valve repair to reduce death and heart failure rehospitalization

76
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Questions?
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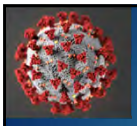


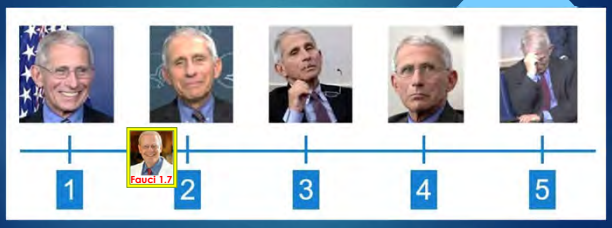
Covid-19 and the Transformation of Healthcare

Robert M. Wachter, MD
Professor and Chair, Dept. of Medicine
Univ. of California, San Francisco
@bob_wachter
robert.wachter@ucsf.edu

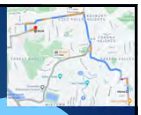
Disclosures

- Dr. Wachter serves on the board of directors of The Doctors Company (malpractice insurer), and on the scientific advisory boards of Teladoc (telemedicine provider), Amino (help employers choose healthcare providers), Curai (AI-enabled urgent care), EarlySense (bed-covering that measures vital signs); Commure (interoperability platform); and Notable (digital process automation). He also advises the San Francisco 49ers (football team) and SCOR (life insurance company) on Covid-19. He holds the Benioff Chair in Hospital Medicine from Marc and Lynne Benioff.

Before we start, let's check in to be sure everybody is feeling OK…



Talk Roadmap

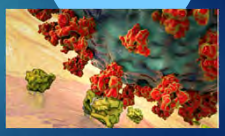


- A few thoughts on the current state of the pandemic and the problems it has exposed in our politics and society
- A few tech innovations that were accelerated by Covid
  - Telemedicine, dashboards
  - Plus a few that might have hit the tipping point, but didn't
- Entering the post-EHR era: why and what that means
- The future of healthcare's digital transformation

America's Unique Response

"Aspects of America's identify may need rethinking after COVID-19. Many of the country's values have seemed to work against it during the pandemic. Its individualism, exceptionalism, and tendency to equate doing whatever you want with an act of resistance meant that when it came time to save lives and stay indoors [and wearing masks & getting vaccinated], some people flocked to bars and clubs [and don't & didn't]. Having internalized years of anti-terrorism messaging following 9/11, Americans resolved to not live in fear. But SARS-CoV-2 has no interest in their terror, only their cells."

Ed Yong, *The Atlantic,* March 25, 2020



Where Are We Now?

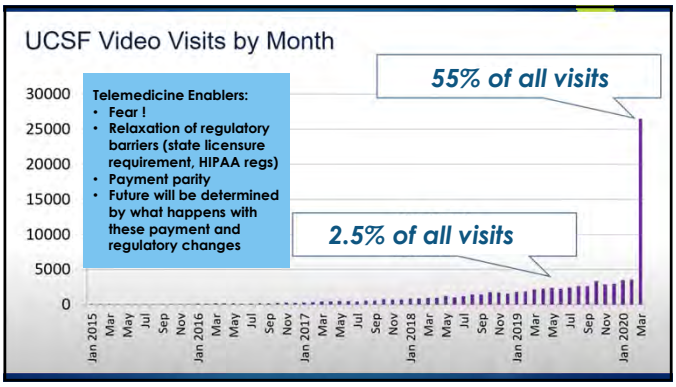
- Clear that Delta is a completely different virus – all prior assumptions about the virus/vaccines need to be reassessed
- Levels of immunity that we thought would be sufficient to create herd immunity are not enough to beat back Delta
- Boosters clearly needed in highest risk groups – others still debatable
- Society's tolerance of the unvaccinated has waned, to near-zero
  - Thus enthusiasm for mandates and other sharp-elbow tactics
- "Back to normal": now impossible to predict given need to reach >85% immune for herd immunity, low vaccine rates, and waning immunity from vaccine and infection

What Will the End Game Be?

Covid-19 and the Digital Transformation of Healthcare

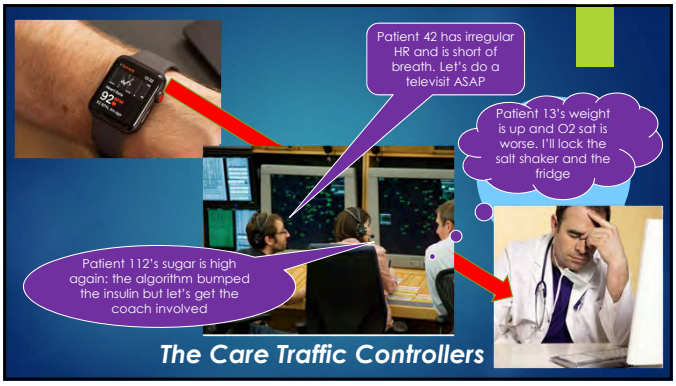
"I joined Mayo on January 1, 2020… and I was handed the 2030 [digital transformation] plan. Do you know that in 2020, we finished the 2030 plan?…. Covid accelerated 10 years into 10 months."

John Halamka, MD
President, Mayo Clinic Platform
on "In the Bubble" podcast, 4/28/21



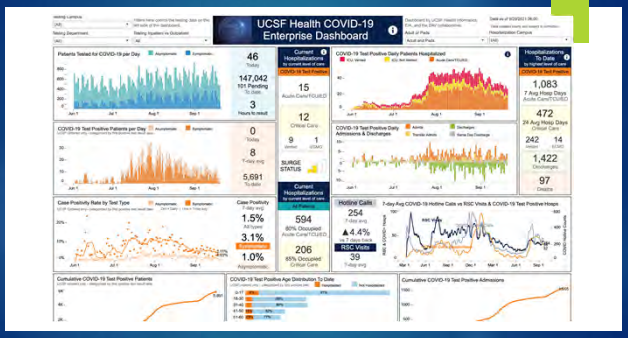
The Fundamental Question About Telemedicine/Virtual Visits

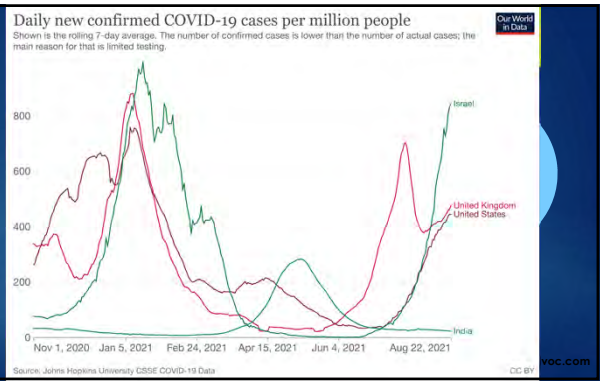
- Is it simply a visit replacement?
  - Fine if so: convenient for patients, maybe for providers
  - Opens up new non-geographically-determined care options
    - Potentially good for patients, but new competitive threats for health systems
- Or does it pave the way for true virtual care – the real game-changer
  - Patients no longer coming into office to get BP, weight, glucose checks, etc. means new dependence on digital data streams
  - Measures less episodic; more semi-continuous
  - The trillion-dollar question: how will we manage these new data flows?

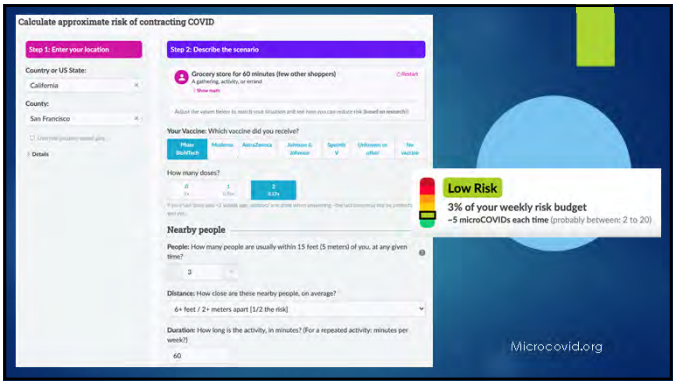


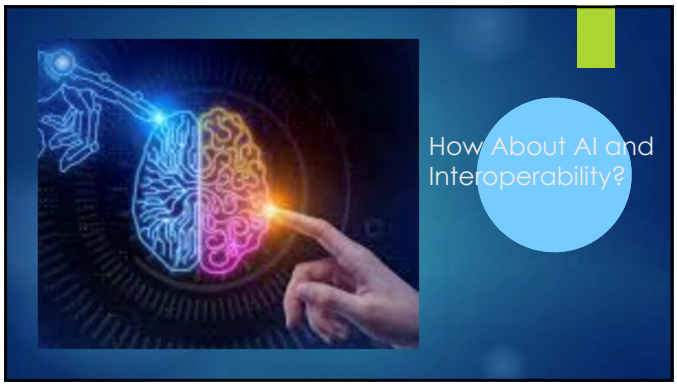
Dashboards

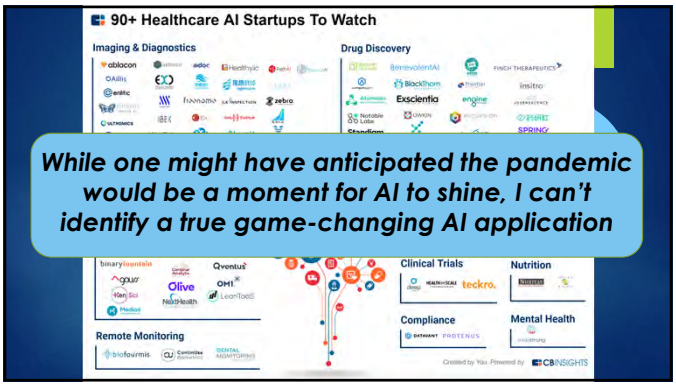
Finally (!)… taking all that data and delivering usable, real-time information in visually attractive and actionable form to managers and clinicians

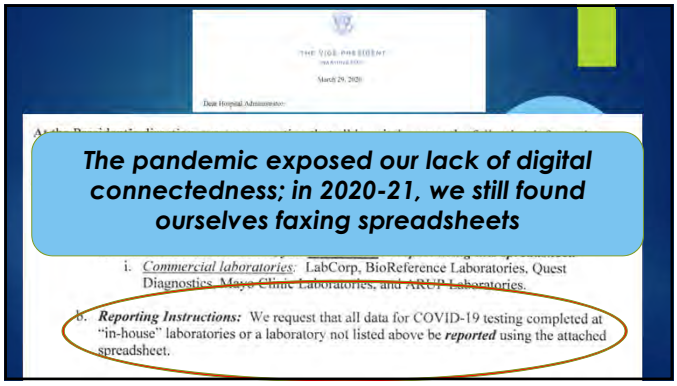







How About AI and Interoperability?


