FEVER IN THE ICU

Management of the Hospitalized Patient
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Disclosures

- I have no disclosures.
Learning Objectives

1. To develop a framework for the differential diagnosis of fever in a patient in the ICU

2. To know the common clinical presentation, diagnosis, and management of common infections in the ICU

3. To recognize the common non-infectious etiologies for fever in the ICU

Outline

1. Review the epidemiology of fever in the ICU and develop a framework for Ddx and work-up

2. Common infections/clinical scenarios in the ICU
   - “Double-covering GNRs”
   - CA-UTI
   - VAP
   - Nosocomial sinusitis
   - Clostridium difficile
   - Candidemia

3. Common non-infectious etiologies for fever in the ICU
   - Drug fever
   - VTE
   - Central fever
   - ARDS
   - Acalculous cholecystitis
Definition of Fever

- Definition of fever is arbitrary
  - ≥38.3°C (101°F) commonly used (IDSA/ACCCM guidelines)
  - Use a lower threshold in immunocompromised patients
  - T < 36.0°C should also prompt an investigation for infection

- Note that patients on CRRT or ECMO may not mount a fever even when infected


Fever in the ICU: Epidemiology

- Fever occurs in 26-70% of patients

- Infectious vs non-infectious?
  - 35-55% are infectious
  - So, at least 50% of febrile episodes are non-infectious!

- Etiologies depended on type of ICU (MICU vs SICU vs NICU)
  - Most common infections: PNA, bloodstream, abdominal infections
  - Most common non-infectious etiologies: post-op fever, central fever

Framework for Building the DDx

1. Is this a complication of the underlying reason for admission?
   • Untreated, relapsed, or metastatic focus of infection
   • Post-surgical infection (surgical site infection, intra-abdominal abscess)

1. Is this a separate nosocomial process?
   • Hospital-acquired PNA (VAP, aspiration)
   • CA-UTI
   • Catheter-Related Bloodstream Infection (CRBSI)
   • Clostridium difficile

1. Is this non-infectious?
   • Drug fever
   • Central fever

DDx: Head-to-Toe Approach

- **CNS**
  - Nosocomial meningitis (post-NSG)

- **HEENT**
  - Nosocomial Sinusitis
  - Hospital-acquired URI

- **Pulmonary**
  - Hospital-acquired PNA
  - Empyema
  - ARDS

- **Cardiac**
  - Endocarditis
  - Pericarditis

- **GI/GU**
  - C. Difficile
  - CA-UTI
  - Post-op abd abscess
  - Peritonitis
  - Acalculous cholecystitis
  - Pancreatitis

- **MSK**
  - Osteomyelitis
  - Septic arthritis
  - Gout

- **Skin**
  - Cellulitis at line sites
  - Infected decub ulcer
  - Surgical site infection

- **Bloodstream**
  - CRBSI
  - Candidemia

- **Other non-infectious etiologies**
  - Drug Fever
  - Central fever
  - DVT/PE
  - Malignancy
  - Rheumatologic
  - Post-op fever
  - Transfusion reaction
  - Transplant rejection
  - Adrenal insufficiency
Initial Evaluation

- **History:**
  - Any change in secretions or respiratory status?
  - Any diarrhea?

- **Exam to include:**
  - Careful neuro exam
  - Sinus exam
  - Back and joint exam
  - Skin exam:
    - Line sites
    - Decubitus ulcers
    - Rashes
    - Remove bandages

- **Labs:**
  - CBC with diff (look for eos)
  - LFTs (drug reaction, acalculous cholecystitis)

- **Micro:**
  - Blood cultures (DTTP)
  - UA +/- Ucx
  - Respiratory cultures?
  - Cdiff?

- **Imaging:**
  - CXR
  - Chest or abdominal imaging?

Approach to Management

- Do you need to treat empirically or can you wait for cultures/diagnostics?

- Is there a source control procedure needed?

- For empiric therapy:
  - How sick is the patient?
  - Where do you think the patient is infected?
  - Prior positive cultures?
  - Prior antibiotics?
  - Is the patient at risk for MDR organisms?
Case # 1

A 57 year old woman with breast cancer undergoing chemotherapy with several recent admissions for UTI treated with ciprofloxacin who is admitted to the ICU with presumed pyelonephritis. She is febrile to 39.6 °C, tachy to 120s, BP stable. WBC is 0.8 (ANC<500), Cr 1.8, other labs normal. Renal US is normal. Blood and urine cultures are drawn and she is started on vancomycin plus meropenem.

