We are called to make a healthy difference in people's lives.

UNDERSTANDING EXTENDED SPECTRUM BETA-LACTAMASE PRODUCING ORGANISMS (ESBLS)

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Disclosure

Tony Maanum has no relevant financial relationships with ineligible companies to disclose. None of the planners, faculty, and others in control of content of this educational activity have relevant financial relationships with ineligible companies to disclose.

Learning Objectives

1. Understand what are ESBL enzymes
2. Recognize how to detect ESBL organisms
3. Understand what makes ESBL organisms more difficult to treat

Abbreviations

- AMR – antimicrobial resistance
- AMS – antimicrobial stewardship
- CDC – Center for Disease Control
- CFU – colony forming units
- CRE – carbapenem resistant enterobacterales
- CTX-M – cefotaximase-Munich
- C-UTI – complicated urinary tract infection
- DOT – duration of therapy
- ESBL - extended spectrum β-lactamase enterobacterales
- GU – genitourinary
- IDSA – Infectious Disease Society of America
- MDRO – Multi-Drug Resistant Organisms
- MIC – minimum inhibitory concentration
- Pip/Tazo - piperacillin-tazobactam
- RBC – red blood cells
- SMX/TMP - sulfamethoxazole-trimethoprim
- UA – urinary analysis
- UTI – urinary tract infection
- WBC – white blood cells

Drug Classes Discussed

- Cephamycins
  - Cefoxitin
  - Cefotetan
- Aminopenicillins
  - Amoxicillin
  - Ampicillin
- Fluoroquinolones
  - Levofloxacin
  - Ciprofloxacin
  - Moxifloxacin
- Carbapenems
  - Meropenem
  - Imipenem-Cilastatin
  - Ertapenem
- β-Lactam + β-Lactamase Inhibitor Combinations
  - Ceftazidime-Avibactam
  - Meropenem-Vaborbactam
  - Imipenem-Cilastatin-Relebactam
  - Ceftolozane-Tazobactam

Patient Case #1

HPI: TR is a 64-year-old male who presents with flank pain and urinary frequency. His urinary analysis and culture are shown below.

URINALYSIS, REFLEX TO CULTURE
Collection Time: 08/30/23 11:27 PM
Specimen: Urine CVMS

Result	Value	Ref Range
Urine Color	Yellow	Straw, Yellow, Amber
Urine Appearance	Turbid (A)	Clear
Urine Specific Gravity	1.019	1.003 - 1.035
Urine pH	5.0	5.0 - 8.0
Urine Glucose	Negative	Negative
Urine Ketones	Negative	Negative
Urine Protein	>=500 (A)	Negative, Trace mg/dL
Urine Nitrites	Positive (A)	Negative
Urine Leukocyte Esterase	Large (A)	Negative
Urine WBC's	>182 (A)	0 - 8 /HPF
Urine RBC's	>182 (A)	0 - 3 /HPF
Urine Squamous Epithelial Cells	None Seen	/HPF
Urine Bacteria	Occasional (A)	None Seen /HPF

Specimen: Urine
Organism: > 100,000 CFU/mL *E. coli*

Antimicrobial	MIC	Interpretive category
Nitrofurantoin	<32	Sensitive
SMX/TMP	<2/38	Sensitive
Ceftriaxone	>2	Resistant
Cefepime	<2	Sensitive
Pip/Tazo	<16/4	Sensitive
Meropenem	<1	Sensitive

ESBL Resistance CTX-M Gene Detected!

Question #1

What would be the most appropriate choice of antibiotic for TR?

1. Pip/Tazo
2. Cefepime
3. Nitrofurantoin
4. Meropenem
5. SMX/TMP

Antimicrobial	MIC	Interpretive category
Nitrofurantoin	<16	Sensitive
SMX/TMP	<2/38	Sensitive
Ceftriaxone	>2	Resistant
Cefepime	<2	Sensitive
Pip/Tazo	<8/4	Sensitive
Meropenem	<1	Sensitive

ESBL Resistance CTX-M Gene Detected!

Patient Case #2

HPI: CT is 35-year-old female who presents with pain while urinating and reports that her urine has been cloudy. Her UA and culture are shown below.

