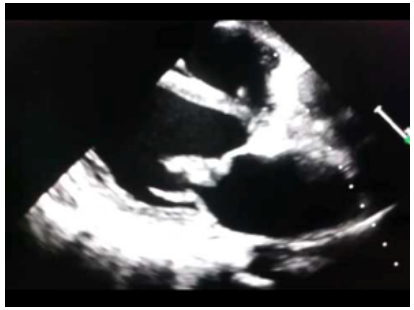

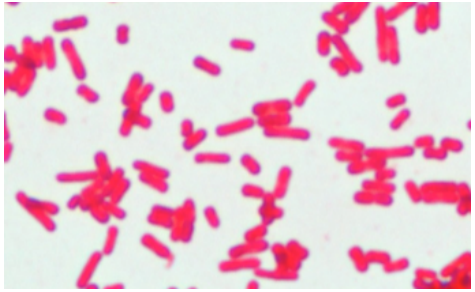

What's New in Hospital Antibiotics?

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23rd ANNUAL
MANAGEMENT OF THE HOSPITALIZED PATIENT
UCSF

Disclosures

- I have no disclosures.

Learning Objectives

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

1. Describe the major findings of recent RCTs in ID that have changed clinical practice

2. Identify the major updates in recent IDSA guidelines that affect the practice of hospital medicine

3. Summarize the results of other recent ID studies that have changed clinical practice

Road Map

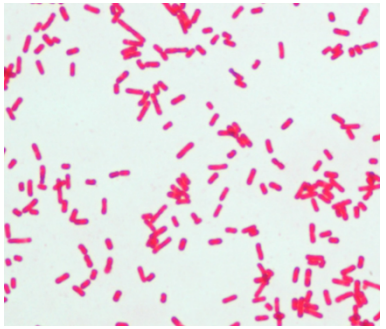
- Antibiotics for ESBL bacteremia (MERINO)
- GNR bacteremia: duration, when to switch to orals
- Oral antibiotics for endocarditis (POET)
- Oral antibiotics for osteomyelitis (OVIVA)
- New IDSA Guidelines for *C. difficile*
- New IDSA Guidelines for Asymptomatic Bacteriuria

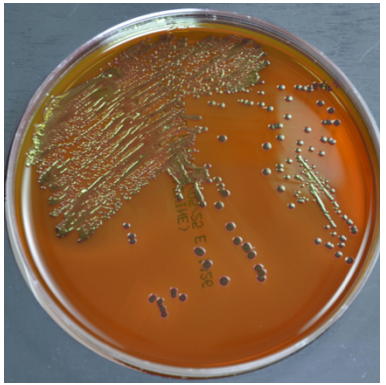
Case #1

A 65 year-old man with pancreatic cancer is admitted with biliary obstruction and cholangitis now s/p stent placement. Blood cultures are positive for *E. coli.*

He is started on pip-tazo on admission and is now stable to improved.

On HD#2, the *E. coli* susceptibilities return and it is an ESBL producer with *in vitro* susceptibility to ertapenem, pip-tazo, and ciprofloxacin.





What Would You Do With His Antibiotics?

1. Continue pip-tazo
2. Change to ciprofloxacin
3. Change to ertapenem
4. Continue pip-tazo and add ciprofloxacin

The ESBL Bacteremia Antibiotic Story Over Time

Carbapenems Established as Drug of Choice

- Prospective study of ESBL bacteremia (n=71)
- Non-carbapenems (mostly cipro) had ~10x ⇧mortality vs carbapenems

Cefepime? → No

- 2 retrospective studies (n=250, 50)
- Cefepime had 2-7x ⇧mortality vs carbapenem for empiric + definitive Rx, even at low MIC
- ? inoculum effect

Pip-tazo? → Maybe

- 1 retrospective study of PTZ vs carbapenem as empiric Rx (n=213): PTZ had 2x ⇧mortality
- 2 retrospective studies (n=966, 150): PTZ = carbapenem for empiric + definite Rx

Paterson et al, CID 2003, 39:31. Lee at al, CID, 2013, 56:488. Wang et al, OFID 2016, Gutierrez-Guitierrez et al, AAC 2016, 60:4159. Ng et al, PLoS ONE 2016. Tamma et al, CID 2015, 60:1319.