6 hours later her blood pressure starts dropping and she is started on pressors and rapidly uptitrated to max doses of 3 pressors.

What Would You Do With Her ABx?

1. No changes (this is a source control issue)

2. No changes (ABx have not had time to work yet)

3. Add an aminoglycoside

4. Add a fluoroquinolone
Case # Continued

- Blood and urine cultures return positive with *Pseudomonas* susceptible to all agents except cipro/levo.

- Should you continue “double-coverage” or change to beta-lactam monotherapy?

What Would You Do With Her ABx Now?

1. Continue “double coverage”

2. Change to beta-lactam monotherapy
“Double-Covering” GNRs

- Also known as “combination therapy”

- Usually refers to a beta-lactam + (aminoglycoside or FQ)

- Reasons to consider combination therapy:
  1. Increase the probability of initial appropriate empiric coverage by expanding the spectrum of activity, especially if concerned about resistance (“empiric combination therapy”)
  2. Synergy between 2 active ABx (“definitive combination therapy”)
  3. Prevent the development of resistance with 2 active ABx (“definitive combination therapy”)

Caveats to Combination Therapy Data

- Often observational, non-blinded studies
- Empiric vs definitive therapy not always defined
- Different beta-lactams, different combinations used (usually beta-lactam + AG)
- Site/type of infections may be different
- Definition of treatment failure variable
- Inclusion of older studies (using older ABx) in some meta-analyses
Reasons To Consider Combination Rx

1. Increase the probability of initial appropriate empiric coverage by expanding the spectrum of activity, especially if concerned about resistance ("empiric combination therapy")

2. Synergy between 2 active ABx ("definitive combination therapy")

3. Prevent the development of resistance with 2 active ABx ("definitive combination therapy")

Appropriate Empiric Abx Improves Survival

Use Local Epidemiology to Inform ABx Choice

- Know your local antibiogram
  - If the beta lactam used for monotherapy is sufficiently broad, there is less of a benefit for empiric combination therapy
  - What is the risk of ESBL or Pseudomonas?

- UCSF ICU example
  - For all GNRs: meropenem 95% → mero + cipro 98%, mero + tobra 99%
  - For Pseudomonas: mero 79% → mero + cipro 95%, mero + tobra 100%

- Patient characteristics
  - Avoid antibiotics that the patient recently received
  - Consider antibiotic penetration issues
  - Balance risk of nephrotoxicity from AG with risk of inappropriate coverage

Reasons To Consider Combination Rx

1. Increase the probability of initial appropriate empiric coverage by expanding the spectrum of activity, especially if concerned about resistance (“empiric combination therapy”)

2. **Synergy** between 2 active ABx (“definitive combination therapy”)

3. Prevent the development of resistance with 2 active ABx (“definitive combination therapy”)
Synergy

- Defined as > 2-log increase in bactericidal activity *in vitro* when using 2 ABx combined compared with either alone

- *In vitro* and animal studies
  - Best data is for beta-lactam plus aminoglycoside
  - Data for beta-lactam plus fluoroquinolone more sporadic

- Does this translate into clinical benefit?


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No Mortality Benefit of Definitive Combination Rx

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Combination therapy</th>
<th>Monotherapy</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
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<tr>
<td>Lebovici 1997</td>
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<td>71</td>
<td>0.85 [0.45, 1.66]</td>
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Total (95% CI) 347 846 100.0% 0.49 [0.47, 1.66]

Total events 77 136

Heterogeneity: X² = 13.30, df = 7 (P = .16), I² = 33%

Test for overall effect: Z = 0.68 (P = .49)

What About in Certain Subgroups?

- Some older studies from the 1980s and early 1990s showed benefit of combination therapy in certain subgroups (septic shock, neutropenia, *Pseudomonas*)

- Issues with older studies:
  - Monotherapy arm was often with an aminoglycoside
  - Older beta-lactams were used, some without anti-Pseudomonal activity

- *Newer observational data/meta-analyses show no benefit of definitive combination therapy for:*
  - Septic shock
  - Neutropenia
  - *Pseudomonas*


Reasons To Consider Combination Rx

1. Increase the probability of initial appropriate empiric coverage by expanding the spectrum of activity, especially if concerned about resistance (“empiric combination therapy”)

2. Synergy between 2 active ABx (“definitive combination therapy”)

3. *Prevent the development of resistance* with 2 active ABx (“definitive combination therapy”)

Prevention of Resistance?

