The Ins-N-Outs of ESBL Management

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Objectives

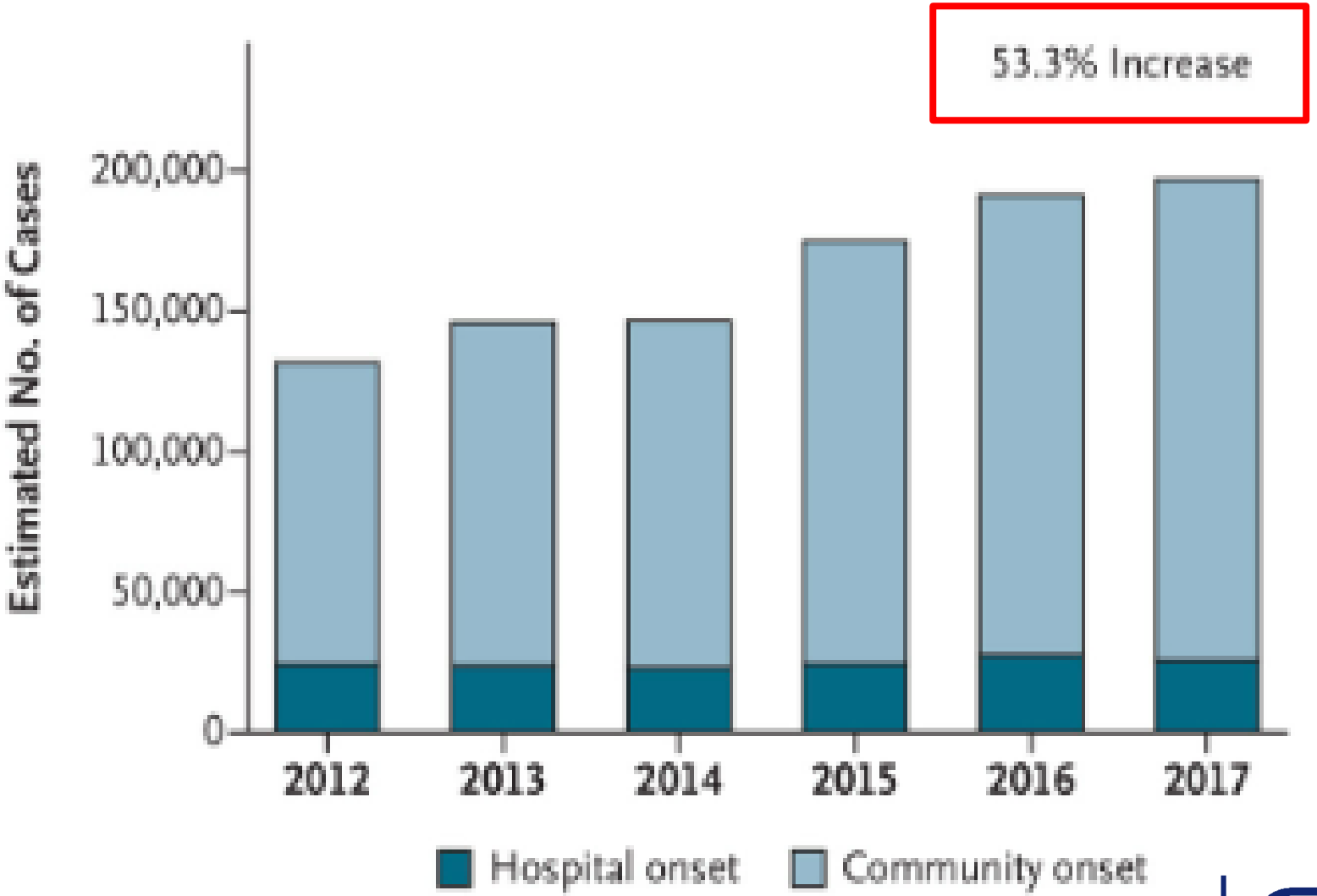
- Apply the 3 moments of antibiotic decision to optimize care in patients with ESBL organisms grown in bacterial cultures
- Understand risk vs benefit of cabapenem vs non-carbapenem therapy in the treatment of ESBL infections

What is an ESBL?

