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

Roadmap

- Introduction/Framework

- Infections in the ICU
  - “Double-covering” GNRs
  - VAP
  - Nosocomial sinusitis
  - Acalculous cholecystitis
  - Candidemia
  - C. difficile
  - (UTI and CLABSI – discussed yesterday in “Common Curbsides”)

- Non-infectious Etiologies for Fever in the ICU
  - Drug fever
  - VTE
  - Central fever
**Definition of Fever**

- Definition of fever is arbitrary
  - $\geq 38.3\, ^\circ C$ (101 °F) commonly used (IDSA/ACCCM)
  - Use a lower threshold in immunocompromised patients
  - $T < 36.0\, ^\circ C$ should also prompt work-up for infection

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

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**Measurement of Fever**

- Central thermometers (bladder, rectal, esoph) $\approx$ pulmonary artery temperatures

- Peripheral thermometers have:
  - Poor correlation with central temperatures
    - 0.5 - 2 °C above or below, worse at extremes of temperature
  - Poor sensitivity for detecting fever (but high specificity ~95%)
    - Oral or tympanic: 75% sensitive
    - Temporal 63% sensitive
    - Axillary 42% sensitive
Does the Height of the Fever Help?

- Hyperpyrexia = Fever >41.1 °C (or >106 °F)
- Conventional wisdom is that infections are a rare cause
- The data show infections are a frequent cause of hyperpyrexia in adults (>50% solely from infection)
- Most common infections: Staph, Strep, GNRs


Fever in the ICU: Epidemiology

- Fever occurs in 25-70% of patients
- Infectious vs non-infectious?
  - 35-55% are infectious
  - 45-65% are non-infectious!
- Etiologies depend on ICU type (MICU vs SICU vs NICU)
  - Most common infections: PNA, bloodstream, abdominal
  - Most common non-infectious etiologies: post-op fever, central fever

Should Fever in the ICU Be Treated?

- Is fever good? (it may enhance immune cell function and inhibit organism growth)

- Is fever bad? (it may put additional physiologic stress on the body)

RCT of 700 ICU patients given acetaminophen or placebo to treat fever in known or suspected infection

- No difference in # ICU-free days or on mortality

Young et al, NEJM 2015, 373:2215.

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-abd abscess)

1. Is this a separate nosocomial process?
   - Hospital-acquired PNA (HAP, VAP)
   - CA-UTI
   - Central Line-Associated Blood Stream Infection (CLABSI)
   - *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

Cardiac
- Endocarditis
- Pericarditis
- 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
- CLABSI
- 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 carbepenems or ciprofloxacin is admitted to the ICU with presumed pyelonephritis.

- She is febrile to 39.6°C, tachy to 120s, rapidly uptitrated to max doses on 3 pressors.
- 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.
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 #2 Continued

- Blood and urine cultures return positive with *Pseudomonas* susceptible to all Abx except cipro/levo.
- Pressor requirement is downtrending.
- 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)

- 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)
  - Inclusion of older studies (using older ABx) in some meta-analyses
3 Reasons To Consider Combination Rx

1. Increase the probability of initial appropriate empiric coverage by expanding the spectrum of activity.
2. Synergy between 2 active antibiotics
3. Prevent the development of resistance

Empiric Combination Therapy

- ↑ mortality by ~2-fold if inappropriate empiric Abx in *Pseudomonas* bacteremia (true also for other GNRs)
- Using empiric combination therapy will increase the likelihood of having at least one active antibiotic

When to Use?
- Patient is critically ill
- Patient is at high risk for MDR pathogens
- Know your local antibiogram: how good is the beta lactam? What is the benefit of adding a FQ vs AG?
- Balance risk of nephrotoxicity from AG with risk of inappropriate coverage

UCSF Pseudomonas Antibiogram

<table>
<thead>
<tr>
<th></th>
<th>MER → MER+TOB</th>
<th>PIPTAZ → PIPTAZ+TOB</th>
<th>CFPM → CFPM+TOB</th>
<th>MER → MER+CIP</th>
<th>PIPTAZ → PIPTAZ+CIP</th>
<th>CFPM → CFPM+CIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>70% → 97%</td>
<td>75% → 97%</td>
<td>86% → 97%</td>
<td>79% → 91%</td>
<td>75% → 97%</td>
<td>86% → 97%</td>
</tr>
<tr>
<td>ICU</td>
<td>77% → 93%</td>
<td>71% → 93%</td>
<td>81% → 93%</td>
<td>77% → 82%</td>
<td>71% → 82%</td>
<td>81% → 84%</td>
</tr>
<tr>
<td>Floor</td>
<td>81% → 97%</td>
<td>76% → 98%</td>
<td>90% → 99%</td>
<td>81% → 90%</td>
<td>83% → 91%</td>
<td>90% → 91%</td>
</tr>
</tbody>
</table>

Definitive Combination Rx: Synergy?