- Combination therapy may prevent development of resistance in vitro
- But in clinical practice, no evidence that combination therapy prevents the development of resistance
- In fact, combination therapy may be associated with an increase in superinfection rate


Combination Rx for GNRs: Take Home Points

- Consider empiric combination therapy in critically ill patients who are at risk of having MDR organisms
- The goal of combination therapy (or “double-covering”) for GNRs is to ensure that an appropriate antibiotic is included in the initial empiric regimen (as this has been shown to decrease mortality)
- Once susceptibilities are known, narrow to monotherapy
- There is no evidence that definitive combination therapy is “synergistic” in vivo (no mortality benefit) or prevents the development of resistance
Case #2

A 65 y/o M is admitted with a stroke. 4 days into his hospitalization he spikes a fever to 39, starts coughing, drops his SaO2 to the low 90s on RA, and becomes altered. He is pan-cultured and started on vancomycin and cefepime. He improves, and work-up reveals:

- CXR with a new LLL infiltrate
- Blood cultures and sputum culture negative at 48h
- UA (from his catheter) shows 30 WBC, Urine cx >100K VRE

Would You Treat the VRE?

1. Yes

2. No
Asymptomatic Bacteriuria

- Asymptomatic Bacteriuria (ASB) = positive urine culture AND no symptoms or signs of UTI

- ASB is common
  - In catheterized patients
    - Up to 25% of short-term catheters (<30 days)
    - ~100% of long-term catheters (>30 days)
  - Of positive urine cultures obtained in the hospital → 90% are ASB

- No treatment unless:
  - Pregnant
  - Urologic procedures
  - Immunosuppression (Neutropenia, renal tx <3 mo ago)

How to distinguish ASB versus CA-UTI?

- Does the UA help? → yes, if negative
  - The presence of pyuria is not helpful (very common in ASB)
  - But the absence of pyuria suggests an alternative diagnosis
  - So always order a UA when ordering a urine culture

- Does the organism help? → NO
  - The same organisms cause ASB and UTI

- Need to use clinical context: are symptoms present?
What if I Can’t Assess Symptoms?

How to define UTI in patients with a catheter?

1. Symptoms or signs c/w UTI
   - New or worsening fever, rigors, AMS, malaise and no other clear cause
   - Flank pain, CVAT, pelvic discomfort
   - Acute hematuria
   - Spinal cord injury: spasticity, autonomic dysreflexia, sense of unease

2. No other source of infection (i.e., diagnosis of exclusion)

CA-UTI: Treatment

- **Antibiotics**
  - Empiric choices: Ceftriaxone, ertapenem, pip/tazo, cefepime
  - Duration:
    - 7 days if there is prompt resolution of symptoms
    - 10-14 days if response is delayed

- **Catheter change?**
  - Yes, if the catheter has been in for >2 weeks, change it
  - This has been associated with:
    - CA-UTI at 28d
    - Time to resolution of sx


Candiduria: Who Needs Treatment?

- Candiduria is very common in patients with catheters

- **Candiduria is usually asymptomatic**
  - In general, don’t treat!
  - Change the foley: can eliminate candiduria in 20-40%
  - Exceptions: Same as for ASB
    - Pregnancy
    - Patients undergoing urologic procedures
    - Neutropenia, Renal transplant <3 mo

- Symptomatic candiduria (uncommon)
  - Look for same symptoms as bacterial UTI
  - Treat


Candida UTI: Treatment Options

- **Fluconazole** is the drug of choice

- Excellent urine levels
  - 10-fold higher than in serum
  - Can get concentrations in the urine that are higher than the MIC for organisms that are intermediate or resistant (like *C glabrata*)

Fluconazole-Resistant Candida UTI

- Try fluconazole and re-check Ucx (if not systemically ill)

- Other options all have poor efficacy or side effect profile:
  - Flucytosine, conventional amphotericin B, ampho bladder washes

- Other azoles? → Vori, posa, itra have poor urinary penetration

- Echinocandins? → Poor urinary penetration, but can use if suspect systemic disease


