Fever in the ICU

Infectious Diseases in Clinical Practice
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Learning Objectives

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

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

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

3. Recognize the common non-infectious etiologies for fever in the ICU
Roadmap

- Introduction/Framework
- Case-based approach to common infectious and non-infectious etiologies for fever in the ICU
  - CLABSI
  - CA-UTI
  - VAP
  - Nosocomial sinusitis
  - Acute cholecystitis
  - “Double-covering” GNRs
  - Non-infectious etiologies (drug, VTE, central, malignancy)

Definition of Fever

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

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

Measurement of Fever

- Central thermometers (bladder, rectal, esoph) ≈ pulmonary artery temperatures

- Peripheral thermometers have:
  - Poor correlation with central temperatures (± 0.5-2°C)
  - High specificity (~95%) but poor sensitivity for detecting fever
    - Oral or tympanic: 75% sensitive
    - Temporal 63% sensitive
    - Axillary 42% sensitive

Fever in the ICU: Epidemiology

- Fever is common (25-70% of ICU patients)
- Non-infectious etiologies occur frequently
- Most common causes:
  - Infections: PNA, bloodstream, abdominal
  - Non-infectious: post-op, central fever, drug 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, abdominal abscess)

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

3. **Is this non-infectious?**
   - Drug fever
   - Central fever
   - Post-op fever

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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 testing?

- **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 36 year old man with AML is in the ICU for leukopheresis and induction therapy and clinically improves. He then spikes a fever but remains stable.

- He is bacteremic with *Staph epidermidis* from both his line and peripheral blood cultures
- He improves with vancomycin. Can we leave the tunneled line in?
Would You Change the Line?

1. Yes
2. No

Central Line Infections

- Exit site infection (<2cm from exit site)
  - With or without BSI
  - If blood cultures neg, can try to salvage the line.

- Tunnel infection (>2cm)
  - With or without BSI
  - Port pocket infection
  - Remove the line, even if blood cultures neg.

- Bacteremia without overlying skin changes
  - BSI by definition
  - Line removal depends on organism, clinical situation
Central-Line Associated BSI (CLABSI): Diagnosis

- **Clinical findings at exit site in <3%**

- **Catheter tip culture:**
  - (+) peripheral box and > 15 cfu/plate from catheter tip
  - 80% sensitive, 90% specific
  - But >80% of catheters removed unnecessarily


CLABSI: Differential Time to Positivity

- Allows for diagnosis without removing the line

- Culture from line + peripheral blood at the same time

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

- **Test characteristics**
  - 85-95% sensitive
  - 85-90% specific
  - Not as good for Candida

When to Remove the Line

**Complicated Infections**
1. Severe sepsis
2. Persistent bacteremia (>72h of appropriate ABx)
3. Septic thrombophlebitis
4. Exit site or tunnel infection
5. Metastatic infection: endocarditis, osteomyelitis

**Virulent Organisms**
1. *Staphylococcus aureus*
2. *Pseudomonas*
3. *Candida*

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Line Management for Other Organisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>PICC/Short-term CVC</th>
<th>Tunneled Cath/Port</th>
<th>HD Catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coag-negative staphylococci</td>
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<td>Remove or retain</td>
<td>Remove, retain, or guidewire exchange</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Remove</td>
<td>Remove or retain</td>
<td>Remove, retain or guidewire exchange</td>
</tr>
<tr>
<td>Other GNRs <em>(not Pseudomonas)</em></td>
<td>Remove</td>
<td>Remove or retain</td>
<td>Remove, retain or guidewire exchange</td>
</tr>
</tbody>
</table>

Use clinical judgment based on:
- Severity of infection
- Access options (talk to renal!)
- Risk of removal/replacement

Mermel et al, Clin Infect Dis 2009, 49:1
Line Salvage: General Principles

- Which patients?
  - Not for complicated infections, exit site infections, or virulent organisms
  - Only studied in long-term catheters

- How to treat?
  - Give systemic ABx + antibiotic lock therapy for 7-14 d
  - Get surveillance blood cultures (1 wk after Abx stop)