URINALYSIS, REFLEX TO CULTURE
Collection Time: 08/28/23 10:44 PM
Specimen: Urine CVMS

Result	Value	Ref Range
Urine Color	Yellow	Straw, Yellow, Amber
Urine Appearance	Cloudy (A)	Clear
Urine Specific Gravity	1.019	1.003 - 1.035
Urine pH	6.0	5.0 - 8.0
Urine Glucose	Negative	Negative
Urine Ketones	Trace (A)	Negative
Urine Protein	Negative	Negative, Trace mg/dL
Urine Nitrites	Positive (A)	Negative
Urine Leukocyte Esterase	Small (A)	Negative
Urine WBC's	57 (A)	0 - 8 /HPF
Urine RBC's	1	0 - 3 /HPF
Urine Squamous Epithelial Cells	Rare	/HPF
Urine Renal Epithelial Cells	Rare	None Seen, Rare /HPF
Urine Bacteria	Rare (A)	None Seen /HPF
Urine Mucous	Present (A)	None Seen

Specimen: Urine
Organism: > 100,000 CFU/mL *Klebsiella pneumoniae*

Antimicrobial	MIC	Interpretive category
SMX/TMP	>4/76	Resistant
Ceftriaxone	>2	Resistant
Cefepime	<2	Sensitive
Meropenem	<1	Sensitive

Question #2

What is a marker in this bacteria that might indicate it is ESBL?

1. Ceftriaxone MIC
2. Bactrim MIC
3. Cefepime sensitive
4. Klebsiella pneumoniae

Specimen: Urine
Organism: > 100,000 CFU/mL *Klebsiella pneumoniae*

Antimicrobial	MIC	Interpretive category
SMX/TMP	>4/76	Resistant
Ceftriaxone	>2	Resistant
Cefepime	<2	Sensitive
Meropenem	<1	Sensitive

Patient Case #3

HPI: DM is a 52-year-old female who has been in the hospital for 7 days. Over the past 6 hours she has become lethargic and pale. Her blood pressure has dropped to 72/54 and her WBC has increased to 17.2. Blood cultures were ordered, and the results are provided.

Blood Culture: Escherichia coli

Antimicrobial	MIC	Interpretive category
Levofloxacin	<1	Sensitive
SMX/TMP	<2/38	Sensitive
Ceftriaxone	>2	Resistant
Cefepime	>16	Resistant
Pip/Tazo	>32/4	Resistant
Meropenem	>4	Resistant

CRE Resistance OXA-48 Gene Detected!

Question #3

What would be the most appropriate choice of antibiotic for DM?

1. Meropenem
2. Meropenem/vaborbactam
3. Ceftazidime/avibactam
4. Levofloxacin
5. SMX/TMP

Blood Culture: Escherichia coli

Antimicrobial	MIC	Interpretive category
Levofloxacin	<1	Sensitive
SMX/TMP	<2/38	Sensitive
Ceftriaxone	>2	Resistant
Cefepime	>16	Resistant
Pip/Tazo	>32/4	Resistant
Meropenem	>4	Resistant

CRE Resistance OXA-48 Gene Detected!

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Antimicrobial Resistance

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Development of Resistance

- In 1945 during his Nobel prize acceptance speech, Alexander Fleming warned about resistance development due to inappropriate antibiotic use
- The CDC estimates that 47 million courses of antibiotics are prescribed unnecessarily every year
- It is estimated that 30% of antibiotics prescribed in the ambulatory setting are not indicated

Rapid Rates of Resistance

Antibiotic approved		Resistance development	
Penicillin 1	1941	Penicillin-resistant E. coli	1940
Cefotaxime 0	1980	ESBL E. coli	1983
Ceftazidime 5	1985	ESBL Klebsiella pneumoniae	1987
Imipenem/cilastatin	1985	KPC-producing K. pneumoniae	1996
Ceftazidime/avibactam 5	2015	Ceftazidime/avibactam-resistant enterobacterales	2015
Cefiderocol 9	2019	Cefiderocol-resistant enterobacterales	2020

Cost of Antimicrobial Resistance

- Deaths associated with antimicrobial resistance were estimated to be 4.95 million people in 2019
- Deaths directly attributed to antimicrobial resistance were estimated to be 1.27 million people in 2019
- Annual cost due to AMR for the United States is estimated to be $20 billion every year

Prevention of MDRO Spread

- Standard precautions for all MDRO
  - Good hand hygiene
  - Gloves
- Contact precautions
  - Gowns + gloved for staff and visitors
  - Single patient rooms
  - Duration is a more conflicted topic
- Difficult to track spread
  - Contacted patients will likely have no signs

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Extended Spectrum β-Lactamase Producing Enterobacterales

(ESBL)