- Defined as > 2-log increase in bactericidal activity *in vitro* with 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?
  - **NO mortality benefit** based on recent meta-analysis for Pseudomonas (same results seen for other GNRs)

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


Definitive Combination Rx: Prevent Resistance?

- Combination therapy may prevent development of resistance *in vitro*

- But in clinical practice, no evidence that combination therapy prevents the development of resistance

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” \textit{in vivo} (no mortality benefit) or prevents the development of resistance

Case #2

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. Add ciprofloxacin
4. Stop antibiotics

Drug Fever

- 3-4% of all drug reactions
- Multiple mechanisms:
  - Altered Thermoregulatory Mechanism (eg amphetamine)
  - Drug Administration (eg amphotericin)
  - Pharmacologic Effects (eg Jarisch-Herxheimer Reaction)
  - Idiosyncratic Reactions (eg malignant hyperthermia)
  - Immune-Mediated/Hypersensitivity Reactions (eg ABx)
Drugs Associated with Drug Fever

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%)

- Timing:
  - 7-10 d after starting a drug (with re-challenge, can be hours)
  - Usually defervesce within 1-2 days of stopping the drug

Drug Fever is Usually High-Grade


![Bar chart showing temperature distribution for Cardiac, ABx, Chemo, CNS, Other categories.]

Treatment

- Discontinue or change to another drug class if possible

- In cases where benefit > risk to continue, can try to pre-treat:
  - Corticosteroids and/or antihistamines
  - But watch for signs/sx of progression of hypersensitivity

- If fever occurs with severe adverse effects, avoid rechallenge

- Important to document potential allergy with as much detail as possible

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!

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

VTE and Leukocytosis?

- Patients presenting to the hospital with acute PE and no other cause for leukocytosis (n=266)

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.
Case #3

60 y/o man is admitted with severe hypoxemic respiratory failure and is intubated then trach’d for several weeks. He has had various complications but now has fever despite broad spectrum Abx.

- No clear localizing signs (but is sedated)
- WBC 20, tibli 4, AST 65, ALT 45, alk phos 105
- CT A/P shown

The Best Management Step Is:

1. Add ganciclovir
2. Add caspofungin
3. Percutaneous cholecystostomy tube
4. Tagged WBC scan
Acalculous Cholecystitis in the ICU

- Rare (~1%) of all ICU patients

- A serious disease:
  - High mortality (30%) due to difficult dx
  - High risk of gangrene (50%) and perforation (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, pericholecystic fluid
    - Gallbladder distention > 5 cm
    - Sonographic Murphy’s
  - HIDA: sensitivity only 70-80% (and takes > 2 hours)

- Treatment
  - Cholecystectomy often not possible → percutaneous chole tube
  - Antibiotics → target GNRs, Enterococcus, anaerobes +/- Candida

Case #4

65 y/o man with cirrhosis is intubated for severe influenza and 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
4. BAL
Pneumonia in the ICU

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

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

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


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HAP/VAP IDSA Guidelines 2016: What’s New?

1. **HCAP** no longer included (not at high risk for MDR)

2. Recommendation for semi-quantitative endotrachaeal aspirate over invasive methods (BAL, mini-BAL)

3. Slightly less emphasis on using 2 antibiotics against *Pseudomonas* for empiric coverage

4. Duration of therapy = 7 days for all pathogens

Kalil et al, IDSA/ATS Guidelines, CID 2016
VAP: Microbiologic Diagnostics

- Get blood cultures in all (~15% are positive)

- Obtain a respiratory culture
  - 2016 guidelines recommend semi-quantitative endotracheal aspirate over invasive sampling (mini-BAL, BAL) (weak recommendation, low quality evidence)

Why Semi-Quantitative ETA?

- Rationale:
  - Studies show no difference in outcomes (mortality, ICU days, mechanical ventilation days)
  - Requires less resources

- Test characteristics:
  - ETA $\rightarrow$ sensitivity 75%, specificity 50% (PPV 60%)
  - Mini-BAL, BAL $\rightarrow$ 60-80% sensitivity, specificity 80% (PPV 80%)

- Some will continue to use mini-BAL/BAL due to ↑ specificity
**VAP: Clinical Diagnosis**

- New or progressive CXR infiltrate + 2 clinical criteria (fever, leukocytosis/leukopenia, or purulent secretions) is 69% sensitive, 75% specific

- Also look at change in oxygenation

- In ARDS, consider PNA if have only ≥1 clinical criteria because may not see CXR change