Antibiotic Lock Therapy

- Goal is to get supra-therapeutic ABx concentrations to penetrate biofilms

- Logistics
  - Work with pharmacy and nursing
  - Mix with heparin, dwell times are variable but usually <48h
  - Common Abx:
    - Gram positives: linezolid, vancomycin, cefazolin
    - Gram negatives: ceftazidime, ciprofloxacin, gentamicin

Mermel et al, Clin Infect Dis 2009, 49:1
Line Salvage with Antibiotic Lock Therapy

**Overall Success Rate (%)**

- Systemic Abx: 30-45%
- Systemic Abx + Lock: 60-75%
- Line removal: >90%

**Abx Lock Efficacy by Organism (%)**

- CoNS: 80-90%
- GNRs: 80-90%
- S. aureus: 40-55%


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What About Guidewire Exchange?

- **Goal is to eliminate biofilm entirely**

- **How good is it?**
  - Limited data, mostly HD catheters
  - Seems at least equal to ABx lock (~70% cure), maybe better
  - Likely better than ABx lock for *S. aureus*

- **When to consider using?**
  - If HD catheter removal is clearly indicated but not feasible (especially for *S. aureus*)
  - If you want to salvage an HD line but can’t use lock therapy

Line Management: Take-Home Points

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

- All lines should be removed for:
  - Any complicated infection
  - *S. 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)

- Use antibiotic lock when possible for line salvage

Case #2

55 y/o woman in the ICU after a complicated spinal surgery. She remains intubated, spikes a fever on POD#3 and is pan-cultured.

- She has thick secretions and a new CXR infiltrate.
- mBAL is growing MRSA.
- UA (catheter): 25-50 WBC, Ucx positive for VRE.
Do You Need to Treat the VRE?

1. Yes
2. No
3. Not sure

Asymptomatic Bacteriuria

ASB = (+) urine culture AND no signs/symptoms of UTI
Asymptomatic Bacteriuria is COMMON!

- Seen in up to:
  - 25% of elderly, diabetic, HD patients, short-term catheters
  - 50% of patients in long term care facilities
  - ~100% of patients with long-term catheters

- Of positive urine cultures obtained on the wards after hospital admission → ~90% are ASB

- Do not treat EXCEPT in pregnant women, GU procedures, neutropenia/renal transplant


The Heart of the Problem

- It’s Hard to Ignore a Positive Culture

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

How To Distinguish ASB vs. CA-UTI?

- Does the UA help? → Yes, but only if negative
  - Pyuria is seen in >50% of catheterized patients with ASB
  - But the absence of pyuria suggests an alternative dx

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

- Use clinical context – does the patient have signs/symptoms of UTI?


What if I Can’t Assess Symptoms?

How to define UTI in patients with a catheter or AMS?

- Signs/symptoms consistent w/ UTI
  - Fever, rigors, AMS, malaise
  - Flank pain, CVAT, pelvic pain
  - Acute hematuria
  - Spinal cord injury: spasticity, autonomic dysreflexia, unease

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

### How to Interpret Urine Studies in a Patient With a Foley or AMS

**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
  - U/A (-), urine cx (+)
    - Asymptomatic bacteriuria
  - U/A (+), urine cx (+)
    - Treat for UTI (If no alternate dx identified)
- **No**
  - Send U/A, urine cx
  - U/A (+), urine cx (-)
    - Do not treat

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### CA-UTI: Treatment

- **Antibiotics**
  - Empiric Rx: 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, especially if the catheter has been in for >2 weeks
  - This has been associated with:
    - CA-UTI at 28d
    - time to resolution of sx

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**Candiduria: Who Needs Treatment?**

- Candiduria is very common in catheterized patients
- **Candiduria is usually asymptomatic**
  - In general, don’t treat! (exceptions: same for ASB)
  - Change the foley: can eliminate candiduria in 20-40%
- Symptomatic candiduria (uncommon)
  - Look for same symptoms as bacterial UTI
  - Treat if you are convinced


**Candida UTI: Treatment Options**

- **Fluconazole** is the drug of choice
- Excellent urine levels
  - 10-fold higher than in serum
  - Can get levels > MIC for fluc-resistant species like *C. glabrata*
- What about a fluconazole-resistant organism?
  - Try fluconazole and re-check a urine culture
  - Other options: flucytosine, conventional amphotericin
  - Other azoles, echinocandins have poor urinary penetration

ASB vs. CA-UTI: Take-Home Points

- ASB is very common and rarely needs Rx in the ICU
- Pyuria ≠ UTI, but the absence of pyuria → alternative dx
- 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

57 y/o man admitted with SAH s/p coiling, c/b vasospasm and stroke, now with persistent fevers. He has a PICC line, foley, and is intubated. He has been on vanc + pip/tazo for 5 days and continues to spike. No diarrhea, secretions unchanged.