What's New? → The MERINO Trial

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

RCT of 379 adults with *E. coli* or *K. pneumoniae* ESBL bacteremia

- Randomized within 72h of initial blood culture
- Pip-tazo vs meropenem for definitive therapy (14 d)

Primary outcome: all cause mortality at 30 days

Harris et al, JAMA 2018, 320:984.

Patient Characteristics and Results

Characteristics

- Groups well balanced
  - 25% immunosuppressed
  - 7% ICU
- Organism
  - *E. coli* 87%
  - *K. pneumoniae* 13%
- Source:
  - Urinary 60%
  - Intra-abdominal 15%

Results

- Study terminated early → 30-day mortality: 12.3% pip-tazo vs 3.7% meropenem (did not meet criteria for noninferiority)
- True irrespective of source of infection, patient subgroup
- No difference in adverse events or carbapenem-resistant organisms

Harris et al, JAMA 2018, 320:984.

The MERINO Trial: Conclusions

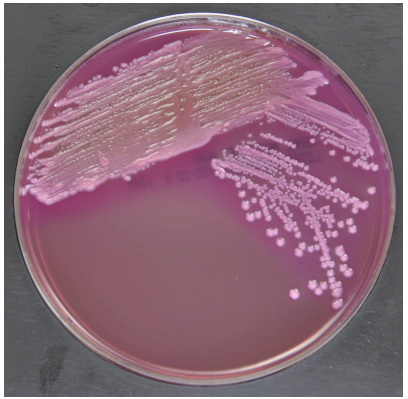
Practice Changing

Pip-tazo should not be used as definitive therapy for ESBL bacteremia:

- Irrespective of the source of infection, patient population, or response to empiric pip-tazo

- Unanswered questions:
  - What about infections without bacteremia?
  - What about newer drugs (e.g. ceftazidime-avibactam)?

Case #2



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

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

She is currently on ceftriaxone and doing well.

How Long Should She Be Treated?

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

Prior RCTs on Short Course Therapy for GNR Infections

Study	Study Results	Bacteremia
2 RCTs in uncomplicated pyelonephritis (2000, 2012)	Ciprofloxacin for 7 days = 14 days of TMP-SMX or ciprofloxacin	5%, 27%
Complicated intra-abdominal infection (STOP-IT trial, 2015)	4 days of antibiotics = 8 days of antibiotics after source control	2%

Talan et al, JAMA 2000, 283:1583. Sandberg et al, Lancet 2012, 380:48. Sawyer et al, NEJM 2015, 372:1996.

WHAT'S NEW? → ANTIBIOTIC DURATION FOR GNR BACTEREMIA

Clinical Infectious Diseases

Seven versus fourteen Days of Antibiotic Therapy for uncomplicated Gram-negative Bacteremia: a Non-inferiority Randomized Controlled Trial

RCT of 604 adults with GNR bacteremia:

- Afebrile and clinically stable by day 5
- Had source control

→ Randomized to 7 vs. 14 days of antibiotics

→ Primary outcome: Composite of all-cause mortality, clinical failure, re-admission, LOS>14d (at 90 days)

Yahav et al, Clin Infect Dis 2018. Dec 11 Epub.