90+ Healthcare AI Startups To Watch
Imaging & Diagnostics
Drug Discovery
While one might have anticipated the pandemic would be a moment for AI to shine, I can't identify a true game-changing AI application
Clinical Trials
Nutrition
Compliance
Mental Health
Remote Monitoring

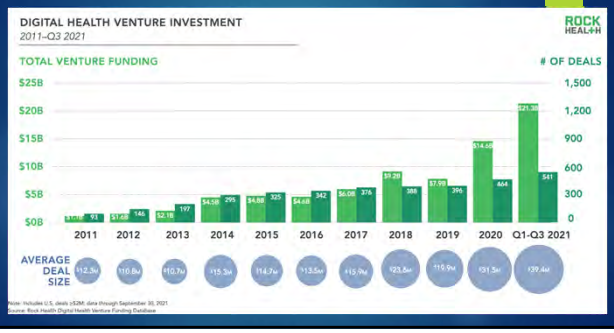

The pandemic exposed our lack of digital connectedness; in 2020-21, we still found ourselves faxing spreadsheets
i. Commercial laboratories: LabCorp, BioReference Laboratories, Quest Diagnostics, Mayo Clinic Laboratories, and ARUP Laboratories.
b. Reporting Instructions: We request that all data for COVID-19 testing completed at "in-house" laboratories or a laboratory not listed above be reported using the attached spreadsheet.


Health IT Needs Its Golden Spike
Epic
Cerner

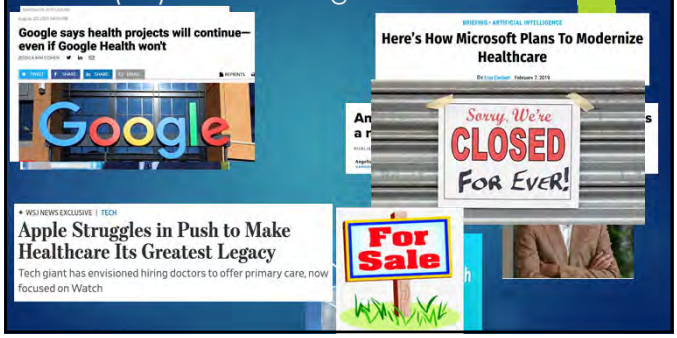
Maybe the Stupidest Thing I Ever Said to a Mentee

"What will you do after we've implemented our EHR?"

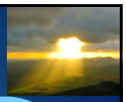
Digital Health Investments Accelerating



(Re) Enter the Digital Giants….



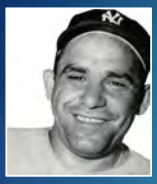
Why Health IT May Finally Be Entering a New (Post-EHR) Phase



- Winners in EHR derby: healthcare-specific companies, good at collecting data & moving it around
  - They were ready when healthcare went digital
  - Not expert in consumer-facing tools, user interface, data visualization, learning from data, communication….
- Now entering the post-EHR era, facilitated by value pressure, more interoperability, labor shortages and the overwhelming problem of the in-box, AI, digital companies maturing… and the obvious limitations of what EHRs can offer
- Healthcare organizations are going to need to remake themselves to thrive in this era

Several Easy Predictions, and a Hard One

- Health IT *will*, ultimately, transform and disrupt health and healthcare
  - Covid has shortened the timeline for this by several years
- The new system will be less institution-focused, less geographically determined, more patient-centric, and deliver higher quality, less expensive, and more equitable care
- The winners will be any one of these four parties:
  - Existing healthcare organizations that thoughtfully embrace transformation
  - EHR vendors that innovate and open their architecture
  - Digital giants that are able to maintain a focus on health (lower probability)
  - New companies (start-ups) that skillfully address important use-cases
- ***The hard thing to predict: when?***



"In theory there is no difference between theory and practice. In practice there is."

- Yogi Berra (maybe)

Neurological Emergencies

S. Andrew Josephson MD
Carmen Castro Franceschi and Gladyne K. Mitchell Neurohospitalist Distinguished Professor
Chair, Department of Neurology
Founder, Neurohospitalist Program
University of California, San Francisco

The speaker has no disclosures

Case #1

- A 67F is hospitalized with a community-acquired pneumonia. On Day#3 she is feeling much better awaiting discharge when her nurse finds her unresponsive with rhythmic shaking of all limbs.
- PMHx: COPD
- Meds: Ceftriaxone, NKDA
- SH: 100pk yr hx tobacco, no hx EtOH
- FH: No neurologic disease

Case #1

- You are called to the bedside and after 3 minutes, these movements have not stopped. Options for your next course of action are….

A. Continue to wait for the spell to subside
B. Administer IV Diazepam
C. Administer IV Lorazepam
D. Administer IV Fosphenytoin

Case #1

- Following Lorazepam 2mg IV x 3 (2 minutes apart), the patient is still having these movements (now 7 minutes). What is your next course of action?

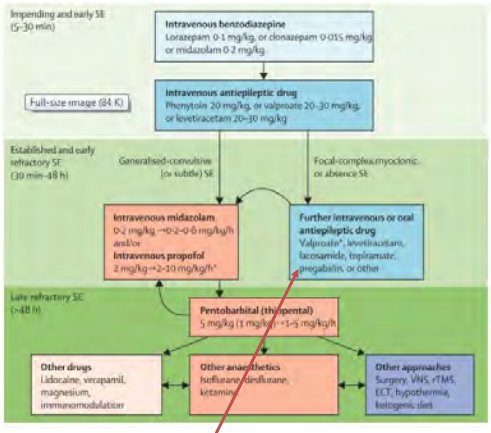
Status Epilepticus

- Changing definition and time window
- Incidence: 100,000 to 150,000 per year nationally
- Contributes to 55,000 deaths per year nationally
- 12 to 30 percent of epilepsy first presents as status
- Generalized convulsive status most dangerous

Status Epilepticus Algorithm: Real World

1. Lorazepam 2mg IV q2 minutes up to 6-8mg or Midazolam 10mg IM*
2. Fosphenytoin 18-20mg/kg (Dilantin Equivalents) IV**

3. General Anesthesia with continuous EEG
   a. IV Midazolam gtt
   b. IV Propofol gtt

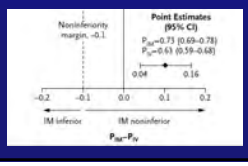


Recent Large Trial

Rossetti AO *Lancet Neurol*, 2011

IM Midazolam: RAMPART

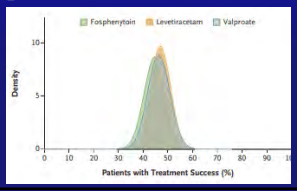
- Out of hospital non-inferiority trial
  - 4 mg lorazepam IV vs. 10 mg midazolam IM (the latter using a novel autoinjector)
- Primary outcome: absence of sz at time of ED arrival without the need for rescue therapy



Silbergleit R, et al. *N Engl J Med*, 2012

Which to Choose After Benzos: ESETT Trial

- After benzos, if still; seizing randomize to:
  - IV Fosphenytoin, Valproate, or Levetiracetam
- Primary outcome was cessation of status and improvement in mental state at 60 min



Kapur J, et al. *N Engl J Med*, 2019

Seizure Management: Once the Spell Stops

- Key Question:

  1st seizure or known epilepsy

Seizure Management: First Seizure

- Careful history of the spell: before (including recent events), during, after
- Determine all meds patient is on
- Careful neuro exam looking for focal signs
  - Focal exam= Partial seizure= Focal lesion

Seizure Management: First Seizure

- Work-up for provokers
  - Head trauma?
  - Utox, EtOH history and possible level
  - CBC, Lytes, Ca/Mg/Phos, BUN/Cr, LFTs
  - CT (usually with contrast)
  - Very low threshold to LP
- Needs outpatient work up including: EEG, MRI, and neurologic consultation

Seizure Management: Known Epilepsy

- 1. Non-compliance
  - Determine AEDs including doses
  - Send levels of AEDs if possible
  - Med-Med interactions
- 2. Infection
  - CXR, urine, blood cx, consider LP
- Best to curbside primary neurologist regarding any medication changes to current regimen

Case #2

- A 50 year-old man is brought in to the ED by his girlfriend with several days of paranoia and unusually aggressive behavior.
- General physical exam is normal. Neurologic examination shows a disoriented man threatening the staff
- Labs: Lytes, CBC, BUN/Cr, LFTs, Utox all nl
- CT head negative, CXR negative, U/A negative

What is the next test you would like to order?