- F 39.1, HR 65, other vitals normal.
- Exam is unremarkable.
- WBC is 11 (eos 0.63), Cr and LFTs normal.
- Blood cultures, UA, CXR, LP all negative
What Would You Do With His Antibiotics?

1. Escalate pip/tazo to meropenem
2. Add tobramycin
3. Add ganciclovir
4. Stop antibiotics

Non-infectious Etiologies for Fever

- Drug Fever
- Central fever
- DVT/PE
- Malignancy
- Post-op fever
- Rheumatologic
- Transfusion reaction
- Transplant rejection
- Adrenal insufficiency
Drug Fever

- Diagnosis of exclusion
- Clinical features:
  - May appear well and be unaware of fevers
  - 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

Drug Fever: Treatment

- Discontinue or change to another drug class if possible
- If benefit > risk to continue, can try to pre-treat:
  - Corticosteroids and/or antihistamines
  - But watch for signs/sx of progression of hypersensitivity
- If fever with severe adverse effects, avoid rechallenge
- Important to document potential allergy with as much detail as possible


Central Fever

- Accounts for ~50% of fever in the NICU
- Which patients?
  - Brain tumors, SAH, intraventricular bleed
  - Associated with vasospasm
- Clinical characteristics:
  - Appears within 72 h of admission
  - Persists for longer than infectious causes of fever
  - No difference in height of fever c/w infectious fever

Hocker et al, JAMA Neurol 2013, 70:1499.
VTE and Fever

- 5-15% 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)

Tumor Fever

- Which cancers?
  - Most common: lymphoma, leukemia, renal cell
  - But any cancer can do it
  - Pathophys: cytokines, tumor necrosis

- Clinical features:
  - Tmax usually between 38-39°C
  - Usually intermittent fevers, spiking once (most common) or twice daily
  - +/- Leukocytosis

- Data is conflicting on use of naprosyn test, but some studies show that defervesence with naprosyn predicts tumor fever


Non-infectious Fever: Take Home Points

- Always consider it, but it’s a diagnosis of exclusion

- Drug fever is usually high grade (>39°C) - look for eosinophils, temp-pulse dissociation, and rash although these are only seen in <20%

- Central fever is associated with SAH, vasospasm

- Fevers due to VTE or malignancy are usually <39°C
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 neg
- CXR unchanged
- Head CT: 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:
  - Gram (+): *S. aureus*, particularly MRSA
  - Gram (-): *Pseudomonas, E. coli, Klebsiella*
  - *Pseudomonas, Stenotrophomonas, Acinetobacter* more common in VAP


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 (~15% are positive)
- 2016 guidelines recommend semi-quantitative endotracheal aspirate over invasive sampling (mini-BAL, BAL) (weak recommendation, low quality evidence)

Why?
- No difference in outcomes (mortality, ICU days, ventilation)
- Requires less resources
- Both ~75% sensitive but mini-BAL/BAL more specific (80% vs 50%)

Kalil et al, IDSA/ATS Guidelines, CID 2016

VAP: Clinical Diagnosis

- Also look at change in oxygenation over time
- In ARDS, consider PNA if have only ≥1 clinical criteria because may not see CXR change

New or progressive CXR infiltrate + 2 clinical criteria
- Fever
- Leukocytosis/leukopenia
- Purulent secretions

VAP/HAP: Empiric ABx

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

- Do you need MRSA coverage?
  - Yes if MDR risk, >20% local *S. aureus* isolates are MRSA, high risk of mortality

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

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

Risk of MDR HAP
- Prior IV Abx in 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>Levo/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/ciprofloxacin</td>
<td></td>
</tr>
</tbody>
</table>
Duration of Antibiotics in VAP (8 vs 15 days)