Patient Characteristics and Results

Characteristics

- Groups well balanced (25% ICH)
- Bacteria:
  - 90% Enterobacteriaceae (19% ESBL)
  - 8% Pseudomonas
- Source:
  - Urinary 68%
  - Intra-abdominal 12%
  - Unknown source 8%
  - Resp 4%, CVC 6%, SSTI 1%

Results

- No difference in primary composite outcome or individual components
- No difference based on source (urinary or not) or resistance (MDR or not)
- Patients in 7-day group had quicker return to baseline (2 vs 3 days, p=.01)
- No difference in adverse effects, *C diff*

Yahav et al, Clin Infect Dis 2018. Dec 11 Epub.

Which Antibiotics Did They Use?

- PO antibiotics for part of the course: 64% of short, 81% of long group
- IV to PO transition not standardized

IV Antibiotics

- 54% Cephalosporin
- 22% BL/BLI
- 12% Aminoglycoside
- 5% Fluoroquinolone
- 6% Carbapenem

PO Antibiotics

- 74% Fluoroquinolones
- 18% beta-lactams
- 8% TMP-SMX

Yahav et al, Clin Infect Dis 2018. Dec 11 Epub.

Antibiotic Duration for GNR Bacteremia: Conclusions

Practice Changing

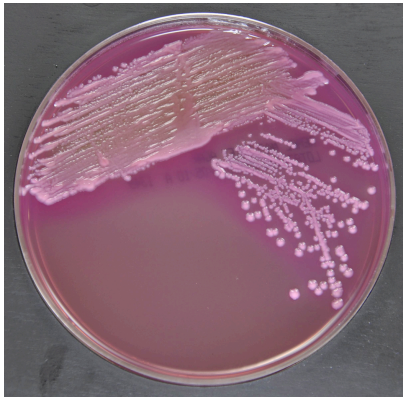
A 7 day course of antibiotics is sufficient for:

- Patients with Enterobacteriaceae bacteremia
- Urinary source
- Have source control
- Clinically stable by day 5

- Unanswered questions:
  - What about non-urinary source? (probably)
  - What about ESBL? (possibly but MERINO trial used 14d)
  - When can you switch to orals?
  - Can you use an oral beta-lactam?

Case #2 Continued

55 year old woman with pan-sensitive *K. pneumoniae* pyelonephritis with bacteremia.



She is doing well on ceftriaxone on day 3. You've now decided on a 7 day total treatment course and she is ready for discharge.

What Would You Send Her Home With?

1. Ceftriaxone
2. Ciprofloxacin
3. Cephalexin
4. Amox/clav

What's New? → Oral Step Down Rx for GNR Bacteremia

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia

Retrospective study of 1478 adults with Enterobacteriaceae bacteremia:

- Clinically stable
- Able to take PO
- Had source control

→

- By day 5: oral step-down therapy vs continued IV therapy
- Both groups got 14d

→

Primary outcome: 30-day all-cause mortality

Tamma et al, JAMA IM 2019, Jan 22 Epub.

Patient Characteristics and Results

Characteristics

- Propensity matched cohort (45% ICH)
- Bacteria:
  - 80% *E coli* and *Klebsiella*
  - 12% *Enterobacter*
- Source:
  - Urinary 40%
  - GI tract 20%, Biliary tract 14%
  - Central line 18%
  - Respiratory 4%
  - SSTI 3%

Results

- No difference in mortality or recurrent bacteremia
- Oral step-down therapy group had shorter LOS (5 vs 7 days, p<.001)

Tamma et al, JAMA IM 2019, Jan 22 Epub.

A Few More Details About the ORAL Antibiotics

Oral group: 3 days IV then 11 days PO

- High bioavailability group (83%)
  - Fluoroquinolone (70%)
  - TMP-SMX (13%)
- Low bioavailability group (17%)
  - Amox-clav and oral cephalosporins
- No difference in mortality between these groups

Tamma et al, JAMA IM 2019, Jan 22 Epub.