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**VAP/HAP: Empiric ABx**

- Cover for *S. aureus, Pseudomonas, GNRs*

- Do you need MRSA coverage?
  - Yes if MDR risk, >20% local *S. aureus* are MRSA, high risk of mortality
  - MRSA unlikely if nasal MRSA screen neg and low local prevalence of PNA due to MRSA

- Do you need 2 drugs for *Pseudomonas*?
  - Yes if MDR risk, >10% local GNRs are resistant to monotherapy agent, high risk of mortality
  - Use clinical judgment

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**Risk of MDR VAP**
- Prior IV Abx within 90 d
- Septic shock
- ARDS
- ≥5 d in hospital
- Acute HD/CRRT

**Risk of MDR HAP**
- Prior IV Abx within 90 d
VAP/HAP: ABx Menu

<table>
<thead>
<tr>
<th>MRSA</th>
<th>Anti-pseudomonal (β-lactam)</th>
<th>2nd Anti-pseudomonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Piperacillin/tazobactam</td>
<td>Levofloxacin/ciprofloxacin</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Cefepime/ceftazidime</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td></td>
<td>Meropenem/imipenem</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>Aztreonam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HAP only: levo/cipro</td>
<td></td>
</tr>
</tbody>
</table>

Kalil et al, IDSA/ATS Guidelines, CID 2016

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, ICU LOS
  - More ABx-free days (9 vs 13%)
  - Less MDR organisms if had recurrent infection (42 vs 65%)
  - But...higher pulmonary reinfection rate (41 vs 25%) if had a glucose nonfermenter (*Pseudomonas, Acinetobacter, or Stenotrophomonas*)

Duration of ABx in VAP

- Systematic reviews of 6 RCTs comparing short (7-8 days) vs long (10-15 days) course therapy:
  - Confirmed short course benefits (more Abx free days, less recurrences with MDRO) and no difference in cure, mortality
  - Glucose-nonfermenter subgroup: no difference in recurrence, mortality

- Bottom line:
  - 7d treatment course, even for glucose non-fermenters
  - Extrapolate data to HAP
  - Note MRSA IDSA guidelines recommend 7-21d for MRSA PNA


VAP/HAP: When to Stop Empiric Vanco?

- Factors which make MRSA less likely:
  - Low clinical suspicion based on disease severity
  - Negative cultures (before antibiotics)
  - Negative MRSA nasal swab with low local prevalence of PNA due to MRSA

- What about negative blood cultures?
  - Caution as bacteremia only found in 5-10% of cases of MRSA PNA

HAP/VAP: Take Home Points

- Diagnosis is based on a combination of clinical and microbiologic parameters
- Think about risk factors for MDR pathogens and local resistance patterns to guide empiric therapy
- Duration of therapy = 7 days in most cases

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

65 y/o F in the ICU for a prolonged course after a Whipple procedure. She is on TPN and 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. BP now trending down and pressors are started
- You get a call from the micro lab that 1/2 blood cultures (peripheral) is growing candida.

The Most Appropriate Next Step Is:

1. Start voriconazole
2. Start fluconazole
3. Start caspofungin (or other echinocandin)
4. Start amphotericin + 5-FC
Management of Candidemia

1. **Start an antifungal**
   - IDSA recommends an echinocandin > fluconazole unless:
     - Not critically ill
     - Low risk of infection with *C. glabrata* or *C. krusei*
   - Narrow to an azole if possible based on Candida speciation/sensitivities
   - Get surveillance cultures → **duration of therapy = 2 weeks from date of 1st negative culture**

2. **Evaluate for source → pull lines**
   1. **Eye exam**

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**Why consider Echinocandin > Fluconazole?**

- >15% of *C. glabrata* are fluconazole-resistant
- *C. krusei* is intrinsically fluconazole resistant
- Fluconazole is the drug of choice for *C. albicans*, *C. parapsilosis*, and *C. tropicalis*

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The Importance of the Eye Exam

- R/o chorioretinitis (in ~10%) or endophthalmitis (in 1-2%)

- Timing:
  - Not an emergency unless having visual symptoms
  - May increase sensitivity by waiting ~1 week after starting Rx

- Why is this important?
  - Intravitreal antifungal injections
  - Longer duration of therapy (4-6 weeks)
  - Choose an agent with good eye penetration
    - Azoles (voriconazole or fluconazole)
    - NOT echinocandins (poor ocular penetration)

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

Case #5 Continued

She is clinically improving after line removal and antifungals. Can we continue her TPN?
Can this Patient Continue TPN?