- Extended-spectrum beta-lactam**ase** (ESBL)
  - Enzyme breaks down “newly” developed “extended spectrum” cephalosporins
    - Breaks down 2nd/3rd generation cephalosporins
  - Multi-drug resistant organism
- Who produces it?
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Klebsiella oxytoca*
  - *Proteus mirabilis*
- ESBL does **NOT** affect non-beta-lactam antibiotics

Why Do We Care about ESBL?

- Centers for Disease Control and Prevention (CDC) considers ESBL-Enterobacterales as “serious threat”



Kentucky Antimicrobial Stewardship Innovation Consortium

ESBL = extended-spectrum beta-lactamase

Jernigan et al. *N Engl J Med*. 2020 Apr 2;382(14):1309-1319.

ESBL Risk Factors

- Recent antibiotic use
- Recent hospitalization
- Residence in long-term care facility
- Recent outpatient procedures
- Colonization or previous infection with ESBL

ESBL = extended-spectrum beta-lactamase

Ben-Ami et al. *Clin Infect Dis*. 2009 Sep 1;49(5):682-90.
Augustine et al. *Infect Control Hosp Epidemiol*. 2017 Mar;38(3):266-272.

The Legend Has It…..

I want **MEROPENEM**!!!!!

ESBL = extended-spectrum beta-lactamase

Carbapenems Do No Harm?

ESBL

Carbapenem use

Carbapenem-resistant Enterobacterales (CRE)

13,000 CRE cases in hospitalized patients in 2017

1,100 estimated deaths in 2017

$130 million healthcare costs in 2017

ESBL = extended-spectrum beta-lactamase

CDC. Antibiotic Resistance Threats in the United States, 2019.

ESBL Grown in Culture: Approach to Optimal Care

Moment #1 Indication

- Does this patient have infection that requires antibiotics?

Moment #2 Antibiotic Choice

Moment #3 Duration of Therapy

ESBL = extended-spectrum beta-lactamase

Tamma et al. *JAMA*. 2019 Jan 15;321(2):139-140.

ESBL Management: Indication

78-year-old female who is transferred to your hospital from long-term care facility after a fall. The patient reports that she tripped over her chair and fell to the floor. Her urine culture obtained in ED grew ESBL E. coli > 100,000 CFU/mL. Patient denies dysuria, urgency, frequency, or flank pain. All vital signs and labs are within normal limits. Patient has no known drug allergies. Which of the following strategies would be the most appropriate?

A. Patient has UTI since bacteria count > 10^5 CFU/mL. Initiate meropenem 500 mg IV q6h

B. Patient has UTI since bacteria count > 10^5 CFU/mL. Initiate ertapenem 1g IV q24h

C. Patient has asymptomatic bacteriuria. Observe off antibiotics

D. Patient has UTI since bacteria count > 10^5 CFU/mL. Initiate nitrofurantoin 100mg PO BID

ESBL = extended-spectrum beta-lactamase

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$\not\simeq$ Infection

Moment #1: ESBL organisms can be colonizers. Growth of ESBL in culture does NOT always necessitate treatment.

ESBL = extended-spectrum beta-lactamase

ESBL Grown in Culture: Approach to Optimal Care

Moment #1 Indication

- Does this patient have infection that requires antibiotics?

Moment #2 Antibiotic Choice

- Based on diagnosis and susceptibility, is carbapenem the only option? Can non-carbapenem therapies be used?

Moment #3 Duration of Therapy

ESBL = extended-spectrum beta-lactamase

Not All Infections Are Created Equal

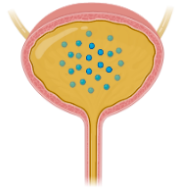
ESBLs do not affect non-beta-lactam antibiotics

- ESBL does NOT always cause severe infection
- Considerable number of ESBL infections are urinary tract infections
  - Cystitis:
    - Nitrofurantoin, fosfomycin, TMP-SMX, **single dose aminoglycoside**
    - Cefepime, piperacillin-tazobactam
  - Pyelonephritis:
    - TMP-SMX, fluoroquinolone
    - Piperacillin-tazobactam, aminoglycoside

ESBL = extended spectrum beta-lactamase
TMP-SMX = trimethoprim-sulfamethoxazole

Tamma et al. *Clin Infect Dis*. 2022 Aug 25;75(2):187-212.