Oral Step Down Therapy: Conclusions

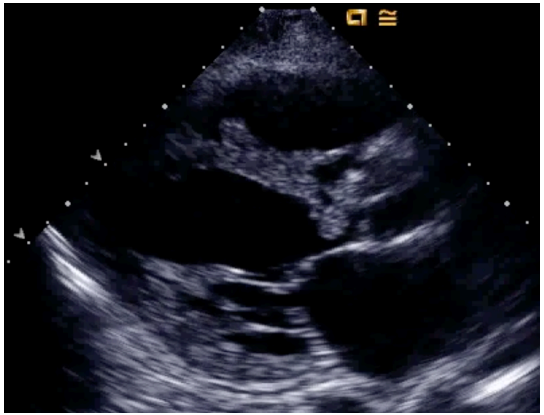
Practice Changing

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

- Enterobacteriaceae bacteremia
- From urinary, GI, lines
- Source control and clinically stable
- Especially with FQ or TMP-SMX but likely oral beta-lactams as well in select cases (other retrospective studies show similar results)

Case #3

35 year old man with IDU admitted with MRSA aortic valve endocarditis. He has completed a week of IV vancomycin, has cleared his cultures, is clinically well, and there are no plans for cardiac surgery.



What Would You Do With His Antibiotics?

1. Vancomycin x 6 weeks
2. PO linezolid x 6 weeks
3. Vanco x 2 weeks then PO linezolid + rifampin x 4 weeks
4. PO Linezolid + rifampin x 6 weeks

WHAT'S NEW? → POET STUDY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

RCT of 400 adults with:
- Left sided endocarditis
- Stable condition
- Gram (+) organisms

→

- IV for 10d → then PO vs. IV
- Had normal GI function
- Seen in clinic 2-3 times/wk

→

Primary outcome (composite, 6 mo):
- all-cause mortality
- cardiac surgery
- embolic events
- relapsed bacteremia

Iversen et al, NEJM 2019, 380:415.

Patient Characteristics

Patients

- Groups well balanced
- Mean age 67, 77% men
- Only 35% had a comorbidity (few immunocompromised)
- PWID 1%
- Valve surgery in 38%

Valves

- Prosthetic valve 27%
- Aortic 54%, Mitral 34%
- Veg size >1cm in 5%
- Mod-severe regurg 10%

Microbiology

- Streptococci 49%
- E. faecalis 24%
- MSSA 22% (no MRSA)
- Coag neg Staph 6%

Iversen et al, NEJM 2019, 380:415.

Which Antibiotics Did They Use?

Both groups: 17 days of IV antibiotics

IV group: + 19 days IV

Oral group: + 17 days PO

- Combination therapy for all
- Most common regimens:
  - **Strep**: amox + (rifampin or moxi)
  - **E. faecalis**: amox + (moxi or linezolid)
  - **MSSA**: (diclox or amox) + rifampin
  - **CONS**: linezolid + rifampin

Iversen et al, NEJM 2019, 380:415.

POET Study: Results

- No difference in composite endpoint (12% in IV group, 9% in oral group) or components
- No difference by organism, surgery or not, involved valve, or valve type
- Shorter LOS: LOS after randomization 19d in IV group vs. 3d in PO group ($p<.001$)
- Outcomes at 3.5 years: no delayed treatment failure, NO patients lost to follow-up

Iversen et al, NEJM 2019, 380:415. Bundgaard H et al. N Engl J Med 2019, 380:415.

POET Trial: Conclusions

Practice Changing

Consider oral therapy for left-sided endocarditis if:

- Relative healthy, clinically stable, mild disease
- Have had ≥17 days of IV antibiotics
- Able to follow-up in clinic
- Streptococci (yes), E. faecalis (maybe), MSSA (maybe)

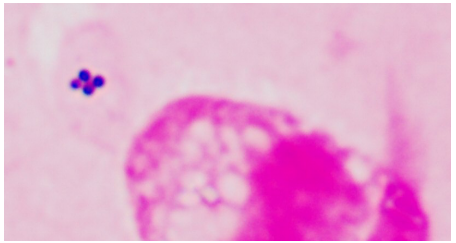
- Unanswered questions:
  - What about MRSA?
  - What about PWID?