1. No, try enteral feeds again
2. No, switch to PPN
3. Yes, but use D5 NS for 2 weeks
4. Yes, continue TPN

Candidemia and TPN

- Risk of line-related blood stream infection from TPN is 10-20% (1-10 episodes per 1000 catheter days)
- 10-20% of these are Candida, likely related to glucose/lipids promoting growth, biofilm production

- Risk:
  - Highest risk with duration > 7 days
  - Risk appears similar with TPN and PPN
  - Risk ↑ if access the line for another reason
  - Risk ↑ with concomitant antibiotics

Should TPN be Delayed After Candidemia?

- No data/guidelines
- Use enteral feeding if possible while waiting for cultures to clear
- But usually the risk of poor nutrition outweighs the risk of infection in the short term
- I usually do not advocate for any delay in TPN if there is no alternative method of nutrition

Candidemia: Take Home Points

- Initial management should involve:
  - Start an antifungal (usually an echinocandin)
  - Evaluate for source → pull lines
  - Eye exam
- Tailor antifungals based on azole susceptibility and treat for 2 weeks if uncomplicated
- TPN is a risk factor for candidemia but benefit may outweigh risk for continuing
Case #6

A 55 y/o woman with HTN is admitted to the ICU 1 week ago with severe PNA requiring intubation. She is being treated with ceftriaxone and azithromycin. She now has new onset of fever, hypotension, and abdominal distention but no diarrhea. She is newly having high residuals from her tube feeds and these have been held.

Data:
- Fever 39.0, HR 120, BP 90/60
- WBC 20,000, Cr 1.7 (baseline 1.0)
- CXR stable
- UA and blood cultures negative
- CT A/P is shown

What is Your Next Step?

1. Wait for a stool sample to test for *C. difficile*, no empiric therapy

2. Wait for a stool sample to test for *C. difficile* and start empiric therapy now

3. Check a rectal swab for *C. difficile*, no empiric therapy

4. Check a rectal swab for *C. difficile* and start empiric therapy now
What Therapy Would You Start?

1. Metronidazole 500mg IV q8h
1. Metronidazole 500mg PO q8h
1. Vancomycin 125mg PO qid
1. Vancomycin 500mg PO qid + metronidazole 500mg IV q8h + PR vancomycin

Rectal Swabs for \(C.\) difficile

- \(C.\) difficile can occasionally present without diarrhea (very early disease or severe disease with ileus)

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

C. difficile Therapy: General Principles

1. Treat with antibiotics against C. difficile
2. Stop other antibiotics if possible
3. Other general points:
   • Avoid anti-peristaltics
   • Hold PPI if possible (associated with severity of disease)

IDSA Guidelines for C. difficile 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 q8 +/- Vanco 500mg PR qid (ileus)

The Benefit of Adding IV Metronidazole?

- Concordance with IDSA guidelines results in:
  - ↓ mortality (5% vs 22%)
  - ↓ infection recurrence (14% vs 36%)
  - Mostly driven by IV metronidazole not added in severe complicated disease

- Retrospective study in 88 ICU patients with C. difficile:
  - Decreased mortality when IV metronidazole was added to oral vancomycin (16% vs. 36%, p=0.03)
  - Combination had higher oral vanc dose, more rectal vanc

Fulminant C. difficile: Other options

- Colectomy: call surgery for severe complicated disease

- IVIG? → case series data only

- Tigecycline? → case reports only, be aware of black box warning due to ↑ risk of death

- FMT? → one case series in severe/complicated disease with high success rate
When Should My Patient Get Better?

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

Fidaxomicin

- General points:
  - Macrocyclic Abx with minimal oral absorption
  - 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 course vs ~$15 for compounded PO vanc)
Management of Recurrent *C. difficile*

<table>
<thead>
<tr>
<th>Recurrence Level</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Recurrence</strong></td>
<td>Treat with same as 1st episode (although most would switch to PO vanco)</td>
</tr>
</tbody>
</table>
| **2nd Recurrence** | - Vanco pulse x 2 wks then taper over 4-6 weeks  
- Taper: bid x 7d → daily x 7d → qod x 8d → q3d x 14d  
- Would consider fidaxomicin here if patient not able to pursue FMT if has another recurrence |
| **3rd or More Recurrence** | - Evaluate for FMT  
- Other options:  
  - Fidaxomicin  
  - Vanco plus chaser (rifaximin or fidaxomicin)  
  - Vanco taper then suppressive therapy (qday or bid)  
  - IVIG  
  - Probiotics |

*C. difficile*: Take-Home Points

- Rectal swabs for *C. difficile* may be useful in patients presenting without diarrhea
- The IDSA treatment guidelines differentiate between mild-moderate, severe, and severe/complicated disease
- 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)
Thank you!

- Questions?