FEVER IN THE ICU

Management of the Hospitalized Patient
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Learning Objectives

1. To learn a rational approach to the differential diagnosis for 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
Fever: Definition and Measurement

- Definition of fever is arbitrary: \( \geq 38.3^\circ C \) (101°F) commonly used (IDSA/ACCM guidelines)

- Use a lower threshold in:
  - Immunocompromised patients
  - Patients on CRRT or ECMO

- \( T < 36.0^\circ C \) should also prompt an investigation for infection


Fever in the ICU: Epidemiology

- Fever occurs in 26-70% of patients
  - Of febrile episodes, only 35-55% are thought to be 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

Differential: Head-to-Toe Approach

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

**HEENT**
- Nosocomial Sinusitis
- URI (hospital-acquired)

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

**Cardiac**
- Endocarditis
- Pericarditis

**GI/GU**
- Abdominal abscess
- SBP
- Acalculous cholecystitis
- Pancreatitis
- C. difficile
- CA-UTI

**MSK**
- Osteomyelitis/septic arthritis
- Gout

**Skin**
- Cellulitis at PIV/CVC
- Infected decubitus ulcer
- Surgical site infection

**Systemic**
- CLABSI
- Candidemia

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

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**Bedside Evaluation**

**Questions to Ask**
- Any change in secretions or respiratory status?
- Any diarrhea?

**Exam Elements to Include**
- Careful neuro exam
- Sinus exam for nasal discharge or tenderness
- Back and joint exam
- Skin exam:
  - Line sites
  - Remove bandages
  - Peri-anal exam
  - Rashes
Diagnostics

- Judicious use of the “pan-culture”
  - Expensive
  - Time-consuming
  - Causes patient discomfort
  - Unnecessary radiation
  - With more testing, you will find more colonizers/contaminants

- Use a rational approach
  - Start with a history and physical
  - Order labs/diagnostics based on clinical suspicion


Case #1

A 55 year old man is admitted to the ICU with severe gallstone pancreatitis. He had been slowly improving but then spikes a fever to 39 associated with new hypotension and rigors. He has a subclavian triple lumen catheter. His exam is unremarkable. You order CXR, UA/Ucx, and peripheral and line blood cultures and then start empiric vanc and pip-tazo.

Blood cultures drawn from his triple lumen subclavian line return positive 3 hours before his peripheral blood culture. Both are growing E. coli.
This is most consistent with:

1. Line infection (CLABSI)
2. Bacteremia from another source

The IDSA Guidelines recommend:

1. Pull the line
2. Ok to attempt line salvage with ABx lock therapy
3. Ok to attempt line salvage by giving systemic ABx through the line
CLABSI: Diagnosis

- Clinical findings unreliable:
  - Inflammation at the exit site is extremely insensitive (<3%)

- Positive peripheral bx and > 15 CFU/plate of same organism from catheter tip
  - 79% sensitive, 92% specific
  - But >80% of catheters withdrawn b/c of clinical suspicion of CLABSI are removed unnecessarily

- Quantitative blood cultures (line vs peripheral) may be most sensitive/specific, but not routinely available


CLABSI: Differential Time to Positivity

- Allows for diagnosis without removing the line

- Draw culture from line + peripheral blood at the same time
  - UCSF protocol: must be drawn within 15 minutes of each other

- CLABSI = blood culture drawn from central line turns positive at least 2 hrs before peripheral culture turns positive

- Test characteristics
  - 85-95% sensitive
  - 83-90% specific

What about for *Candida*?