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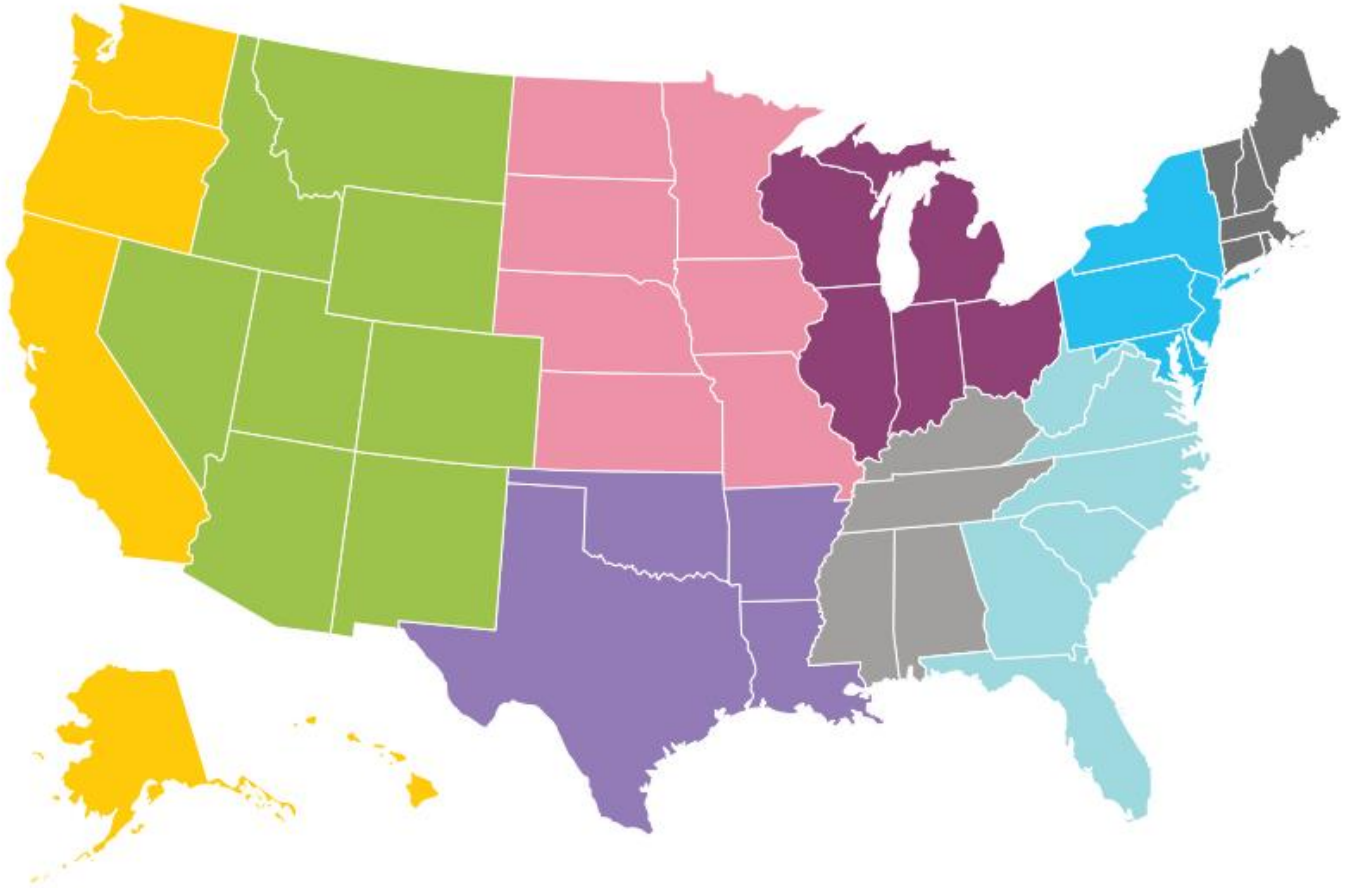
Background

- Rates grew by 53% from 2012 to 2017 and continuing to rise
- Listed as a serious threat on CDC antibiotic resistance threat report
- Estimated 197,400 cases in 2019
- Estimated mortality rate of 4.6% based on 2019 CDC data

2019 antibiotic resistance threats report. Centers for Disease Control and Prevention. November 23, 2021. Accessed August 20, 2023. https://www.cdc.gov/drugresistance/biggest-threats.html#extend.