ASB vs. CA-UTI: Take-Home Points

- Pyuria ≠ UTI, but the absence of pyuria points to an alternative source

- ASB and asymptomatic candiduria do not require Rx except for:
  - Pregnancy
  - Urologic procedures
  - Neutropenia, renal transplant <3 mo

- UTI diagnosis in a patient with a catheter requires:
  - Signs and symptoms compatible with UTI
  - No other source for infection (i.e., diagnosis of exclusion)

- CA-UTI can be treated with 7 days of antibiotics if symptoms resolve quickly

- Fluconazole is the drug of choice for *C. albicans* (and often non-albicans)
Case #3

85 y/o man is admitted with fever and respiratory failure to the ICU and treated with vanc/pip-tazo. He initially responds but then 5 days into therapy he began spiking high fevers up to 39 °C daily. His respiratory status is unchanged. He is escalated to vanc/meropenem with no change in his fever or respiratory status after another 5 days. Extensive work-up for other sources of infection is negative.

What is Your Next Step?

1. Change vanco to linezolid
2. Add tobramycin
3. Stop antibiotics
Drug Fever

- 3-4% of all drug reactions

- Multiple mechanisms:
  - Altered Thermoregulatory Mechanisms (e.g., amphetamine)
  - Drug Administration (e.g., amphotericin)
  - Pharmacologic Effects (e.g., Jarisch-Herxheimer Reaction)
  - Idiosyncratic Reactions (e.g., malignant hyperthermia)
  - Immune-Mediated/Hypersensitivity Reactions (e.g., most ABx)

Drugs Associated with Drug Fever

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
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<tr>
<td>Antibiotics</td>
<td>Aminopenicillins, amoxicillin, ampicillin, clindamycin, erythromycin, furadantin, imipenem, sulfonamides, clindamycin, erythromycin, clindamycin, rifampicin, streptomycin, tetracycline, trimethoprim-sulfamethoxazole, vancomycin, amphotericin, ampicillin, cefuroxime, cephalaxin, cefaclor, oxacillin, penicillin, piperacillin, tetracycline, sulphonamides, trimethoprim, vancomycin</td>
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| Antineoplastic agents | Cisplatin, cyclophosphamide, ifosfamide, nitrosoureas, busulfan, melphalan, mitoxantrone, topotecan, vincristine, dacarbazine, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, gemcitabine, ifosfamide, mitomycin, vincristine, cytarabine, daunorubicin, doxorubicin, etoposide, g

Clinical

- Diagnosis of exclusion

- Clinical features:
  - May appear well and be unaware of fevers (but not necessarily)
  - No typical fever pattern
  - Pulse-temperature dissociation (11%)
  - Rash (5-10%)
  - Eosinophilia (~20%)


Timeline of Fever Onset

<table>
<thead>
<tr>
<th>Class of Offending Agent</th>
<th>Episodes</th>
<th>Lag Time</th>
</tr>
</thead>
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<td>N</td>
<td>Mean</td>
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<td>44.7</td>
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<tr>
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<td>CNS</td>
<td>24</td>
<td>18.5</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>18.8</td>
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</table>

- But with re-challenge, fever can occur within hours

Fever Characteristics

- Fever is high
- Usually defervesce within 1-2 days of stopping drug

![Graph showing fever characteristics](Mackowiak, et al, Ann Intern Med 1987, 106:728.)

Treatment

- Discontinue all potentially causative meds, together or sequentially
- In cases where benefit > risk in continuing, can try to pre-treat:
  - Corticosteroids
  - Antihistamines
  - But watch for signs/sx of progression of hypersensitivity
- If fever was accompanied by severe adverse effects, avoid rechallenge
- Important to document suspected drug fever in the allergy section with as much detail of associated symptoms as possible

![Graph showing treatment options](Patel, et al, Pharmacotherapy 2010, 30:57.)
Cross-Reactivity of Antibiotics?

- **Change to another class if possible** (i.e. Beta-lactam to fluoroquinolone)

- No studies exist which address drug fever cross reactivity specifically – focus is on all symptoms of hypersensitivity

Drug Fever: Take Home Points

- Always consider it in the ddx for fever in the hospital

- Look for eosinophils, temp-pulse dissociation, rash although remember these are present in <20% of cases

- Consider stopping the ABx or switching classes if you really suspect it

- Remember to document drug fever as an allergy!
Other Non-Infectious Causes of Fever

- Venous thromboembolism
- Central fever
- ARDS
- Acalculous cholecystitis

VTE and Fever

- Seen in 5-15% of patients presenting with PE/DVT

- Characteristics:
  - Usually <38.9
  - Peaks on day of PE
  - Gradually subsides within 1 week

Central Fever

- Accounts for ~50% of fever in the NICU
- Seen in patients with brain tumors, SAH, intraventricular hemorrhage
- Associated with vasospasm
- Appears within 72 hours of admission, persists for longer than infectious causes of fever
- No difference in height of fever

Hocker et al, JAMA Neurol 2013, 70:1499.