• DTTP cut-off of 2 hours is 85% sensitive, 82% specific

• The special case of *C. glabrata*:
  • It is the most slow growing *Candida* with median TTP of 37h (other species 17-29h)
  • Using 2hr cut-off DTTP: sensitivity 77%, specificity 50%
  • Optimal DTTP cut-off was 6 hours → sensitivity 63%, specificity 75%

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**CLABSI: Possible Scenarios**

- **Line (+) and peripheral (+)**
  - DTTP ≥ 2 hrs
  - CLABSI
- **Line (+) and peripheral (−)**
  - DTTP < 2 hrs
  - Possibilities
    - Line colonization
    - Contaminant
    - Bacteremia from other source with 1/2 positive cultures
  - Look for another source
General Principles of Line Management

- The line should be removed in complicated infections:
  - Severe sepsis
  - Persistent bacteremia (>72 h of appropriate ABx)
  - Septic thrombophlebitis
  - Exit site infection/abscess
  - Evidence of metastatic infection: endocarditis, osteomyelitis

- Line salvage ok in certain cases (see next slide)
  - Studied primarily in long-term catheters
  - Treat with ABx lock therapy + systemic ABx for 7-14 days
  - ABx lock therapy: only if no signs of exit site/tunnel infection
  - Give ABx through the line? → good in theory but no data

Line Management (IDSA Guidelines)

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<thead>
<tr>
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<th>Tunneled Cath/Port</th>
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<td>Remove</td>
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<td>Remove</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>Remove</td>
<td>Remove</td>
<td>Remove</td>
</tr>
<tr>
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Mermel et al, Clin Infect Dis 2009, 49:1
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<td><em>Candida</em></td>
<td>Remove</td>
<td>Remove</td>
<td>Remove</td>
</tr>
<tr>
<td>Coag-negative staphylococci</td>
<td>Remove or retain</td>
<td>Remove or retain</td>
<td>Retain or guidewire exchange</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Remove</td>
<td>Remove or retain</td>
<td>Retain or guidewire exchange (or remove)</td>
</tr>
<tr>
<td>Other GNRs</td>
<td>Remove</td>
<td>Remove or retain</td>
<td>Retain or guidewire exchange (or remove)</td>
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* Mermel et al, Clin Infect Dis 2009, 49:1

Line Management: Take-Home Points

- Differential time to positivity (line positive at least 2 hours before peripheral) allows for diagnosis of CLABSI without line removal

- All lines should be removed for any complicated infection or for *Staph aureus, Pseudomonas, or Candida*

- Line management for other organisms depends on line type (lower barrier to remove line for short term catheter > long-term catheter > HD catheter)
A 65 y/o M is admitted with an STEMI. 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 has a foley. He is started on vancomycin and pip/tazo and improves.

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

**Case #2**

**What Would You Do with His Vanco?**

1. Continue vancomycin
2. Stop vancomycin
3. Change vancomycin to linezolid
CA-UTI is a Diagnosis of Exclusion!

- Asymptomatic CA-bacteriuria is common:
  - 9-23% of patients with short-term (<30d) catheters

- CA-bacteriuria usually represents ASB and NOT infection
  - Of all positive urine cultures in catheterized pts, ~90% are ASB!

- What about pyuria?
  - Pyuria is common in catheterized patients with ASB (up to 75%)
  - The presence or degree of pyuria cannot differentiate ASB from UTI
  - But, the absence of pyuria suggests an alternative diagnosis


Catheter-associated UTI: Definition

1. Patient with a catheter currently or within the last 48 h
2. Symptoms or signs c/w UTI
3. No other source of infection (i.e., diagnosis of exclusion)
4. ≥10^3 cfu of ≥1 bacterial species in a urine culture

The Million Dollar Question...

- What are “signs and symptoms compatible w/UTI” in a patient with a catheter?
  - New onset or worsening of fever, rigors, altered mental status, malaise or lethargy with no other identified cause
  - Flank pain or CVAT
  - Acute hematuria
  - Pelvic discomfort
  - Spinal cord injury patients: increased spasticity, autonomic dysreflexia, or sense of unease