ESBL Resistance Patterns



West North Central
ESBL = 10.5%
LEVO-R = 21.5%
TMP-SMX-R = 30.4%

National
ESBL = 15.7%
LEVO-R = 24.3%
TMP-SMX-R = 32.1%

East North Central
ESBL = 11.6%
LEVO-R = 20.7%
TMP-SMX-R = 26.8%

New England
ESBL = 11.9%
LEVO-R = 22.2%
TMP-SMX = 33.5%

Mid Atlantic
ESBL = 29.6
LEVO-R = 38.1%
TMP-SMX-R = 43.5%

Pacific
ESBL = 20.8
LEVO-R = 23.8%
TMP-SMX = 31.0%

Mountain
ESBL = 11.3%
LEVO-R = 18.0%
TMP-SMX-R = 29.3%

West South Central
ESBL = 12.5%
LEVO-R = 22.1%
TMP-SMX-R = 35.3%

East South Central
ESBL = 15.3%
LEVO-R = 27.9%
TMP-SMX-R = 28.8%

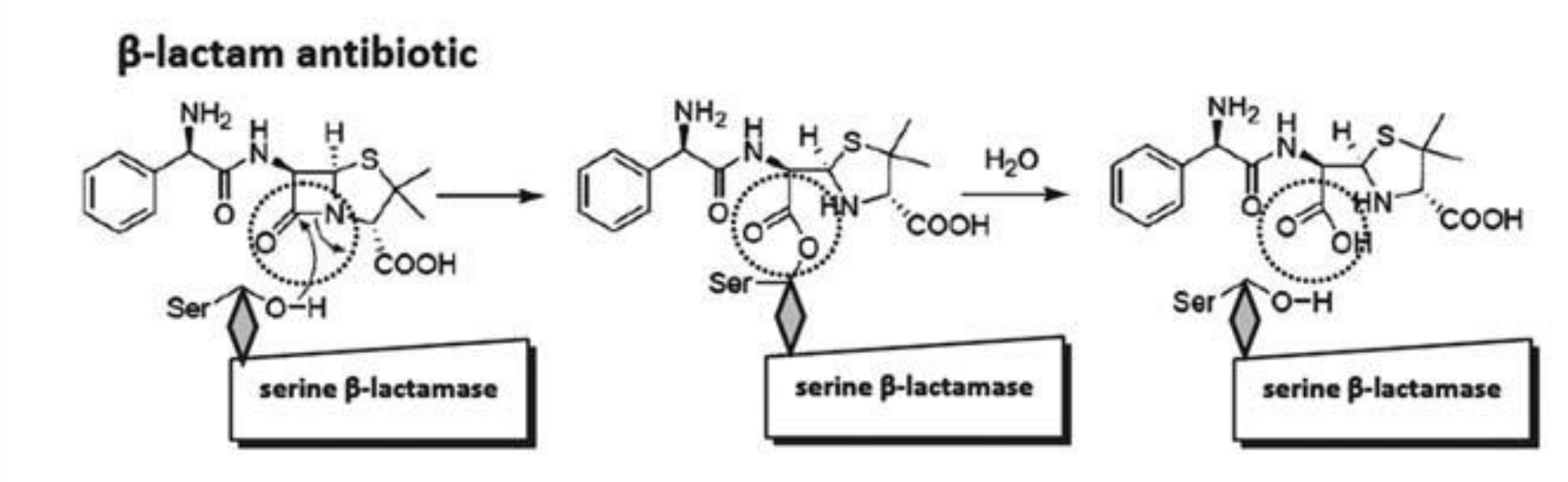
South Atlantic
ESBL = 11.6%
LEVO-R = 23.9%
TMP-SMX-R = 31.8%

Mechanisms & Genes

- β-lactamase enzymes deactivate most β-lactams
- CTX-M, TEM, SHV, OXA are common β-lactamase enzymes around the world
- CTX-M-15 is the most commonly seen β-lactamase enzyme in the United States
- Over 300 different or variations of β-lactamase enzymes that have been discovered