Can ARDS Itself Cause Fever?

- The fibroproliferative phase of ARDS can cause fever and leukocytosis that is indistinguishable from infection
- Open lung biopsy in 7/9 patients with late ARDS and fever → fibroproliferative phase of DAD with no evidence of infection
- So...probably, but would look very hard elsewhere and this is a diagnosis of exclusion

Acalculous Cholecystitis in the ICU

- Rare (~1%) of all ICU patients

- A serious disease:
  - High mortality (30%) due to difficulty in dx
  - High risk of gangrene (50%) and perf (10%)

- Pathophysiology:
  - Bile stasis aggravated by dehydration or TPN
  - GB ischemia in setting of sepsis, hypotension
  - Infection likely secondary


Acalculous Cholecystitis in the ICU

- Diagnosis:
  - Symptoms/signs often not helpful (if patients are intubated)
  - LFT abnormalities in >60% but non-specific (but may make you image!)
  - US = CT
    - GB wall thickness ≥ 3.5 mm (80% sensitive, 98% specific)
    - Sludge
    - Gallbladder distention > 5 cm
    - Sonographic Murphy’s
    - Pericholecystic fluid
  - HIDA: sensitivity only 70-80% (and takes > 2 hours)

- Treatment
  - Drainage: cholecystectomy often not possible → percutaneous chole tube
  - Antibiotics → target GNRS, Enterococcus, anaerobes +/- Candida

Case #4

65 y/o man with HCV cirrhosis is intubated for severe influenza A leading to ARDS. He had been slowly improving but then over the last 2 days has starting having fevers to 38.4 with new production of thick secretions. He has trouble following commands when sedation is lifted.

Blood and urine cultures are negative. CXR is unchanged. Head CT shows pansinusitis.

Your Next Diagnostic Step is:

1. Sinus puncture
2. Lumbar puncture
3. Mini-BAL or endotracheal aspirate
Pneumonia in the ICU

- **Hospital-Acquired PNA (HAP)** = PNA acquired after 48 hours in the hospital and not incubating at the time of admission

- **Ventilator-Associated PNA (VAP)** = PNA acquired after 48 hours of intubation (subset of HAP)

- Microbiology overall is similar:
  - **GPCs**: *S. aureus*, particularly MRSA
  - **GNRs**: *P. aeruginosa*, *E. coli*, *Klebsiella pneumoniae*
  - More common in VAP: *Pseudomonas*, *Stenotrophomonas*, *Acinetobacter*


VAP: Diagnosis

- **Clinical Criteria**
  - Use to prompt testing, empiric Rx
  - New or progressive CXR infiltrate + 2/3 clinical criteria:
    - F > 38 °C
    - ↑ or ↓ WBC
    - Purulent secretions
  - 69% sensitive, 75% specific
  - ARDS: consider PNA with ≥ 1 clinical criteria b/c may not see CXR change


- **Microbiologic Diagnosis**
  - Obtain lower respiratory tract culture before ABx
  - Quantitative cultures preferred
    - BAL and mini-BAL both ~80% sensitive and specific
    - Endotracheal aspirate (quantitative) ~75% sensitive and specific
  - Blood cultures positive in <25%
  - Thoracentesis if an effusion is large or the patient is toxic
**VAP/HAP: Empiric ABx (IDSA Guidelines)**

**Risk Factors for MDR Pathogens Present?**
- HCAP
- HAP/VAP with ≥ 5 days in the hospital
- Immunosuppression
- ABx in last 90 days
- High frequency of ABx resistance in a specific unit