Diagnosis

- Step 1: Do you need a UA/urine culture if you have a high suspicion for an alternative source (eg PNA)?
- Step 2: If you are sending a urine culture, always get a UA
- Step 3: How to get the best culture?
  - A catheter culture may not accurately reflect what is in the bladder
  - If a catheter has been in place for >2 weeks, change it and get a Ucx from the newly placed catheter
  - In a patient with a condom cath, get a specimen from a freshly placed condom cath after cleaning the glans because skin can be colonized
How to Interpret Urine Studies in a Patient Without Classic UTI Signs/Sx (e.g., with a Catheter)

Alternate Diagnosis Likely? (Signs/ sx of other illness present)

- **Yes**
  - Do not order U/A, urine cx
  - U/A, urine cx (-)
  - Do not treat for UTI
- **No**
  - Send U/A, urine cx
  - U/A (-), urine cx (+)
  - Asymptomatic bacteriuria
    - No treatment* (unless pregnant, urologic procedure, neutropenia)
    - Look for alternate dx
  - U/A (+), urine cx (+)
  - Treat for UTI if no alternate dx identified
  - On abx
  - No abx
  - U/A (+), urine cx (-)
  - Do not Rx for UTI

*Slide courtesy of Catherine Liu.

CA-UTI: Treatment

- **Antibiotics**
  - Empiric choices: Ceftriaxone, ertapenem, pip/tazo
  - 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-bacteriuria and 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: Patients at high risk of dissemination
    - Neutropenia
    - Patients undergoing urologic procedures
    - (Pregnancy)

- Symptomatic candiduria (uncommon)
  - Same symptoms as bacterial UTI
  - Treat


Candida UTI: Treatment Options

- **1st line**: Fluconazole
  - Excellent urine levels, 10-fold higher than serum levels
  - Can get concentrations in the urine that are higher than the MIC for organisms that are intermediate or resistant (like *C. glabrata*)
  - 200-400mg PO daily

Fluconazole-Resistant Candida UTI

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

- Other options all have poor efficacy or side effect profile
  - Flucytosine
  - Amphotericin B (conventional formulation)
  - Ampho bladder washes: Resolve candiduria in >90% but high number of relapses

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

- Caspofungin?
  - Poor urinary penetration, but use if suspect systemic disease


CA-UTI: Take-Home Points

- ASB and pyuria are common in patients with a foley

- To diagnose a CA-UTI, the patient must have:
  - Signs and symptoms compatible with UTI
  - No other source for infection

- Treat for 7-14 days depending on clinical response

- Candiduria is almost always asymptomatic and does not require treatment
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>Drugs Reported in the Literature to Cause Drug Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobials</strong></td>
</tr>
<tr>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Penicillins</td>
</tr>
<tr>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Macrolides</td>
</tr>
<tr>
<td>Folic acid, folic acid analogs, trimethoprim, sulfa</td>
</tr>
<tr>
<td><strong>Cardiovascular agents</strong></td>
</tr>
<tr>
<td>Cilostazol</td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
</tr>
<tr>
<td>Azathioprine, cyclosporine, tacrolimus, rapamycin,</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
</tr>
<tr>
<td><strong>Antipsychotics and Antidepressants</strong></td>
</tr>
<tr>
<td>Amphetamine, haloperidol, levomepromazine, clonidine,</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
</tr>
<tr>
<td>Carbamazepine, phenytoin, fosphenytoin, oxcarbazepine</td>
</tr>
<tr>
<td><strong>Antihypertensives</strong></td>
</tr>
<tr>
<td>Amlodipine, enalapril, valsartan, losartan, captopril</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Allopurinol, benzbromarone, glibenclamide, metformin</td>
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Clinical

- May appear well and be unaware of fevers (but not necessarily)
- No typical fever pattern
- Pulse-temperature dissociation (11%)
  - Expected pulse = [(last digit in F -1 ) x 10] +100
- 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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<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>Cardiac</td>
<td>36</td>
<td>44.7</td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>44</td>
<td>7.8</td>
</tr>
<tr>
<td>Antineoplastic</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>CNS</td>
<td>24</td>
<td>18.5</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>18.8</td>
</tr>
</tbody>
</table>