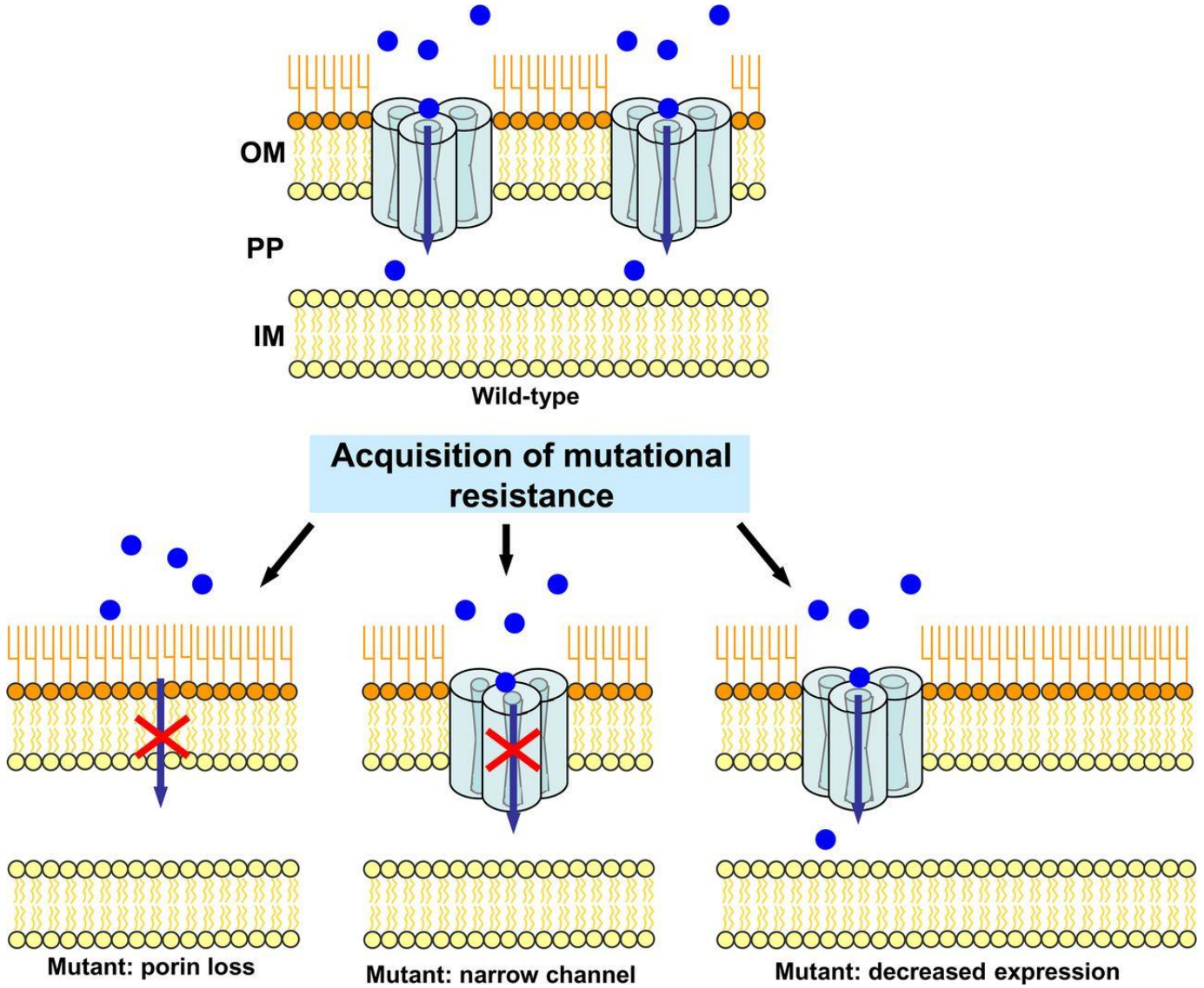
Bush K, Bradford PA. β-Lactams and β-Lactamase Inhibitors: An Overview. Cold Spring Harb Perspect Med. 2016 Aug 1;6(8):a025247. doi: 10.1101/cshperspect.a025247. PMID: 27329032; PMCID: PMC4968164.