- 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 and less MDR organisms if recurrent
  - But...higher pulmonary reinfection rate (41 vs 25%) if had a glucose nonfermenter (*Pseudomonas, Acinetobacter, or Stenotrophomonas*)

- This led to the recommendation for 15 days for glucose nonfermenters and 8 days for everyone else


New IDSA Guidelines: Duration of ABx in VAP

- Systematic reviews of 6 RCTs comparing short (7-8 days) vs long (10-15 days) course therapy:
  - Confirmed benefit of short course Rx (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 and 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

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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
Short Take: 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

- **Treatment duration:** 7 days


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Short Take: Acalculous Cholecystitis

- **Rare (~1%) of all ICU patients**

- **Diagnosis:**
  - Symptoms/signs often not helpful
  - LFT abnormalities in >60% but nonspecific
  - US > CT
    - GB wall thickness ≥ 3.5 mm (80% sensitive, 98% specific)
    - Sludge, pericholecystic fluid, GB distention > 5cm, sonographic Murphy’s
  - HIDA: sensitivity only 70-80%

- **High risk death (30%), GB gangrene (50%), perforation (10%)**

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

Case #5

A 57 year old woman with metastatic breast cancer undergoing chemo and extensive prior antibiotic treatment (including recent levofloxacin) is admitted to the ICU with septic shock.

- She is febrile to 39.6°C, tachy to 120s, rapidly uptitrated to max doses on 3 pressors.
- WBC is 1.4 (ANC 800), Cr 1.8, other labs 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 #5 Continued

- Blood cultures: *Pseudomonas* susceptible to all Abx except cipro/levo.
- Pressor requirement is downtrending.

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 fluoroquinolone)
- Caveats to Combination Therapy Data:
  - Often observational, non-blinded studies
  - Empiric vs definitive therapy not always defined
  - Different beta-lactams, different combinations, old ABx

3 Reasons To Consider Combination Rx

1. Increase the probability of appropriate empiric coverage by expanding the spectrum of activity
2. Synergy between 2 active antibiotics
3. Prevent the development of resistance
Reason #1: Empiric Combination Therapy

- ↑mortality if inappropriate empiric Abx for GNR bacteremia
- Using empiric combination therapy will increase the likelihood of having at least one active antibiotic

**When to empirically “double cover” for GNRs?**

- Patient is critically ill
- Patient is at high risk for MDR pathogens
- How to choose between fluorquinolone (FQ) and aminoglycoside (AG)?
  - 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
  - Has the patient been on recent FQ?


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**Example: UCSF Pseudomonas Antibiogram**

<table>
<thead>
<tr>
<th></th>
<th>MER -&gt;</th>
<th>PIPTAZ -&gt;</th>
<th>CFPM -&gt;</th>
<th>MER -&gt;</th>
<th>PIPTAZ -&gt;</th>
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<tbody>
<tr>
<td></td>
<td>MER+TOB</td>
<td>PIPTAZ+TOB</td>
<td>CFPM+TOB</td>
<td>MER+CIP</td>
<td>PIPTAZ+CIP</td>
<td>CFPM+CIP</td>
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<tr>
<td>All Patients</td>
<td>79% → 97%</td>
<td>75% → 97%</td>
<td>89% → 97%</td>
<td>79% → 91%</td>
<td>75% → 97%</td>
<td>86% → 97%</td>
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<td>ICU</td>
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<td>71% → 93%</td>
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<td>77% → 82%</td>
<td>71% → 82%</td>
<td>81% → 84%</td>
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<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>
Reason #2: Combination Rx for Synergy?

- *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 observational data and meta-analyses

What About in Certain Subgroups?

- Older studies from the 1980s/1990s showed benefit of combination Rx in septic shock, neutropenia, *Pseudomonas*

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

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

Reason #3: Combination Rx to 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 “double-covering” for GNRs is to ensure an appropriate Abx is included in the initial empiric regimen

- Once susceptibilities are known, narrow to monotherapy

- There is no evidence that definitive combination therapy is “synergistic” *in vivo* or prevents the development of resistance
Thank you!

- Questions?