**Options:**
- Ceftriaxone
- Fluoroquinolone
- Ertapenem
- Amp/sulbactam

**No**

**Yes**
- Linezolid or Vancomycin
- Anti-pseudomonal beta-lactam
- Anti-pseudomonal FQ or AG

*Use local resistance patterns for guidance*

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**Duration of ABx in VAP**

- RTC of 400 patients with VAP randomized to 8 vs. 15 days of ABx

- 8-day group had:
  - No difference in mortality, recurrent infections, length of ICU stay
  - More ABx-free days (9 vs 13%)
  - Less MDR organisms if had recurrent infections (42 vs 65%)
  - But...higher pulmonary reinfection rate (41 vs 25%) if had a glucose nonfermenter (*Pseudomonas, Acinetobacter, or Stenotrophomonas*)

- **Bottom line:**
  - *Pseudomonas, Acinetobacter, Stenotrophomonas: 14 (or 15) days*
  - MRSA: 7-21 days depending on extent of infection (IDSA MRSA guidelines)
  - 7 (or 8) days for everyone else

**IDSA/ATS Guidelines, Am J Resp Crit Care Med 2005.**

**Chastre et al, JAMA 2003, 290:2588.**
Linezolid vs. Vancomycin for MRSA PNA?

- **Historical perspective:**
  - Post-hoc analysis of RCT subgroups showed that linezolid had ≥ clinical cure and ≥ mortality compared to vanc.
  - Vancomycin was not dose optimized and so due to low vanco levels.
  - Proposed MOA: linezolid could be inhibiting toxin production.

- **RCT of linezolid (IV) vs vancomycin in 448 patients with MRSA HAP/VAP/HCAP**
  - Vanco dose-optimized by unblinded pharmacist.
  - Treated for 7-14 days (up to 21 days if bacteremia).
  - Primary outcome: Clinical cure.


---

**Linezolid vs. Vancomycin: Outcomes**

![Bar chart showing clinical cure and mortality outcomes for linezolid vs. vancomycin.](Wunderink et al, Clin Infect Dis 2012; 54: 621.)
Linezolid vs. Vancomycin: Conclusions

- Compared to vancomycin, linezolid has a modest benefit in clinical response but no effect on mortality.

Limitations:
- Were the vanco patients sicker?
  - Compared to linezolid group: ventilation, concurrent MRSA bacteremia, kidney disease, and diabetes
  - Did not evaluate length of ICU stay, length of hospitalization, mechanical ventilation

- When do I use linezolid for MRSA PNA?
  - The patient isn’t getting better on vancomycin
  - Trouble getting vancomycin therapeutic

VAP/HAP: When to Stop Empiric Vanco?

- Low suspicion or negative cultures (before antibiotics)

- Sometimes difficult as respiratory specimens are not obtained at all or not obtained before ABx

- Are negative blood cultures enough? How often is there bacteremia with MRSA PNA?
  - Only 5-10%!! So beware of stopping vanco just with negative blood cultures if your suspicion is high

HAP/VAP: Take Home Points

- Think about risk factors for MDR pathogens and use that to guide empiric therapy

- Diagnosis is based on a combination of clinical and microbiologic parameters

- Duration of therapy = 7 (or 8) days with the exception of the glucose nonfermenters +/- MRSA

- Consider linezolid for MRSA if not responding to vancomycin

Nosocomial Sinusitis

- Epidemiology:
  - Radiographic sinusitis in 25-75% of ICU pts
  - But etiology of nosocomial fever in ~5%
  - Radiographic sinusitis ≠ infectious sinusitis

- Micro: *Pseudomonas, S. aureus*, can be polymicrobial

- Clinical: classic signs/sx of sinusitis often absent

- Dx: CT, aspirate by ENT to confirm dx and guide ABx therapy

- Treatment duration: 7 days

Case #5

A 65 y/o woman is admitted to the ICU for sepsis due to cholangitis with retained stone. She gradually improves after ERCP and ertapenem.

On her 4th day in the ICU she develops a new fever, leukocytosis to 18, and diarrhea. She is found to have C. difficile. Creatinine is baseline and blood pressure is stable.

What Would You Start?

- PO metronidazole
- PO vancomycin
- PO vancomycin + IV metronidazole
- Fidaxomicin
Case #5 continued

She is started on PO vancomycin 125mg qid. Fever and leukocytosis resolve but she has not yet had improvement of her diarrhea after 4 days of treatment.

What Would You Do With Her ABx?