Case #4

55 year old woman with rheumatoid arthritis is admitted with a septic right knee associated with osteomyelitis of the femur. She gets an I+D of the knee and is on IV vancomycin. She doesn't think she can give herself home IV antibiotics.

Knee cultures: MSSA

Blood cultures: negative



How Would You Treat Her With?

1. Cefazolin x 6 weeks
2. Nafcillin x 6 weeks
3. Ciprofloxacin + rifampin x 10 weeks
4. Cephalexin x 10 weeks

WHAT'S NEW? → OVIVA STUDY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

RCT of 1054 adults with bone or joint infection

- No SAB, endocarditis, native septic arthritis
- "Likely to comply w/ Rx"

→

- Within 7d of surgery or Abx start → IV vs. PO for 6 wks
- Follow-on oral Abx in both groups

→

Primary outcome:

Definitive treatment failure at 1 year

Li et al, NEJM 2019, 380:425.

Patient Characteristics and Results

Patients

- Groups well balanced
  - Diabetes 20%
  - Immunosuppressed 15%
  - No PWID
- Infections
  - Hardware 61%
  - Surgical debridement 92%
  - Lower limb 81%, upper limb 10%, vertebral 7%

Microbiology

- Staph aureus 38%
  --10% MRSA, 90% MSSA
- Coag neg Staph 27%
- Streptococcus 15%
- Pseudomonas 5%
- Other GNRs 17%
- Culture negative 16%
- Polymicrobial 18%

Li et al, NEJM 2019, 380:425.

Which Antibiotics Did They Use?

Both groups: Up to 7 days of IV antibiotics

IV group: total 6 wks IV (80%) then 5 wks PO

- Glycopeptides 41%
- Cephalosporins 33%
- Carbapenems 8%
- Penicillins 7%
- Rifampin for >2 wks in 37%

Oral group: total 10 wks PO
High adherence

- Ciprofloxacin 37% (84% w/rifampin)
- Penicillins 16%
- Doxycycline 11%
- Macrolides or clinda 13%
- Other or combination 27%
- Rifampin for >2 weeks in 49%

Li et al, NEJM 2019, 380:425.

OVIVA: Results

- No difference in definitive treatment failure between groups (15% in IV group, 13% in oral group)

- PO group also had:
  - Fewer catheter related complications (1% vs 9%)
  - Shorter LOS (11 vs 14 days)

Li et al, NEJM 2019, 380:425.

OVIVA Trial: Conclusions

Practice Changing

Oral therapy ok for bone/joint infections when:

- Surgical debridement
- High adherence
- No SAB, endocarditis
- Varied regimens but most common: FQ + rifampin
- Total duration prolonged (10 weeks in the study)

- Unanswered questions:
  - What about PWID?
  - What about MRSA (likely ok)? ESBL or Pseudomonas (not known)?
  - What is the best oral Abx regimen? For how long?

Case #5

75 year-old woman is admitted with diarrhea, abdominal pain, and dehydration after a recent course of antibiotics for sinusitis.

Data:

WBC 12.4

Cr 1.2 (baseline 0.9)

C diff (+)

How Would You Treat Her?

1. Oral metronidazole
2. Oral vancomycin (125mg qid)
3. Oral vancomycin (250mg qid)
4. Fidaxomicin

WHAT'S NEW? → NEW IDSA C DIFF GUIDELINES

Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

McDonald et al, Clin Infect Dis 2018:66:e1.

Main Changes From the 2010 Guidelines

Treatment of an Initial Episode

- Fidaxomicin in, metronidazole out
- Vanc or fidax are now first line
- 10d treatment course is sufficient
- Some renaming:
  - Mild-moderate → "non-severe"
  - Severe,complicated → "fulminant"

Treatment of Recurrences

- Vanc taper has moved up a step
- Fidaxomicin now an option
- Fecal transplant recommended for 3rd or more recurrence

McDonald et al, Clin Infect Dis 2018:66:e1.