A. MRI Brain
B. LP
C. Blood Cultures
D. Urinary Porphyrins
E. EEG

Lumbar Puncture

- Opening Pressure 19 cm H_20
- 18 WBCs (94% Lymphocytes)
- CSF Protein 58
- CSF Glucose 70
- Gram stain negative

- Empiric treatment begun

HSV-1 Meningoencephalitis

- Diagnosis
  - CSF lymphocytic pleocytosis (can be normal)
  - EEG (can be normal)
  - MRI (can be normal)
  - CSF HSV PCR
- If suspected, start IV acyclovir 10-15mg/kg q 8 hours

Meningitis Treatment by the Neurologist

- Perform LP immediately after imaging if any CSF infection suspected
- Empiric Bacterial Treatment
  - Vanco 1 gram IV q6-8 hrs
  - CTX 2 grams IV q12 hrs
  - Amp 2 grams IV q4 hrs (if immunosup., >60)
  - Dexamethasone 10mg IV q6

Treatable Causes of a Lymphocytic Pleocytosis

- Viral
  - Acute HIV
  - HSV, VZV
  - CMV
- Bacterial
  - Syphillis
  - Lyme
  - Leptospirosis

Treatable Causes of a Lymphocytic Pleocytosis

- Fungal
- TB
- Neoplastic
- Incompletely treated bacterial meningitis
- Parameningeal Focus

Case #3

- A 63yo man comes to the ED with 3 days of inability to walk. The patient reports a 2 week history of tingling in his hands and feet while also stating that he has been stumbling while walking for five days.

Case #3

- Exam
  - General exam nl with stable vitals
  - Mental status, cranial nerves normal
  - Motor exam with mild-moderate symmetric weakness prox>distal in the upper ext., distal>prox in the LEs
  - Sensory exam completely normal
  - Reflexes 2+ throughout except 0 ankles, plantar response flexor bilaterally

Case #3: Additional Tests

FVC/MIF: 1.2L, -30

Lumbar Puncture: Opening pressure normal, 2 WBC, Zero RBC, Protein 102, Glucose normal

Guillain Barre Syndrome: Key Points

- Clinically must think in the setting of paresthesias and weakness
  - Normal sensory exam, weakness not always ascending
  - Areflexia the rule, but not early in the disease
  - High protein with no cells on LP the rule, but not early in the disease
- EMG/NCS for diagnosis
  - Axonal and Demyelinating forms
- Antecedent illness or infection only 30%
- Other Variants: Miller Fisher variant w/ GQ1b Ab

Guillain Barre Syndrome: Key Points

- What will kill the patient
  - Respiratory Failure: Intubate for less than 20cc/kg
    - Frequent MIF/FVC
    - ICU or stepdown care always
  - DVT/PE: SQ heparin
  - Autonomic instability: cardiac (telemetry), ileus
- Treatment
  - IVIg or Pheresis, NOT steroids
  - The earlier the better

Case #4

- A 40 yo man comes to the ED with increasing weakness and dyspnea. The patient states that he has a history of myasthenia gravis diagnosed at an OSH two weeks ago but "things are going downhill." He is on Mestinon (pyridostigmine) 60mg PO q4hrs and Prednisone 60mg PO qd. MIF is –10, FVC 250cc

Myasthenic Crisis

- True crisis vs. cholinergic crisis
- Triggers
  - Infection, surgery, initial steroids
- Management
  - Usually stop all anti-cholinesterase meds
  - Pheresis or IVIg
  - ICU, intubation, DVT/PE prophylaxis

Myasthenia Gravis: Key Points

- Two types of myasthenia
  - Young F>M
  - Old M=F
- Diagnosis
  - Antibodies (90% in generalized mysathenia)
  - EMG with repetitive stimulation

Myasthenia Gravis: Key Points

- Management
  - Pyridostigmine (Mestinon)
  - Immunosuppression
    - Prednisone first then Imuran/CellCept/Cytoxan
  - What about the Thymus?

Case #5

- A 32M comes to the emergency room with the "worst headache of his life" for 8 hours
- Non contrast CT is normal

Which of these historical points is most useful to differentiate SAH from benign headache syndromes?

A. Associated nausea/vomiting
B. Associated photophobia
C. Severity of pain
D. Peak time to maximal pain
E. Pain location

SAH Diagnosis

- CT sensitivity greatest early
- LP sensitivity greatest late
  - What do you look for?
    - Xanthrochromia?
    - Blood that fails to clear?

Wijdicks 2004

First 6-8 Hours

6-8hrs to 1-2 weeks

SAH Treatment

- Urgent Blood Pressure Management
- Etiology
  - 1. Aneurysm
    - Need to secure with clipping or coiling ASAP
      - ISAT trial (Lancet 2005)
  - 2. Trauma

Case #6

- A 65 year-old man with a history of DM, HTN presents with 1 day of imbalance and severe vertigo
- Examination shows R>L severe ataxia of the limbs with inability to walk due to imbalance. Power is normal throughout.

Which of the following most reliably distinguishes central from peripheral vertigo?

A. Severe vomiting
B. Inability to walk
C. Inability to sit upright without falling to one side
D. Presence of nystagmus
E. Slurred speech

Case #6 (con't)

- Patient discharged from the ED
- BIBA 24 hours later after respiratory arrest at home, now in coma

Emergent ICP Management

- Step 1: Head of bed to 30 degrees
- Step 2: Hyperventilation
  - Cerebral vasoconstriction with decreased P_aCO_2
  - Onset rapid
  - Lasts only 1-2 hours as buffering occurs
- Step 3: Mannitol 1 gram/kg IV (50-100g)
  - Removes brain water
  - Tolerance develops, must follow serum osms
- Step 4: Barbiturates (bolus then infusion)
- Consider ventriculostomy if indicated!

Emergent CPP Management

Cerebral Perfusion Pressure (CPP)

CPP = MAP - ICP

Cerebellar Ischemic Stroke

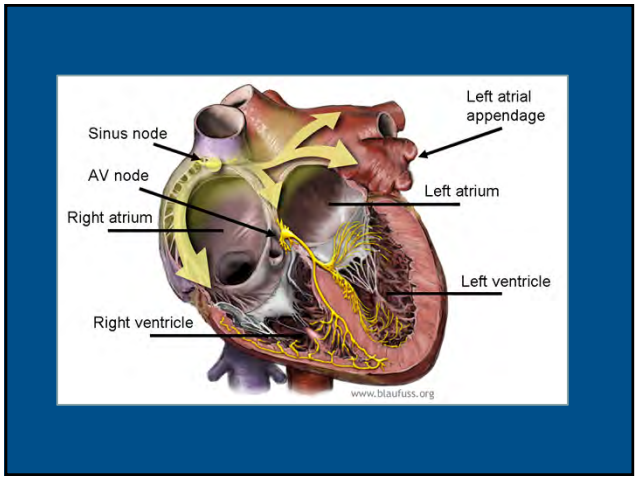
- Maximal swelling: 3-5 days
- Decompression indicated if patient decompensates
- Will only see on MRI
- “Malignant Meniere’s”

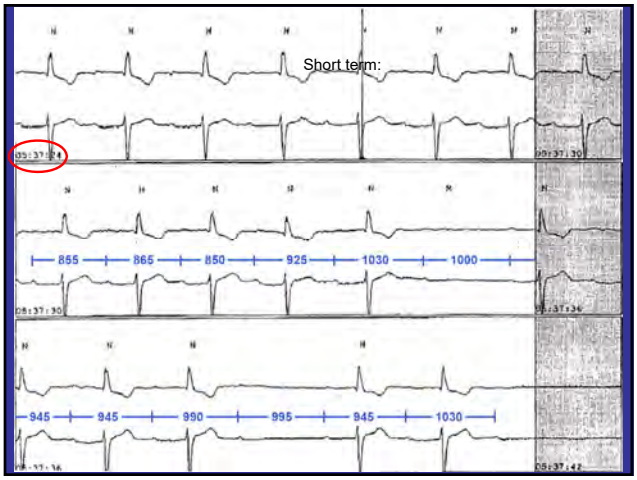
Disclosures

Research:
- NIH
- PCORI
- Baylis
- Eight Sleep
- Medtronic

Consultant:
- J&J
- InCarda

Equity
- InCarda





Sinus pauses (and vagotonic AV block are common and usually benign)

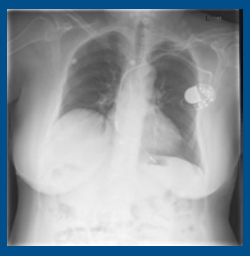
- Sleep study?

When do you consider a pacemaker for sinus node disease?