1. No change
2. Add IV metronidazole
3. Switch to fidaxomicin
When Should My Patient Get Better?

- Resolution of diarrhea takes ~5-7 days (longer for PO metronidazole)
- Symptoms can be prolonged 1-2 days with concomitant ABx
- Failure rate only 5-15% so most will get better eventually

Cdiff Therapy: General Principles

1. Treat with anti-Cdiff antibiotics
2. Stop other ABx if possible
3. Other general points:
   - Avoid anti-peristaltics
   - Hold PPI if possible (has been associated with higher severity of disease)
**IDSA Guidelines for Cdiff Treatment**

**Mild to moderate**
- WBC < 15
- Cr < 1.5x baseline

**Severe**
- WBC ≥ 15
- Cr ≥ 1.5x baseline

**Severe + Complications**
- Hypotension
- Ileus
- Toxic megacolon

- Metronidazole 500mg PO tid x 10-14d
- Vancomycin 125mg PO qid x 10-14d

- Vanco 500mg PO qid + Metronidazole 500mg IV q8h +/- Vanco 500mg PR qid (ileus)

---

**The Benefit of Adding IV Metronidazole?**

- In IDSA guidelines for severe, complicated disease
  - To ensure drug levels in the colon in the case of ileus (when PO vanc may not transit to the colon)

- Previously no clinical data for the combination but anecdotal observation of possible benefit

- Recent retrospective study showing mortality benefit in critically ill patients
  - Mortality in vanco monotherapy group (36%) vs combination group (16%)
  - In multivariable analysis, getting IV metronidazole was associated with survival (OR 4.54)

---

Fulminant Cdiff: Other options

- Colectomy
  - Always call surgery for severe complicated disease

- IVIG
  - Case series data

- Tigecycline
  - Case reports only
  - Be aware of black box warning for risk of death

- FMT
  - High success rate in one small study


Fidaxomicin

- General points:
  - First-in class macrocyclic antibiotic with minimal absorption from GI tract
  - Treatment dose: 200mg PO bid x 10 days

- Efficacy:
  - Equivalent to vancomycin for cure rate in initial episode (~85-90%) and may have slight advantage if patient is on concomitant ABx
  - Lower recurrence rate than PO vanco (15% vs 25%)

- Issues:
  - Not as much experience with fulminant disease
  - No data for switching from vanco to fidaxomicin in case of failure
  - $$$$$ ($2600 for a treatment course vs ~$15 for compounded PO vanc)

Recurrent Cdiff: Recommendations

1st Recurrence
- Treat with same as 1st episode (although most would switch to PO vanco)

2nd Recurrence
- Vanco pulse then taper over 4-6 weeks
- Many options for taper:
  - bid x 1 wk → qday x 1 wk → q2 or q3d x 2-8 weeks (IDSA)
  - tid x 1 wk → bid x 1 wk → daily x 1 wk → q2d x 1 wk → q3d x 1 wk

3rd Recurrence
- **FMT**
- Vanco plus chaser (rifaximin or fidaxomicin)?
- Vanco taper then suppressive therapy (eg once daily or bid)?
- Fidaxomicin?
- IVIG?
- Probiotics?

Rectal Swabs for C. difficile

- C. difficile can occasionally present without diarrhea (especially very early in disease or with severe disease complicated by ileus)

- Rectal swabs for C. difficile PCR testing:
  - Sensitivity 96-100%
  - Specificity 100%
  - Studies done on patients having diarrhea, so unclear if test characteristics would be different in patients without diarrhea

C. difficile: Take-Home Points

- Use PO vancomycin for severe Cdiff (WBC ≥ 15 and Cr ≥ 1.5x baseline)

- Resolution of diarrhea takes ~5-7 days (longer for PO metronidazole and if on concomitant ABx)

- The main benefit of fidaxomicin is in its lower risk of recurrence (rather than initial treatment efficacy)

- Rectal swabs for C. difficile may be useful in patients presenting without diarrhea

Case #6

65 y/o F in the ICU for a prolonged course after a Whipple procedure. Her course has included a VAP and UTI and she has received multiple courses of antibiotics. She has been spiking fevers for the last 3 days despite linezolid and meropenem. You get a call from the micro lab that 1/2 blood cultures (peripheral) is growing yeast.
The Most Appropriate Next Step Is:

1. Start voriconazole
2. Start fluconazole
3. Start caspofungin

What is the Ddx for “Yeast in the Blood”?