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

**Fever Characteristics**

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


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**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 S/Sx of progression of hypersensitivity

- Rechallenge will usually cause recurrence of fever within a few hours, confirming the diagnosis
  - 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

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

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Drug Fever: Take Home Points

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

- Look for eos, 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


Central Fever

- Accounts for ~50% of fever in the Neuro-ICU
- 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 found fibroproliferative phase of DAD and no evidence of infection

- So...probably, but would look very hard elsewhere and this is a diagnosis of exclusion


Case #4

35 y/o man with alcoholic cirrhosis is admitted to the ICU with severe influenza A and is intubated and eventually requires ECMO. He was slowly improving but then over the last 2 days has starting having fevers to 38.3 with increasing O2 requirement. He has trouble following commands when sedation is lifted.

Blood and urine cultures are negative. CXR is unchanged. Head CT shows pansinusitis but is otherwise negative.
Your Next Diagnostic Step is:

1. Sinus puncture
2. Lumbar puncture
3. Mini-BAL or endotracheal aspirate

Defining CAP, HAP, VAP, HCAP

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  - Days 1-5 (3%/d)  
  - Days 5-10 (2%/d)  
  - Days > 10 (1 %/d) |

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- Hospitalization for ≥2 days in the last 90 days  
- Residence in a nursing home or long-term care facility  
- Intravenous antibiotics, wound care, dialysis, or chemotherapy within the last 30d  
- Family member with an MDR pathogen |

Why Do We Care About These Distinctions?

- To characterize the risk of MDR bacteria, and therefore inform your empiric antibiotic approach

- Risk of MDR organisms in PNA:
  - HCAP
  - HAP/VAP with ≥ 5 days in the hospital
  - Immunosuppression
  - Abx in last 90 days
  - High frequency of ABx resistance in a specific unit

**VAP: Diagnosis and Treatment**

**STEP 1**
Is there a clinical suspicion for PNA?
1. New or progressive CXR infiltrate +
2. 2 out of 3 clinical criteria:
   - F > 38°C
   - ↑ or ↓ WBC
   - Purulent secretions
   - 69% sensitive, 75% specific
   - With ARDS: consider PNA when have 1 clinical criteria b/c may not see CXR changes

**STEP 2**
Obtain lower respiratory tract culture before ABx
- Quantitative cultures preferred
- BAL and mini-BAL both are ~80% sensitive and specific
- Even 24 hrs of prior ABx can make a sample negative

**STEP 3**
- Other diagnostics:
  - Blood cultures positive in <25%
  - Thoracentesis if an effusion is large or the patient is toxic
- Start empiric therapy
- Re-evaluate each day based on culture results, clinical course
- Consider stopping ABx if cultures are negative

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

*Use local resistance patterns for guidance

No

Yes

Linezolid or Vancomycin
+ Anti-pseudomonal beta-lactam
+ Anti-pseudomonal FG or AG


Duration of ABx

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

• No difference in: mortality, recurrent infections, length of ICU stay

• 8-day group had:
  • 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)

• Take-home:
  • 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

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 for MRSA PNA
  - Vancomycin was not dose optimized and so due to low vanco levels
  - Pathophysiologic rationale: linezolid might have advantage by 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 d if bacteremia)
  - Primary outcome: Clinical cure


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Linezolid vs. Vancomycin: Outcomes

![Clinical Cure and Mortality Chart](chart.png)

Linezolid vs. Vancomycin: Conclusions

- Linezolid has a modest benefit in clinical response over vancomycin in MRSA HAP/VAP/HCAP

- Limitations:
  - Were the vanco patients sicker?
  - Compared to linezolid group: ↑ ventilation, concurrent MRSA bacteremia, kidney disease, and diabetes
  - No difference in mortality
  - Did not evaluate length of ICU stay, length of hospitalization, mechanical ventilation


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 paramters

- Duration of therapy 7 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

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)
Back to the Case...