- SYMPTOMS
  - Presyncope or syncope with a sinus pause > 3 seconds
    - NOTE: not JUST a sinus pause > 3 seconds
  - This does include post-conversion pauses
    - An AF ablation MAY be sufficient in those cases
  - Chronotropic incompetence
    - Need to ambulate the patient
    - May require an exercise treadmill test
    - More of a quality of life issue than a safety issue

Ms. Jones has a Pacemaker

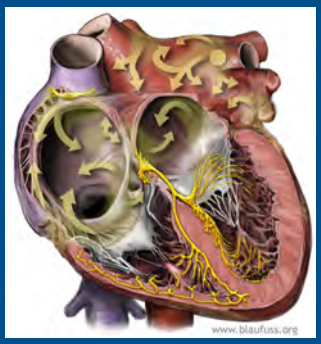
- Do I need to have the pacemaker checked?
  - Pacemaker in place is not itself an indication for a pacemaker interrogation
    - Pacemaker interrogations drain battery
  - Can assess:
    - If the leads are working
    - Timing of various tachyarrhythmias



Ms. Jones has a Pacemaker

- The device site looks red and maybe is infected?
  - DON'T STICK A NEEDLE IN IT!
  - Device infections are a big deal
  - Can be hard to eradicate infections without removing WHOLE DEVICE
  - Chronic leads adhere to the great vessels and the heart
  - Extraction tools work well, but still high risk
  - Bacteremia plus pacemaker (or ICD) should be considered possible endocarditis
    - Low threshold to get ID and EP involved

Atrial Fibrillation



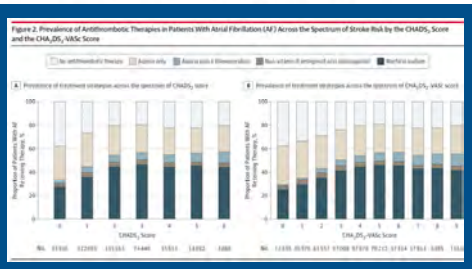
Atrial Fibrillation

- NOACs are now DOACs (no longer novel)
- We generally UNDER-ANTICOAGULATE

Original Investigation

Oral Anticoagulant Therapy Prescription in Patients With Atrial Fibrillation Across the Spectrum of Stroke Risk
Insights From the NCDR PINNACLE Registry

Jonathan C. Hsu, MD, MAS; Thomas M. Maddox, MD, MSc; Kevin F. Kennedy, MS; David F. Katz, MD; Lucas N. Marzec, MD; Steven A. Lubitz, MD, MPH; Anil K. Gehi, MD; Mintu P. Turakhia, MD, MAS; Gregory M. Marcus, MD, MAS



In the Spirit of trying to Enhance Appropriate Anticoagulation in AF

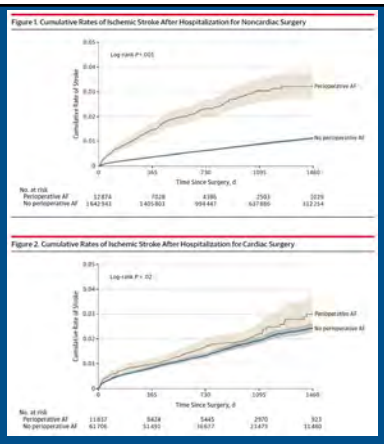
- "Your patient never calls you in the middle of the night to thank you for not having a stroke."

In the Spirit of trying to Enhance Appropriate Anticoagulation in AF

- "Your patient never calls you in the middle of the night to thank you for not having a stroke."

How is This Relevant to Hospital Medicine?

- That patient who develops atrial fibrillation in the setting of cellulitis or pneumonia
  - ASSUME YOU WERE LUCKY TO CATCH IT BECAUSE THE PATIENT WAS BEING MONITORED
- ANTICOAGULTE UNLESS THERE IS A COMPELLING REASON NOT TO
  - Examples:
    - CHADSVASC of 0 or perhaps 1
    - History of hemorrhagic stroke



Gialdini et al. *JAMA* 2014

Net Clinical Benefit of Warfarin in Patients With Atrial Fibrillation : A Report From the Swedish Atrial Fibrillation Cohort Study
Leif Friberg, Mårten Rosenqvist and Gregory Y.H. Lip

Circulation. 2012;125:2298-2307; originally published online April 18, 2012;

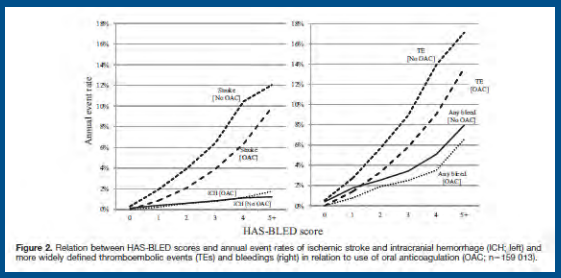


Figure 2. Relation between HAS-BLED scores and annual event rates of ischemic stroke and intracranial hemorrhage (ICH; left) and more widely defined thromboembolic events (TEs) and bleedings (right) in relation to use of oral anticoagulation (OAC; n=159 013).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., John Eikelboom, M.B., B.S., Campbell Joyner, M.D., for the AVERROES Steering Committee and Investigators*

Outcome	Apixaban (N=2808)		Aspirin (N=2791)		Hazard Ratio with Apixaban (95% CI)	P Value
	no. of patients with first event	%/yr	*no. of patients with first event*	%/yr		
Stroke or systemic embolism	51	1.6	113	3.7	0.45 (0.32–0.62)	<0.001
Stroke, systemic embolism, or death	143	4.6	223	7.2	0.64 (0.51–0.78)	<0.001
Stroke, systemic embolism, myocardial infarction or death from vascular cause	132	4.2	197	6.4	0.66 (0.53–0.83)	<0.001
Stroke, systemic embolism, myocardial infarction, death from vascular cause, or major bleeding event	163	5.3	220	7.2	0.74 (0.60–0.90)	0.003
Stroke†	49	1.6	105	3.4	0.46 (0.33–0.65)	<0.001
Ischemic	35	1.1	93	3.0	0.37 (0.25–0.55)	<0.001
Hemorrhagic	6	0.2	9	0.3	0.67 (0.24–1.88)	0.45
Unspecified	9	0.3	4	0.1	2.24 (0.69–7.27)	0.18
Disabling or fatal	31	1.0	72	2.3	0.43 (0.28–0.65)	<0.001

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	no. of patients with first event	%/yr	*no. of patients with first event*	%/yr		
Bleeding event						
Major	44	1.4	39	1.2	1.13 (0.74–1.75)	0.57
Intracranial	11	0.4	13	0.4	0.85 (0.38–1.90)	0.69
Subdural‡	4	0.1	2	0.1	—	—
Other intracranial, excluding hemorrhagic stroke and subdural‡	1	<0.1	2	0.1	—	—
Extracranial or unclassified	33	1.1	27	0.9	1.23 (0.74–2.05)	0.42
Gastrointestinal	12	0.4	14	0.4	0.86 (0.40–1.86)	0.71
Non-gastrointestinal	20	0.6	13	0.4	1.55 (0.77–3.12)	0.22
Fatal§	4	0.1	6	0.2	0.67 (0.19–2.37)	0.53
Clinically relevant nonmajor	96	3.1	84	2.7	1.15 (0.86–1.54)	0.35
Minor	188	6.3	153	5.0	1.24 (1.00–1.53)	0.05

Oral anticoagulant and reduced risk of dementia in patients with atrial fibrillation: A population-based cohort study

Heart Rhythm, Vol 17, No 5PA, May 2020

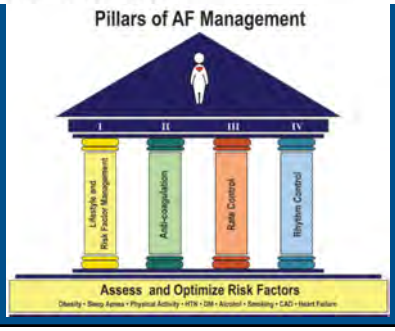
Pajaree Mongkhon, PharmD,[*†‡§] Laura Fanning, BPharm (Hons), MPH,[¶] Wallis C.Y. Lau, PhD,[§‖**] Gary Tse, PhD, FACC, FRCP,[††‡‡] Kui Kai Lau, DPhil,[**§§] Li Wei, PhD,[¶**¶¶] Chuenjid Kongkaew, PhD,[*§] Ian C.K. Wong, PhD[§‖**¶¶]

Type of dementia	Group	No. of event	Person-years at risk* (y)	Follow-up time (y) (mean ± SD)	IR per 1000 person-years (95% confidence interval)	HR (95% confidence interval)	*P* value
Alzheimer disease	OAC	315	163,512	5.6 ± 3.6	1.93 (1.73–2.15)	0.99 (0.86–1.14)	.868
(Ref = non-OAC)	Non-OAC	520	259,834	6.3 ± 3.8	2.00 (1.84–2.18)		
Vascular dementia	OAC	482	163,173	5.6 ± 3.6	2.95 (2.7–3.23)	0.89 (0.80–0.99)	.049
(Ref = non-OAC)	Non-OAC	803	259,375	6.3 ± 3.8	3.1 (2.89–3.32)		
Unspecified dementia	OAC	400	163,379	5.6 ± 3.6	2.45 (2.22–2.70)	0.74 (0.66–0.83)	.001
(Ref = non-OAC)	Non-OAC	873	259,174	6.3 ± 3.8	3.37 (3.15–3.60)		

- Multiple studies have now shown:
  - Heightened risk of dementia with AF
  - Dementia/ cognitive decline risk mitigated by anticoagulation

AHA SCIENTIFIC STATEMENT

Lifestyle and Risk Factor Modification for Reduction of Atrial Fibrillation: A Scientific Statement From the American Heart Association

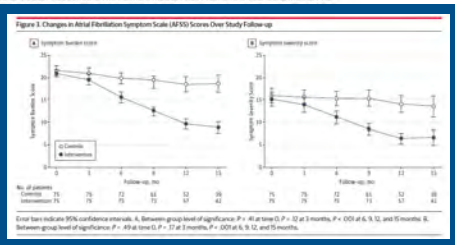


Original Investigation

Effect of Weight Reduction and Cardiometabolic Risk Factor Management on Symptom Burden and Severity in Patients With Atrial Fibrillation

A Randomized Clinical Trial

Hany S. Abed, BPharm, MBBS, Gary A. Wittert, MBBch, MD, Darryl P. Leong, MBBS, MPH, PhD; Masoumeh G. Shirazi, MD, Bobak Bahrami, MBBS, Melissa E. Middeldorp, Michelle F. Lorimer, BSc; Dennis H. Lau, MBBS, PhD; Nicholas A. Antic, MBBS, PhD; Anthony G. Brooks, PhD; Walter P. Abhayaratna, MBBS, PhD; Jonathan M. Kalman, MBBS, PhD; Prashanthan Sanders, MBBS, PhD

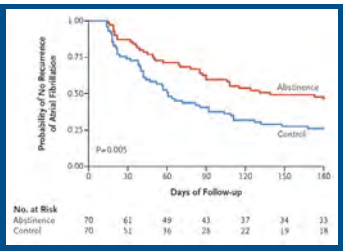


ORIGINAL ARTICLE

Alcohol Abstinence in Drinkers with Atrial Fibrillation

Aleksandr Voskoboinik, M.B., B.S., Ph.D., Jonathan M. Kalman, M.B., B.S., Ph.D., Andrew J. Taylor, M.B., B.S., Ph.D., and Peter M. Kistler, M.B., B.S., Ph.D.