Treatment of an Initial Episode of *C. difficile*

Non-severe	Severe	Fulminant
WBC ≤15 Cr ≤1.5	WBC > 15 Cr >1.5	Hypotension, shock, ileus, megacolon
Vanc 125mg PO qid x 10d *OR* Fidax 200mg PO bid x 10d (Alternate: Metronidazole)	Vanc 125mg PO qid x 10d *OR* Fidax 200mg PO bid x 10d	• Vanc 500mg PO qid PLUS metronidazole 500mg IV q8h • If ileus: add PR vanc

McDonald et al, Clin Infect Dis 2018:66:e1.

Why the Changes?

Fidaxomicin IN

- Same clinical cure rate as vancomycin (~87%)
- Lower recurrence rate for fidaxomicin (15%) vs vanc (25%)

Metronidazole OUT

Multiple RCTs show that metronidazole is ~10% **less effective** than PO vancomycin in:

- Resolution of diarrhea
- Decreased recurrence rate

McDonald et al, Clin Infect Dis 2018:66:e1.

TREATMENT OF RECURRENT *C. difficile*

FIRST Recurrence

Initial episode treated with **metronidazole**

↓

PO vanc x 10d

Initial episode treated with **PO vancomycin**

↓

PO vanc pulse-taper *OR* fidaxomicin

SECOND or More Recurrences

- PO vanc pulse-taper *OR*
- PO vanc and rifaximin chaser *OR*
- Fidaxomicin *OR*
- Fecal microbiota transplantation (on 3rd recurrence)

McDonald et al, Clin Infect Dis 2018:66:e1.

NEW *C. difficile* GUIDELINES: CONCLUSIONS

Practice Changing

- Use PO vancomycin or fidaxomicin as first line therapy for severe and non-severe C diff
- Avoid metronidazole for initial episode if possible and do not use for recurrences
- Use FMT on the 3rd recurrence if patients have failed prior courses of antibiotics

Case #6

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

Afebrile, vitals stable.

WBC 10.0

UA 25-50 WBC/hpf

Would You Start Antibiotics?

1. Yes
2. No
3. Not sure

Case Continued

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

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

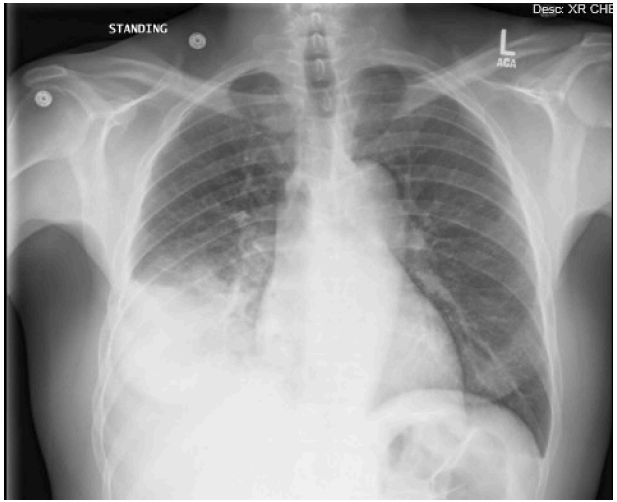
What Would You Do with Her Antibiotics?

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

CASE #7

55 year old woman is 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.
- Sputum is growing MRSA.
- UA (catheter): 11-20 WBC, Ucx positive for VRE.



Do You Need to Treat the VRE?

1. Yes
2. No
3. Not sure

WHAT'S NEW? → NEW IDSA GUIDELINES FOR ASB

Clinical Infectious Diseases

IDSA FEATURES

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

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

Asymptomatic Bacteriuria: Definition

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

Caveats:

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

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

Asymptomatic Bacteriuria is COMMON!