Single Dose Aminoglycoside for ESBL Cystitis



High concentration in urine and last for several days

Single dose aminoglycoside is as effective as comparators

Convenient and reduces hospital admission

Low *Clostridioides difficile* infection

Reduce bacterial resistance

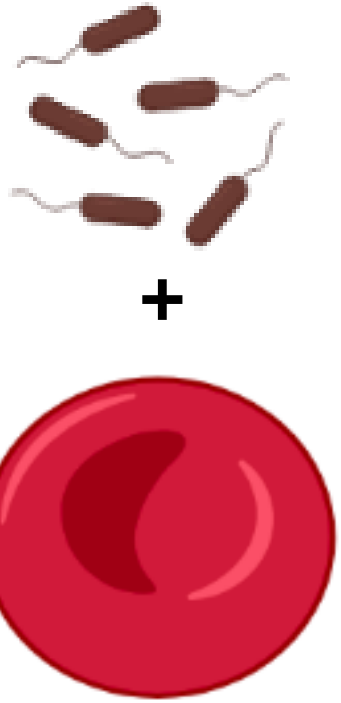
Rate of 0.5%

ESBL = extended-spectrum beta-lactamase

Goodlet et al. *Antimicrob Agents Chemother*. 2018 Dec 21;63(1):e02165-18.

Bacteremia: Meropenem vs Piperacillin-Tazobactam?

Screening



Adult patients with **ESBL bacteremia**

Randomized 1:1

Meropenem 1g q8h X **up to 14 days**

Piperacillin-tazobactam 4.5g q6h x **up to 14 days**

30-day-all-cause mortality was higher in those treated with piperacillin-tazobactam (12.3%) than those treated with meropenem (3.7%)

Carbapenem is preferred over piperacillin-tazobactam for severe ESBL infections (bacteremia)

ESBL = extended-spectrum beta-lactamase

Harris et al. *JAMA*. 2018 Sep 11;320(10):984-994.

For Severe ESBL Infections, Do We Need Carbapenem for the Entire Duration of Therapy?

Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Authors

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] & Cornelius J. Clancy[6]

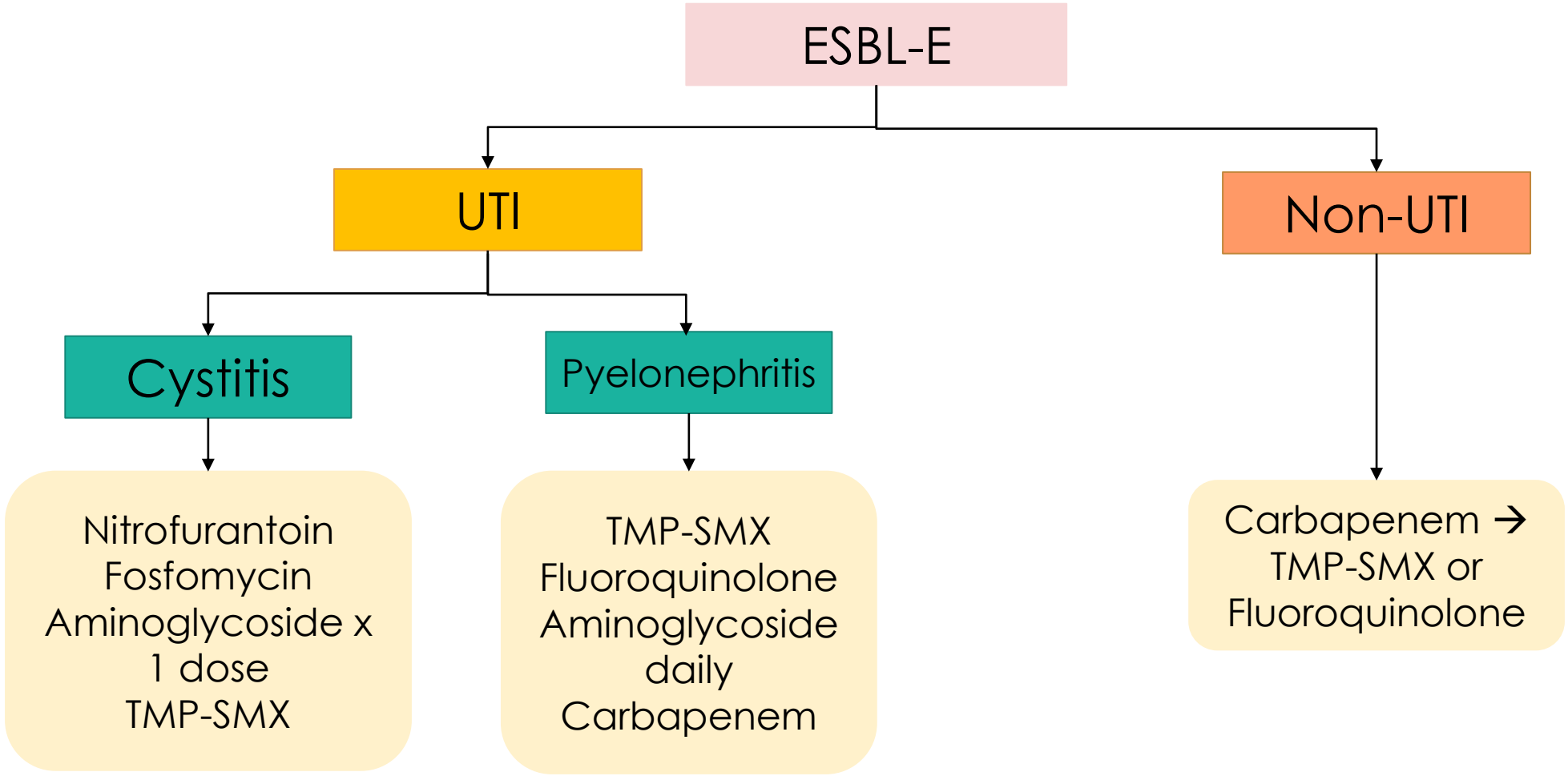
"…oral step-down therapy has been shown to be a reasonable treatment consideration for ESBL infections when:

- TMP-SMX and/or fluoroquinolone susceptible
- Hemodynamically stable
- Reasonable source control
- No concern about intestinal absorption…"

ESBL = extended spectrum beta-lactamase
TMP-SMX = trimethoprim-sulfamethoxazole

Tamma et al. *Clin Infect Dis*. 2022 Aug 25;75(2):187-212.

Antibiotic Selection: Carbapenem Drug of Choice?



Moment #2: Carbapenem is NOT the only drug that can effectively treat ESBL infections.

ESBL = extended spectrum beta-lactamase
UTI = urinary tract infection
TMP-SMX = trimethoprim-sulfamethoxazole

Tamma et al. *Clin Infect Dis*. 2022 Aug 25;75(2):187-212.

ESBL Grown in Culture: Approach to Optimal Care

Moment #1 Indication

- Does this patient have infection that requires antibiotics?

Moment #2 Antibiotic Choice

- Based on patient's infection, is carbapenem the only option? Can non-carbapenem therapies be used?

Moment #3 Duration of Therapy

- What is the shortest duration of therapy that can be used effectively for the patient's diagnosis?

ESBL = extended-spectrum beta-lactamase

ESBL = Require Longer Duration of Therapy?

Don’t you see that patient has an ESBL? That’s a **multidrug-resistant organism**!!! We need to treat it with a **long course** of antibiotic **just to make sure**.

Hello Dr. X. This patient has uncomplicated ESBL E coli bacteremia secondary to pyelonephritis. Patient improves quickly on therapy. Is there particular reason why patient needs **14 days** of antibiotic **instead of 7 days?**

ESBL = extended-spectrum beta-lactamase

Moment #3: Shorter is Better Even If It's ESBL

Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

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"….duration of therapy **should not differ** for infections caused by organisms with resistant phenotypes compared to infections caused by more susceptible phenotypes…."

ESBL = extended-spectrum beta-lactamase

Tamma et al. *Clin Infect Dis*. 2022 Aug 25;75(2):187-212.

The Ins-N-Outs of ESBL Management Key Takeaway

- Growth of ESBL organisms in cultures does NOT always indicate infection
- Carbapenem is NOT the only drug that can be used to treat ESBL infections
  - Non-carbapenem therapy should be used whenever feasible to prevent development of carbapenem-resistant organisms
- Infections caused by ESBL organisms do NOT automatically require a longer duration of therapy

ESBL = extended-spectrum beta-lactamase

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