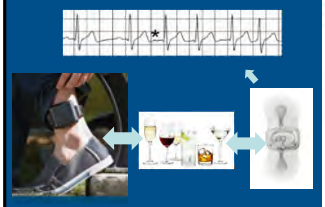
Andrew J. Taylor, M.B., B.S., Ph.D., and Peter M. Kistler, M.B., B.S., Ph.D.



Annals of Internal Medicine ORIGINAL RESEARCH

Acute Consumption of Alcohol and Discrete Atrial Fibrillation Events

Gregory M. Marcus, MD, MAS; Eric Vittinghoff, PhD; Isaac R. Whitman, MD; Sean Joyce, BS; Vivian Yang, BA; Gregory Nah, MA; Edward P. Gerstenfeld, MD; Joshua D. Moss, MD; Randall J. Lee, MD, PhD; Byron K. Lee, MD; Zian H. Tseng, MD, MAS; Vasanth Vedantham, MD, PhD; Jeffrey E. Olgin, MD; Melvin M. Scheinman, MD; Henry Hsia, MD; Rachel Gladstone, BA; Shannon Fan, BA; Emily Lee, BS; Christina Fang, BA; Kelsey Ogomori, BA; Robin Fatch, MPH; and Judith A. Hahn, PhD, MA



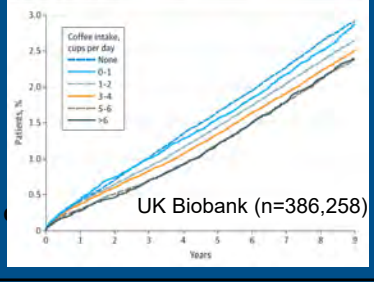
What about the other most commonly consumed beverage in the world?

JAMA Internal Medicine | Original Investigation

Coffee Consumption and Incident Tachyarrhythmias
Reported Behavior, Mendelian Randomization, and Their Interactions

Eun-jeong Kim, MD; Thomas J. Hoffmann, PhD; Gregory Nah, MA; Eric Vittinghoff, PhD; Francesca Delling, MD; Gregory M. Marcus, MD, MAS

Figure 1. Cumulative Incidence of Any Arrhythmia by Coffee Consumption



UK Biobank (n=386,258)

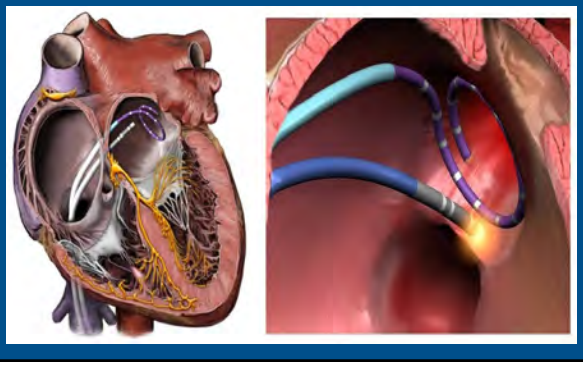
Table 2. Polygenic Score of Caffeine Metabolism and Risk of Incident Arrhythmia[a]

Arrhythmia type	Hazard ratio (95% CI)[b]	P value
All arrhythmia	1.00 (0.99-1.00)	.75
Atrial fibrillation or flutter	1.00 (0.99-1.00)	.96
Supraventricular tachycardia	1.01 (0.998-1.00)	.38
Ventricular tachycardia	1.00 (0.996-1.00)	.94
Premature atrial complex	1.00 (0.99-1.02)	.76
Premature ventricular complex	1.00 (0.99-1.00)	.39

- Caffeinated could reduce AF via:
  - Anti-inflammatory effects
  - Anti-vagal effects
  - Caffeine may prolong LA effective refractory periods

Kim EJ et al. *JAMA Intern Med* 2021

Atrial Fibrillation Ablation



Atrial Fibrillation Ablation

- Success in 60-90%
- Overall risks (4-6%):[1-5]
  - Risk of death or permanent disability <1%
- A great option for symptomatic patients
- An ELECTIVE PROCEDURE

1. Circulation 2003;108:2355-60
2. JACC 2003;42:185-197
3. JACC 2004;43:2044-53
4. JAMA 2005;293:2634-40
5. N Engl J 2006; 354: 934-41

Atrial Fibrillation Ablation

- CLASS 1 INDICATIONS:
  - Selected patients with symptomatic paroxysmal AF refractory or intolerant to at least one class I or III antiarrhythmic drug when a rhythm control strategy is desired
- CLASS III: Don't do it to get a patient off anticoagulation

Atrioesophageal Fistula

- Presents 1-3 weeks AFTER ablation
  - Fever
  - TIA or other embolic phenomena
  - Chest pain
  - Odynophagia (but not necessarily)
  - Leukocytosis
  - Hematemesis (more rare)

Atrioesophageal Fistula

- High mortality
- Get electrophysiology involved
- Get CT surgery involved
- Diagnose with CT with intravenous and water soluble GI contrast
- DO NOT DO EGD WITH INSUFLATION
- If test negative, may need to look again
- In some cases with high suspicion, take to OR directly even with negative tests


VOLUME 347 DECEMBER 5, 2002 NUMBER 23

A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*

The New England Journal of Medicine

A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH RECURRENT PERSISTENT ATRIAL FIBRILLATION

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STAF (n=200)- no difference in composite endpoint of death and thromboembolic events

PIAF (n=252)- No difference in symptomatic improvement

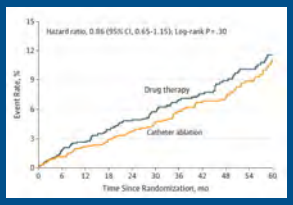
HOT CAFÉ (n=205)- No difference in composite death, thromboembolic events, hemorrhage

Why ever consider rhythm control?

- Unlikely to include symptomatic patients in those studies
  - Rationale for rhythm control is primarily symptoms
- Warfarin was stopped when sinus apparent
- Evidence that those in sinus lived longer

JAMA | Original Investigation

Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation
The CABANA Randomized Clinical Trial



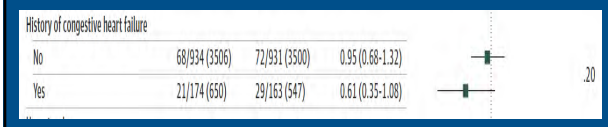
Intention to treat

Per protocol
9.2% cross-over ablation→ medicine
27.5% cross-over medicine→ablation

1. JAMA 2019

JAMA | Original Investigation

Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation
The CABANA Randomized Clinical Trial



Intention to treat

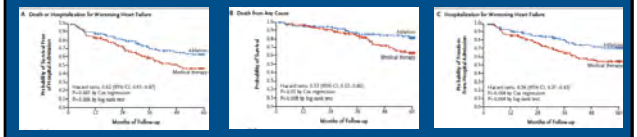
1. JAMA 2019

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2018 VOL. 378 NO. 5

Catheter Ablation for Atrial Fibrillation with Heart Failure

Nassir F. Marrouche, M.D., Johannes Brachmann, M.D., Dietrich Andresen, M.D., Jürgen Siebels, M.D., Lucas Boersma, M.D., Luc Jordaens, M.D., Béla Merkely, M.D., Evgeny Pokushalov, M.D., Prashanthan Sanders, M.D., Jochen Proff, B.S., Heribert Schunkert, M.D., Hildegard Christ, M.D., Jürgen Vogt, M.D., and Dietmar Bänsch, M.D., for the CASTLE-AF Investigators*

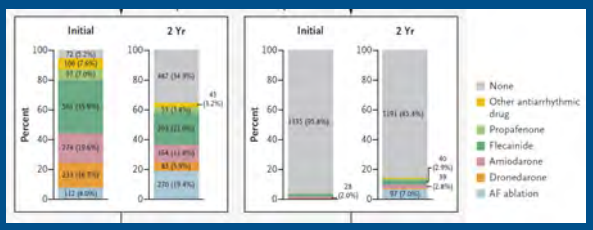


ORIGINAL ARTICLE

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation

P. Kirchhof, A.J. Camm, A. Goette, A. Brandes, L. Eckardt, A. Elvan, T. Fetsch, I.C. van Gelder, D. Haase, L.M. Haegeli, F. Hamann, H. Heidbüchel, G. Hindricks, J. Kautzner, K.-H. Kuck, L. Mont, G.A. Ng, J. Rekosz, N. Schoen, U. Schotten, A. Suling, J. Taggeselle, S. Themistoclakis, E. Vettorazzi, P. Vardas, K. Wegscheider, S. Willems, H.J.G.M. Crijns, and G. Breithardt, for the EAST-AFNET 4 Trial Investigators*