- Seen in up to:
  - 20% of elderly, diabetic, HD patients
  - 50% of patients in long term care facilities
  - 70% of patients with spinal cord injury
  - Acquired at 3-5% per day in patients with short-term catheters
  - ~100% of patients with long-term catheters

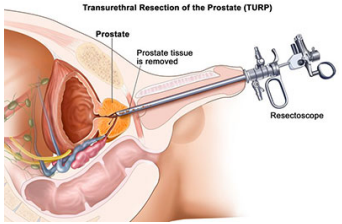
- Of positive urine cultures obtained on the wards after hospital admission → ~90% are ASB

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

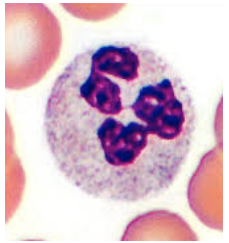
Exceptions: Who With ASB Should Be Treated?

- Pregnant women
  - ↓ risk pyelo, premature delivery

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



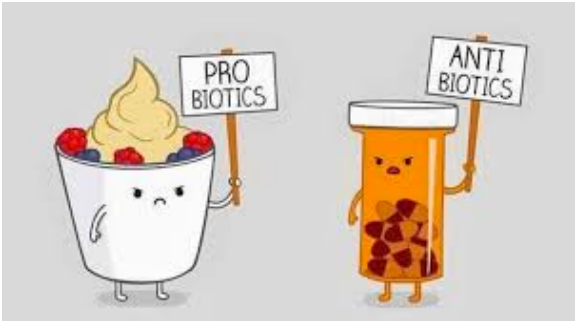
- Immunosuppressed patients (2019 guidelines)
  - Renal transplant in the first month
  - High risk neutropenia? (IDSA makes no formal rec for or against, but state GU tract is an infrequent source for bacteremia)



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

Hazards of ASB Treatment

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



- May increase risk of recurrent UTI by getting rid of “good” interfering bacteria
- Increased LOS (new study)

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

What's New? → Treating ASB Leads to Increased LOS

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Risk Factors and Outcomes Associated With Treatment of Asymptomatic Bacteriuria in Hospitalized Patients

Retrospective study of 2733 hospitalized patients with ASB in the Michigan Hospital Safety Consortium

- 78% women
- Median age 77 years
- 83% treated with antibiotics!!

- Treatment of ASB associated with **increased LOS (4 vs 3 days)**
- No other differences

The Heart of the Problem

- It's Hard to Ignore a Positive Culture

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

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

How To Distinguish ASB vs. 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?

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

What if I Can't Assess Symptoms?

How to define UTI in patients with a catheter?