• So you know it’s candidemia, so now what do you do?

• You need to do 3 things:
  1. Start an echinocandin*
  2. Evaluate for source → pull lines
  3. Eye exam

*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

Why an Echinocandin and Not 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%)
  • 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 fluconazole susceptibilities!

- If it comes back sensitive to fluconazole → switch to fluconazole to finish the course

Candida Susceptibilities

Table 3. General patterns of susceptibility of *Candida* species.

<table>
<thead>
<tr>
<th>Species</th>
<th>Fluconazole</th>
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<th>Ampstatericin B</th>
<th>Caspofungin</th>
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<tr>
<td><em>Candida albicans</em></td>
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<tr>
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<tr>
<td><em>Candida glabrata</em></td>
<td>S-DD to R</td>
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<td><em>Candida krusei</em></td>
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<td>S to R</td>
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</tr>
</tbody>
</table>

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

- *C albicans or C tropicalis:*
  - Fluc 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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<thead>
<tr>
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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 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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NOTE. I, intermediate susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent.
* 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)

Candida Susceptibilities

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NOTE: 1, intermediate susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent.
* 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


Candida Susceptibilities

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NOTE: 1, 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

- Note that this data is less compelling in neutropenic patients, so recommendation to remove catheters is less strong in this population

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

Why Does This Matter?

- Intravitreal antifungal injections

- Longer duration of therapy (4-6 weeks)

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

1. Start an echinocandin empirically
   • Check surveillance cx in 48hr
   • Get susceptibilities if it’s C glabrata and change to fluc if sensitive
   • Change to fluc if it’s a susceptible species (albicans, tropicalis, parapsilosis)
   • 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

Case #6

A 45 y/o woman is admitted to the ICU with sepsis following an ERCP and sphincterotomy for retained stone in the setting of cholangitis. Blood cultures were negative and she improves with supportive care and pip/tazo. However, on her 4th day in the ICU she develops a new fever to 38.3°C in association with a new leukocytosis to 16. The only notable finding is new abdominal distention with mild tenderness. She has not had a stool since admission to the ICU. She has a negative CXR and UA. Blood cultures are pending.
What is Your Next Step in Management?

1. Empiric C difficile therapy while awaiting stool specimen
2. Abdominal CT
3. Rectal swab for C difficile testing

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

### IDSA Guidelines for Cdiff Treatment

<table>
<thead>
<tr>
<th>Mild to moderate</th>
<th>Severe</th>
<th>Severe + Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• WBC &lt;15 &lt;br&gt; • Cr &lt;1.5x baseline</td>
<td>• WBC ≥ 15 &lt;br&gt; • Cr ≥ 1.5x baseline</td>
<td>• Hypotension &lt;br&gt; • Ileus &lt;br&gt; • Toxic megacolon</td>
</tr>
</tbody>
</table>

- **Mild to moderate:**
  - Metronidazole 500mg PO tid x 10-14d
- **Severe:**
  - Vancomycin 125mg PO qid x 10-14d
- **Severe + Complications:**
  - Vanco 500mg PO qid <br> + Metronidazole 500mg IV q8 +/- <br> +/− Vanco 500mg PR qid (ileus)


### Guidelines Concordance for C. difficile

- Concordance with IDSA guidelines for *C difficile* resulted in significant:
  - ↓ mortality (5.4% vs 21.8%)
  - ↓ infection recurrence (14% vs 35.6%)

- Guidelines were followed in 80% of mild, 35% of severe, and only 20% severe complicated infections

- Why discordance?
  - Mild disease: Treating recurrent disease inappropriately
  - Severe disease: Treating with metronidazole and treating recurrent disease inappropriately
  - Severe complicated disease: Treating with metronidazole alone or PO vanco alone (without IV metronidazole)

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)


Fever in the ICU: Fever of Too Many Origins?

Horowitz, NEJM 2013, 368:197.
Thank you!

• Questions: jennifer.babik@ucsf.edu