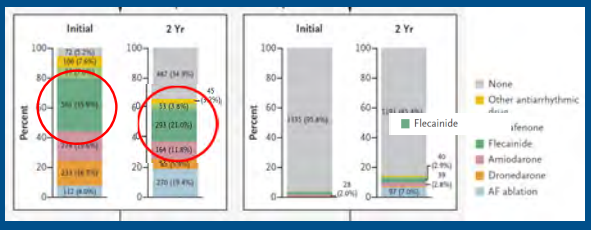
- 2,789 patients with recent AF and CV co-mordibities (median 36 days) randomized to rate v rhythm control followed median 5.1 years
- ANTICOAGULATION CONTINUED EVEN IF IN SINUS



Rhythm Control

Rate Control

Kirchof et al NEJM 2020



Rhythm Control

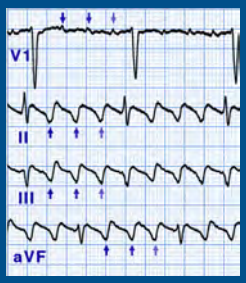
Rate Control

Kirchof et al NEJM 2020

Outcome	Early Rhythm Control	Usual Care	Treatment Effect
First primary outcome — events/person-yr (incidence/100 person-yr)	249/6399 (3.9)	316/6332 (5.0)	0.79 (0.66 to 0.94)†
Components of first primary outcome — events/person-yr (incidence/100 person-yr)			
Death from cardiovascular causes	67/6915 (1.0)	94/6988 (1.3)	0.72 (0.52 to 0.98)‡
Stroke	40/6813 (0.6)	62/6856 (0.9)	0.65 (0.44 to 0.97)‡
Hospitalization with worsening of heart failure	139/6620 (2.1)	169/6558 (2.6)	0.81 (0.65 to 1.02)‡
Hospitalization with acute coronary syndrome	53/6762 (0.8)	65/6816 (1.0)	0.83 (0.58 to 1.19)‡

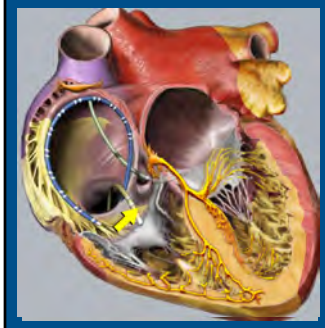
Kirchof et al NEJM 2020

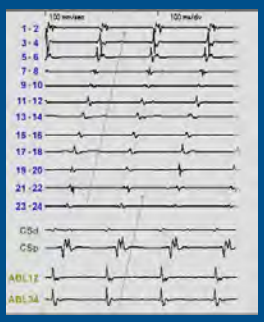
Atrial FLUTTER



- Anticoagulation=AF
- Often difficult to rate control
  - "Decremental conduction" of the AV node
- Hard to suppress with drugs
- Easy to ablate

Atrial FLUTTER

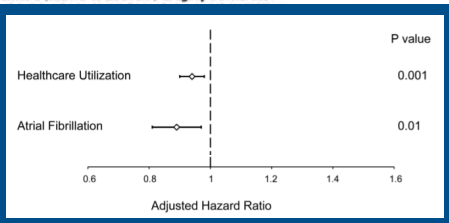




OPEN ACCESS Freely available online PLOS ONE

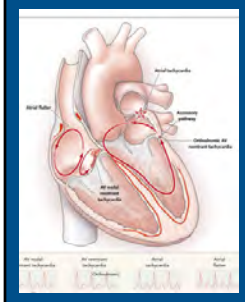
Healthcare Utilization and Clinical Outcomes after Catheter Ablation of Atrial Flutter

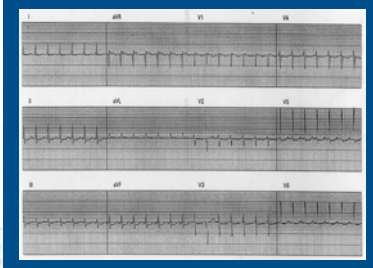
Thomas A. Dewland[1], David V. Glidden[2], Gregory M. Marcus[1]*



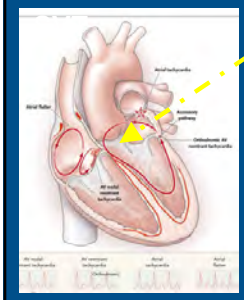
- N=>32,000 atrial flutter patients in California over 5 years

Supraventricular Tachycardias





Supraventricular Tachycardias



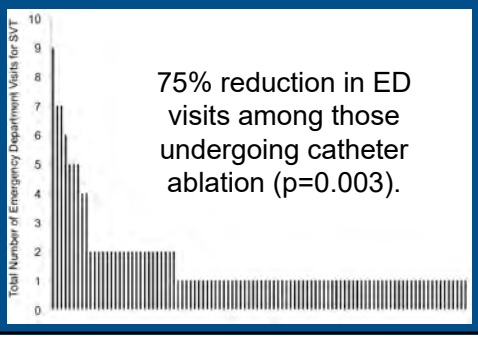
Adenosine

- **Metabolized by red blood cells and endothelium**
- **Give 6 mg IV with 20 cc flush**
- **Repeat with 12 mg IV X 2**
- **How do I know if I've given enough?**

J Interv Card Electrophysiol (2017) 49:103–109
DOI 10.1007/s10840-017-0259-1

Health care utilization among adenosine-sensitive supraventricular tachycardia patients presenting to the emergency department

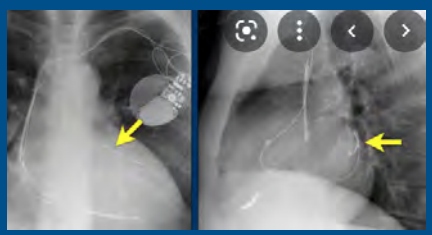
Thomas A. Dewland[1] · Adam Oesterle[2] · John Stein[3] · Gregory M. Marcus[2]



75% reduction in ED visits among those undergoing catheter ablation (p=0.003).

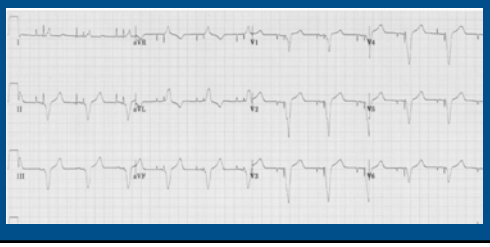
Avoiding Left Ventricular Dyssychrony

- Left bundle branch block may lead to heart failure



RV Pacing Causes Left Ventricular Dyssychrony

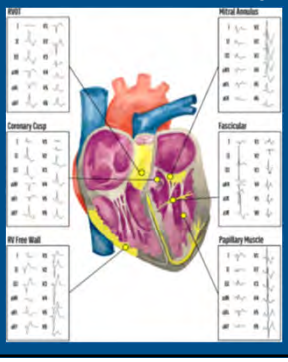
- We try to avoid RV pacing
- NEED to avoid RV pacing with low EF



RV Pacing Causes Left Ventricular Dyssychrony

- We try to avoid RV pacing
- NEED to avoid RV pacing with low EF
  - Change mode to only pace in the atrium if AV conduction is intact
  - Upgrade or place a Biventricular pacemaker
  - Conduction system pacing (pacing the His or left bundle branch) is gaining in popularity

Another Cause of Left Ventricular Dyssychrony: PVCs

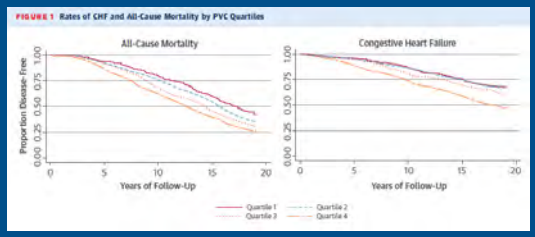


- Suppression or elimination of PVCs in those with reduced EF can improve (sometimes completely) systolic dysfunction

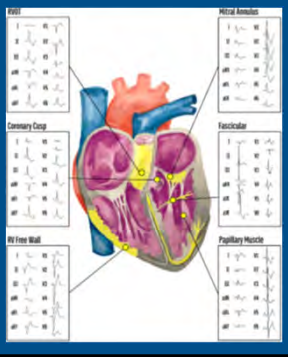
Ventricular Ectopy as a Predictor of Heart Failure and Death

Jonathan W. Dukes, MD,* Thomas A. Dewland, MD,† Eric Vittinghoff, PhD, MPH,‡ Mala C. Mandyam, MD,§ Susan R. Heckbert, MD, PhD,‖ David S. Siscovick, MD, MPH,‖¶ Phyllis K. Stein, PhD,# Bruce M. Psaty, MD, PhD,‖** Nona Sotoodehnia, MD,†‖ John S. Gottdiener, MD,‖§ Gregory M. Marcus, MD, MAS*

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY



Another Cause of Left Ventricular Dyssychrony: PVCs



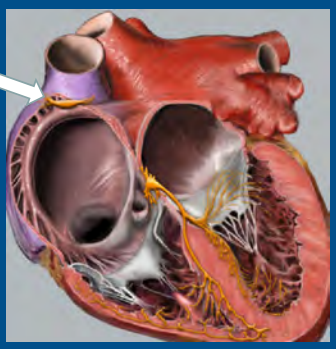
- Frequent PVCs (>5%) with low EF→ refer to EP
- Symptomatic PVCs→ refer to EP
- Frequent PVCs (>5%) asymptomatic and normal EF, annual echos, consider referral cardiology

Conclusions

Pacemaker for SYMPTOMATIC sinus problems

Generally leave pacemakers alone

…BUT if they are pacing in the RV all the time and have any reduced EF, let EP know!