- Yeast in the blood almost always = candida
- Rarely it could be cryptococcus in the right host (e.g., HIV, transplant)
Management of Candidemia

1. Start an antifungal (*echinocandin or fluconazole)
   • IDSA guidelines recommend an echinocandin over fluconazole if:
     • Recent azole exposure
     • Moderate to severe illness
     • High risk of infection with *C. glabrata* or *C. krusei*

2. Evaluate for source → pull lines

   1. Eye exam

Why consider Echinocandin > Fluconazole?

- What kinds of candida are there?
  - *C albicans* (50-65%)
  - *C glabrata* (~20%) – can be fluconazole resistant
  - *C parapsilosis* (6-17%)
  - *C tropicalis* (7-11%)
  - *C krusei* (2%) – intrinsically fluconazole resistant
  - *C lusitaniae* (<1%)
  - *C dublinensis* (<1%)

Back to the Case...

- The candida comes back as *C. glabrata*...anything else to do?
- Yes – ask the lab for azole susceptibilities!
- If it comes back sensitive → can switch to fluconazole (or voriconazole) as oral stepdown therapy

Candida Susceptibilities

<table>
<thead>
<tr>
<th>Species</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
<th>Fluocinolone</th>
<th>Amphotericin B</th>
<th>Caspofungin</th>
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<tbody>
<tr>
<td>Candida albicans</td>
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<td>Candida tropicalis</td>
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</tbody>
</table>

*NOTE. I, intermediate susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent.
^* Echinocandin resistance among *C. parapsilosis* isolates is uncommon.

- **C. albicans or C. tropicalis:**
  - Fluconazolene resistance very rare: *C. albicans* ~1-2 %, *C. tropicalis* ~4%
  - Fluconazole is drug of choice

Candida Susceptibilities

Table 3. General patterns of susceptibility of Candida species.

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* Echinocandin resistance among C. parapsilosis isolates is uncommon.

- C. parapsilosis:
  - Echinocandin MICs are in general higher, although clinical significance unclear
  - Fluconazole is drug of choice (~4% fluc resistance seen)


Candida Susceptibilities

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* Echinocandin resistance among C. parapsilosis isolates is uncommon.

- C. glabrata:
  - Fluc resistance is ~15% nationally, vori resistance ~10%
  - Echinocandin is drug of choice to start, then narrow to fluc based on sensitivities (or consider vori as oral step-down alternative if sensitive)

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* Echinocandin resistance among *C. parapsilosis* isolates is uncommon.

- C. *krusei*:
  - Intrinsic fluconazole resistance
  - Echinocandin is drug of choice, consider step-down to vori as oral option


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*NOTE.* I, intermediate susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent.

* Echinocandin resistance among *C. parapsilosis* isolates is uncommon.

- C. *lusitaniae*:
  - Can be amphotericin resistant

Duration of Therapy

**IDSA guidelines:**
- If no metastatic foci of infection, treat for 2 weeks from date of 1st negative culture (so be sure to get surveillance cx)

- This is based on the results of several prospective, randomized trials in which treatment for 2 weeks was associated with few complications and relapses

---

Pull the Line!

- **Remove the line if possible:**
  - Often difficult to tell if the source is the line or a GI source
  - Exception: C parapsilosis is often catheter-associated

- Removal is associated with more rapid clearance of blood cultures and decreased mortality

---

Get an Eye Exam

- Rule out chorioretinitis (seen in ~10%) or endophthalmitis (seen in 1-2%)

- This is not an emergency (unless having visual symptoms)

- In fact, may increase your sensitivity by waiting ~1 week after starting therapy

Oude Lashof et al., Clin Infect Dis 2011, 53:262.

Why Does This Matter?

- Intravitreal antifungal injections

- Longer duration of therapy (4-6 weeks)

- Choose an agent with good eye penetration
  - Azoles (voriconazole > fluconazole)
  - Amphotericin + 5-FC
  - NOT echinocandins (have poor ocular penetration)
Candidemia: Take Home Points

1. Start antifungals (echinocandin or fluconazole) empirically
   • Check surveillance cx in 48hr
   • Change to fluc if it’s a susceptible species (albicans, tropicalis, parapsilosis) or when you have sensitivities back for C.glabrata
   • Treat for 2 weeks from the date of the 1st negative culture

2. Pull the line

3. Eye exam
   • If positive, use vori if sensitive
   • Duration of therapy 4-6 weeks for eye involvement

Thank you!

- Questions? → jennifer.babik@ucsf.edu