Surrogate signs/symptoms of UTI

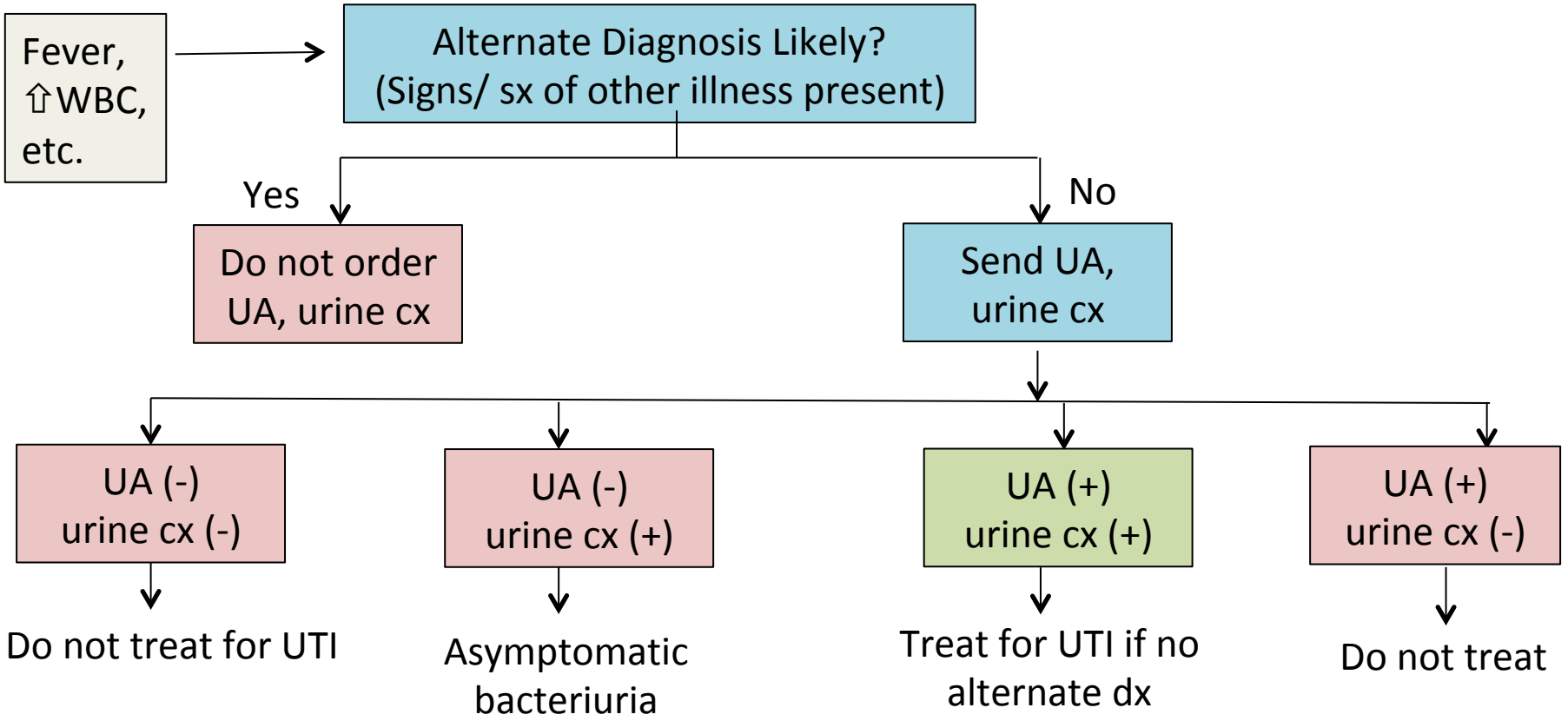
- Fever, rigors, malaise
- Flank pain, CVAT, pelvic pain
- Acute hematuria
- Spinal cord injury: ⇧spasticity, autonomic dysreflexia, unease

AND

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

Hooton et al, Clin Infect Dis 2010, 50:625.

Interpreting Urine Studies in a Patient With a Foley



Slide courtesy of Catherine Liu.

What About Older Patients with Confusion?

An elderly patient with functional/cognitive impairment presents with bacteriuria and either AMS or fall

IDSA Guidelines 2019

If no local GU symptoms or other systemic signs of infection → look for other causes; careful observation without antibiotics (*strong rec, low quality evidence)*

Why?

- Current data does now show causality between bacteriuria and MS changes, and treatment does not improve clinical outcomes
- Places high value on avoiding adverse effects of Abx (Cdiff, resistance)

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

New ASB Guidelines: Conclusions

Practice Changing

- For elderly patients admitted with bacteriuria and AMS, look for other causes and closely observe without antibiotics
- For patients getting a GU procedure, give 1-2 doses of antibiotics starting 30-60 min before the procedure

Other important take-home points about ASB:

- ASB is very common and rarely needs treatment
- Pyuria ≠ UTI, but its absence suggests an alternative dx
- UTI diagnosis in a patient with a catheter requires surrogate signs/symptoms of UTI and no other source of infection

Thank You!

- Questions?