Conclusions

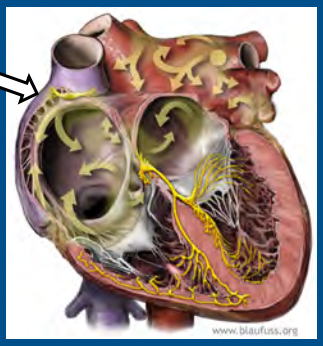
Anticoagulation generally GOOD

Exercise GOOD

Alcohol BAD

Caffeine/ Coffee probably OK

Rhythm control probably PREFERRED

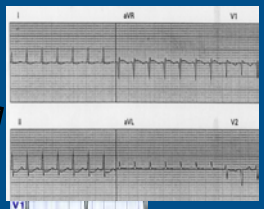


Conclusions

Low threshold to refer to EP

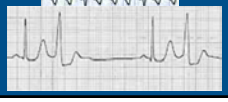
Usually fine to do upon discharge

Referral to PMD is not the same



SVT

Atrial flutter



Frequent PVCs

Thank You

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Join the Health eHeart Study https://www.health-eheartstudy.org/

ACC/AHA/HRS GUIDELINE

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

Recommendation for Percutaneous Approaches to Occlude the LAA

Referenced studies that support the new recommendation are summarized in Online Data Supplement 4.

COR	LOE	Recommendation
IIb	B-NR	1. Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation.[54.4 F-1–54.4.1-5] **NEW:** Clinical trial data and FDA approval of the Watchman device necessitated this recommendation.

The Potential Dangers of False Positives

- Among 359, 315 AF patients in the NCDR PINNACLE registry, 27% of all patients with CHA_2DS_2-VASc of 0 were prescribed an anticoagulant.

Hsu JC. *JAMA Intern Med* 2015

ACC/AHA/HRS GUIDELINE

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

I	B-NR	3. Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure.[54.3-2] **NEW:** New evidence has been published about idarucizumab to support LOE B-NR.
IIa	B-NR	4. Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding.[54.3-3;54.3-4] **NEW:** New evidence has been published about andexanet alfa to support LOE B-NR.

Bridging

Bridging

- OK to just start warfarin without heparin
- Pharmacokinetics of NOACs can be considered similar to lovenox
- On warfarin:
  - Low risk: can hold for a week
    - For NOACs, should be gone in 2 days
  - High risk (mechanical valve, prior stroke, higher CHA_2DS_2-VASc), can consider unfractionated or low molecular weight heparin for warfarin
  - Continue (as is done in many EP procedures)

Bridging

- On novel agent:
  - Hold for 1 day prior to the procedure (2 doses if BID, 1 dose if QD)
  - When need complete hemostasis (eg, spinal puncture, major surgery), hold for 48 hours
  - Consider continuing (as we now do in many EP procedures)

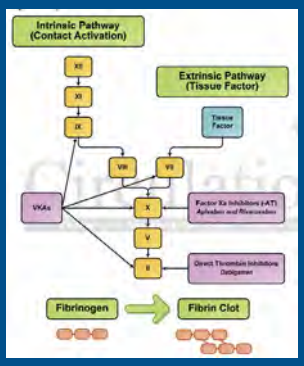
What is the first thing I need to do?

- RATE CONTROL
  - If unstable→ DC shock
- Your favorite beta-blocker or calcium channel blocker
- When BP goes down:
  - Consider MORE AV nodal blockage
  - Consider Dig
  - Consider amiodarone
  - Consider esmolol
  - Consider cardioversion

Drug	Dose reduction	Other idiosyncracies
Dabigatran=Pradaxa	CrCl 15-30 ml/min	Dyspepsia ~11% (acid core)
Rivaroxaban=Xarelto	CrCl 15-50 ml/min	pK maybe really 2x day drug
Apixiban=Eliquis	2 out of 3: Creatinine > 1.5, age >80, weight <60 kg	Might be used in hemodialysis
Edoxaban=Savaysa	CrCl 15-50 ml/min	Contraindicated if CrCl > 95 ml/min Drug interactions (verapamil and dronaderone increases)

Novel Anticoagulants

- Reversibility?

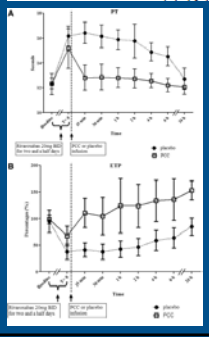


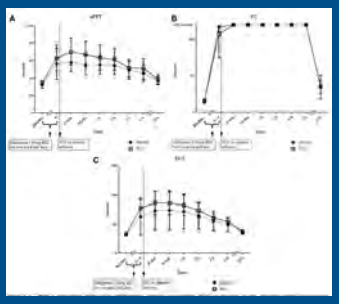
Circulation
American Heart Association

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate: A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

Circulation. 2011;124:1573-1579; originally published online September 6, 2011;





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

N ENGL J MED 373;6 NEJM.ORG AUGUST 6, 2015

- Announcement of FDA approval 10/16/15

"Let's just cardiovert back to sinus rhythm so we don't need to worry about anticoagulation."

I decide to go with

•Cardioversion can reduce left atrial appendage function

– Even from AF to sinus

• The pericardioversion period is a particularly pro-thrombotic time

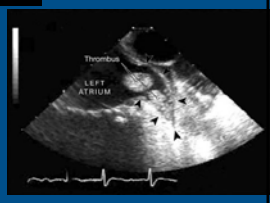
– Regardless of mode: DC/ electrical, pharmacologic, spontaneous

I decide to go with

• Prior to cardioversion:[1, 2]

– Can exclude preexisitng thrombus by TEE

– Can anticoagulate (therapeutic/ for at least 3 weeks) prior to cardioversion



1. JACC 2006;48:e149-246
2. Chest 2004;126:429S-456

I decide to go with

• During and after cardioversion:[1, 2]

– Anticoagulation for at least 4 weeks

– Applies even to those who would otherwise not require anticoagulation

1. JACC 2006;48:e149-246
2. Chest 2004;126:429S-456

Epidemiology

- AF is the most common sustained arrhythmia in adults
- Affects ~4% of everyone over age 60 and ~10% of everyone over age 80
- The age-adjusted incidence is increasing[1]

1. Miyasaka Y. Circulation 2006;114:119-125

Oncologic Emergencies in Hospital Medicine

Sam Brondfield, MD, MAEd

Disclosures

- Consulting fees:
  - Gemini Health
  - IDEO
  - American Physician Institute
  - Blackstone
  - PAI Pharmaceuticals
- Honorarium:
  - Doximity

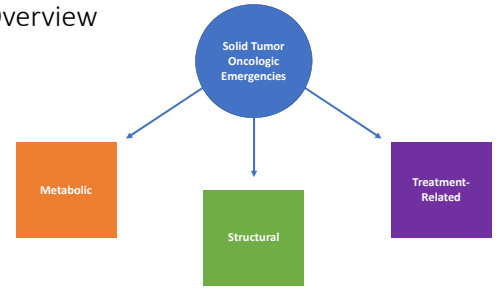
Learning Objective

Describe inpatient management of solid tumor oncologic emergencies.

Outline

- Five cases of oncologic emergencies (4 old, 1 new)
- Review of key take-aways

Overview



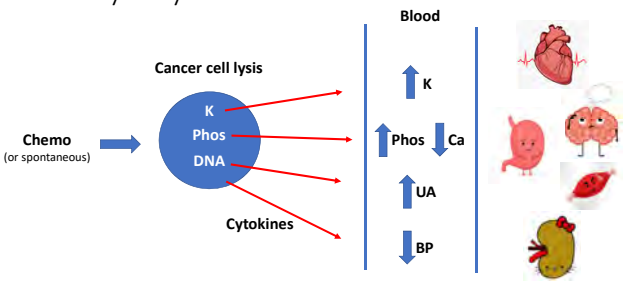
Case 1

A 60 year-old man is diagnosed with metastatic small cell lung cancer, including an 8 cm hilar lung mass, mediastinal lymphadenopathy, and diffuse bone lesions. He is admitted for expedited workup. Baseline labs, including chemistries, are normal. Oncology administers inpatient carboplatin/etoposide. You ponder the risk of tumor lysis syndrome.

Which of these lab abnormalities is consistent with the pathophysiology of TLS?

A) Elevated calcium
B) Low potassium
C) Low phosphorus
D) Elevated uric acid

Tumor lysis syndrome



N Engl J Med 2011;364:1844-54

Tumor lysis syndrome

Cairo-Bishop Criteria for laboratory TLS (2 of 4)

Element	Value
Potassium	≥6.0 mEq/L
Calcium	≤7.0 mg/dL
Phosphorus	≥4.5 mg/dL
Uric acid	≥8.0 mg/dL

Or 25% change from baseline

Clinical TLS

Laboratory TLS plus one of:

- **Cr >1.5x ULN (or >1.2-1.3)**
- **Arrhythmia**
- **Seizure**

Tumor lysis syndrome

- Step 1: Risk stratification
  - **Bulky small cell lung cancer** and **bulky germ cell tumors** = intermediate risk
  - Other solid tumors mostly low risk
  - Check baseline TLS labs
- Step 2: Interventions

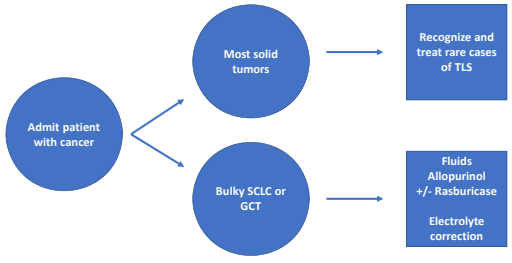
Risk of Clinical TLS	Low	Intermediate	High	Established
Fluids	Fluids with chemotherapy	4-6L/day; 150-200 cc/hr UOP	4-6L/day; 150-200 cc/hr UOP	4-6L/day; 150-200 cc/hr UOP
Allopurinol*	Not needed	+	+	+
Rasburicase	Not needed	+/-	+	+
Lab monitoring	Daily	q8-12 hrs	q6-8 hrs	q4-6 hrs

*Requires renal dosing if renal impairment present.

Case Wrap-Up

- Develops TLS 24 hrs after chemotherapy
- Fluids, allopurinol, rasburicase given
- Labs improve, discharged once normalized
- Admitted for cycle 2 of chemotherapy for TLS monitoring
- No recurrence, further cycles given as outpatient

Tumor lysis syndrome: Your role



Case 2

A 58 year-old woman with metastatic non-small cell lung cancer received carboplatin/paclitaxel and is admitted 12 days later with fever and chills. Temperature is 38.5. There are no focal infectious symptoms or signs. WBC is 1.0 and ANC is 200. CXR is normal. Cultures are drawn. She has no central line.

What empiric therapy would you start?

A) Vancomycin and piperacillin-tazobactam
B) Cefepime
C) Ceftriaxone and azithromycin
D) Levofloxacin

Neutropenic fever

- Definition: 38.3 x1 or 38.0 over 1 hour with ANC <500 (or "close")
- Primary risk factor is type of chemotherapy
- Infectious source identified in minority of cases
- Most cases are bacterial (translocation of gut flora)
- Gram negatives, *S. aureus*, and enterococci cause severe illness
- *S. epidermidis* is a common pathogen
- Anaerobes are infrequent causes of neutropenic fever

Arch Intern Med. 2011 Sep;171(16):1502-3
Clin Infect Dis. 2011;52(4):e56

Neutropenic fever: Treatment

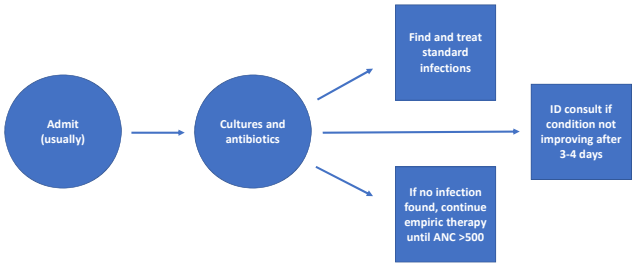
- Cultures → timely antibiotics → sign/symptom-directed workup
- Empiric therapy: cefepime, pip-tazo, meropenem, (cipro/amox-clav)
  - Vanc if unstable or suspect for gram+
  - Do not broaden for persistent fever alone
- Target infection if found
- If not, continue empiric regimen until ANC >500
- G-CSF generally not recommended
- Some VERY stable patients may be treated as outpatient

J Clin Oncol. 2018;36(14):1443
nccn.org

Case Wrap-Up

- Cefepime started
- Fevers resolve within 72 hours
- No organism identified
- On hospital day 5, feels well, ANC 600
- Discharged without antibiotics
- G-CSF given with next cycle of chemotherapy

Neutropenic fever: Your role



Case 3

A 73 year-old previously healthy non-binary person with a 40 pack-year smoking history presents with confusion. Calcium is 16.0 and renal function is normal. CT reveals a 6 cm hilar lung mass with multiple liver lesions. No bone lesions are present. Head imaging is normal.

What is the most likely cancer and mechanism of hypercalcemia in this case?

A) Parathyroid carcinoma secreting PTH
B) Lung adenocarcinoma with occult lytic bone metastases
C) Squamous cell lung cancer secreting PTHrP
D) Lymphoma causing elevated 1,25-dihydroxyvitamin D3

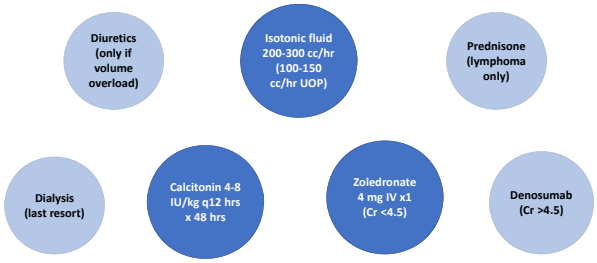
Hypercalcemia of malignancy

- Most common cause of hypercalcemia in hospitalized patients
- Most common causes: breast, lung, renal, myeloma
- Workup: PTHrP, vit D, imaging, +/- SPEP
- Indications to treat: Ca>14 (albumin corrected), symptoms, or fast rise

Mechanism	Frequency
PTHrP	80%
Osteolytic lesions	20%
1,25-dihydroxyvitamin D	Rare
PTH	Very rare

N Am J Med Sci. 2015 Nov; 7(11): 483–493

Hypercalcemia of malignancy: Management



Case Wrap-Up

- PTHrP elevated
- Fluids, calcitonin, and zoledronate given
- Calcium improves, mental status follows
- Liver biopsy shows squamous cell carcinoma
- Discharged with outpatient oncology appointment

Hypercalcemia of malignancy: Your role

Case 4

A 65 year-old woman with newly diagnosed triple-negative breast cancer with diffuse spine metastases not yet on treatment presents to the ED with two weeks of progressive back pain, 24 hours of bilateral leg weakness, and urinary incontinence. MRI shows a T10 lesion causing cord compression. Performance status is otherwise excellent.

What is the next step in management?

A) Glucocorticoids
B) Urgent radiation
C) Surgical resection
D) Urgent systemic cancer therapy

Neoplastic epidural spinal cord compression

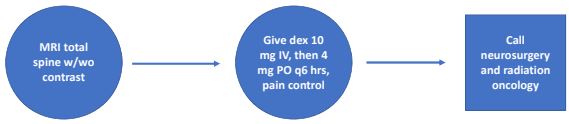
- Back pain may precede neurologic changes by weeks
- Thoracic spine most common site
- Obtain whole spine imaging (MRI)
- 10 mg IV dexamethasone x1, then 4q6 IV or PO
  - Caution if lymphoma on ddx
- Surgery vs XRT depends on severity, radiosensitivity, and prognosis
  - Radiosensitive: lymphoma, myeloma, testicular seminoma

N Engl J Med 2017; 376:1358-1369

Case Wrap-Up

- Dexamethasone started
- Laminectomy and fusion performed
- Steroids tapered over four weeks, recovers well
- Sees oncology to start systemic therapy

Neoplastic epidural spinal cord compression: Your role



Case 5

A 60 year-old man with metastatic melanoma and no other comorbidities who started ipilimumab and nivolumab 3 months ago presents with subacute progressive dyspnea. CT shows shrinkage in all metastatic lesions and new diffuse ground glass opacities in both lungs. He is afebrile. Hypoxemia progresses rapidly requiring intubation. Exam shows diffuse inspiratory crackles and flat JVP. Pulmonology performs BAL with results pending. Broad-spectrum antibiotics are started.

What is the next step in management?

A) Switch to oral ipilimumab/nivolumab
B) Start oral prednisone
C) Start IV methylprednisolone
D) Start IVIG and infliximab

Brief Overview of Immune-Related Adverse Events (IRAEs)

- IRAE = inflammatory side effect
- Occur weeks to months after initiation of checkpoint inhibitor
- Variable severity
- Can affect any organ system
- Some are “emergencies” (prompt attention to avoid bad outcome)

N Engl J Med 2018; 378:158-168

Severe IRAE Treatment Approaches

- Rule out other causes (e.g. BAL)
- Consult organ-specific specialist
- For most severe IRAEs, IV steroids are first step
- Additional immunosuppression if no improvement in 48 hrs

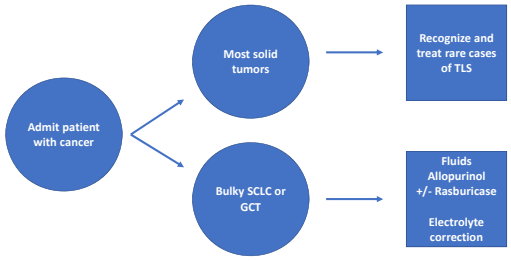
Case Wrap-Up

- IV methylprednisolone 2 mg/kg started
- Infectious workup returns negative
- Oxygen requirement decreases
- Steroids tapered over 6 weeks as outpatient
- Immunotherapy discontinued permanently

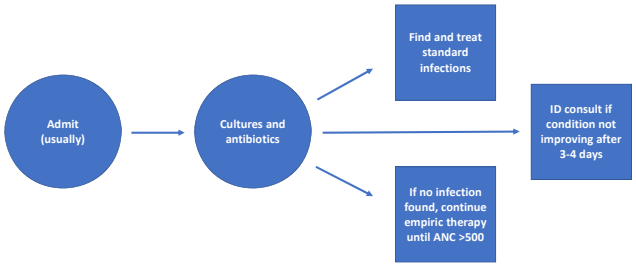
Severe IRAE: Your role

Review of key take-aways

Tumor lysis syndrome: Your role

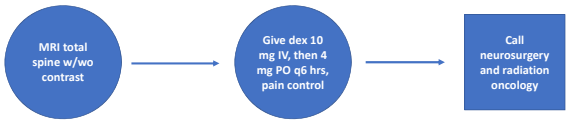


Neutropenic fever: Your role



Hypercalcemia of malignancy: Your role

Neoplastic epidural spinal cord compression: Your role



Severe IRAE: Your role

Thanks!

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UCSF Management of the Hospitalized Patient

October 2021

Year in Review

Brad Sharpe, MD
Brad Monash, MD

The Year in Review will highlight key articles from the last year in the field of hospital medicine, from September 2020 to September 2021. Articles were selected based on article quality and ability to impact and change practice. We will not be presenting articles related to COVID.

The articles will be presented in an interactive case-based format as we will follow a few patients through their hospital stay.

In order to avoid duplicating articles of other speakers, we are in the final stages of selecting the articles and a version of the slides will be posted ahead of the conference.