Mechanism of β-Lactamase

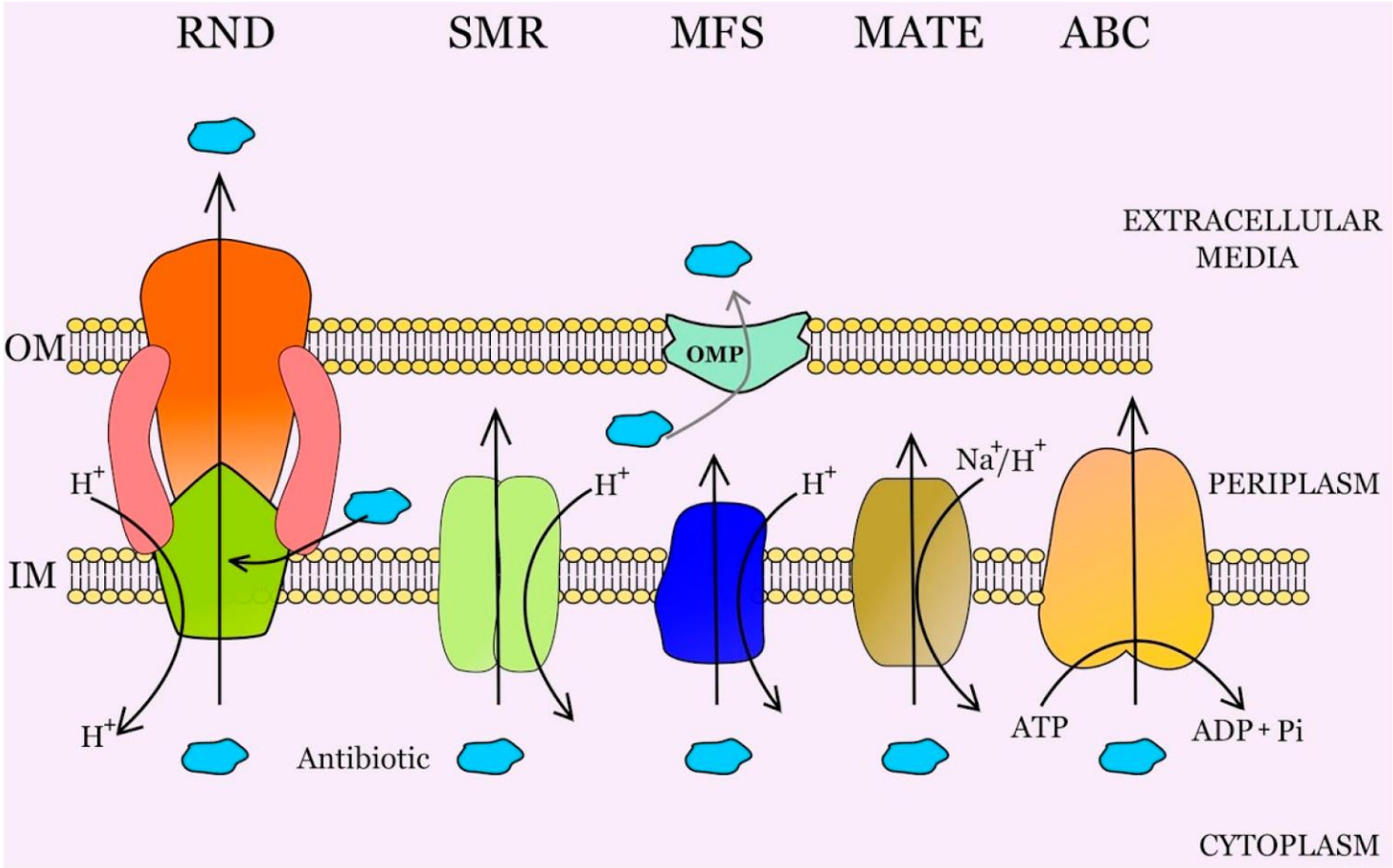


Olszańska, Dorota & Zórawski, Marcin & Hauschild, Tomasz & Wieczorek, Piotr & Sacha, Pawel & Tryniszewska, Elzbieta. (2008). Metallo-beta-lactamases of Pseudomonas aeruginosa--a novel mechanism resistance to beta-lactam antibiotics.. Folia Histochemica et Cytobiologica. 46. 10.5603/4440.

Mechanism of Resistance: Membrane Permeability



Mechanism of Resistance: Efflux Pumps



Sensitivities

- ESBL genes can be tested
- Ceftriaxone MIC > 2
- Resistance to **most** penicillins, cephalosporins, and aztreonam
- Carbapenem activity is preserved
- Many ESBL have poly-resistance

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

Most Common ESBL Producing Bacteria

- Escherichia coli
- Klebsiella pneumoniae
- Klebsiella oxytoca
- Proteus mirabilis
- Any gram-negative bacteria

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

Cystitis Treatment

Primary therapy	• Nitrofurantoin or SMX/TMP
Secondary therapy	• Levofloxacin, ciprofloxacin, carbapenems
Alternative therapy	• Single-dose aminoglycoside or fosfomycin

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

Fosfomycin Pearl

- Fosfomycin should only be used in ESBL E. coli
- Most other bacteria carry a fosA hydrolase gene
- This enzyme will confer fosfomycin resistance to the bacteria by conjugating glutathione to fosfomycin

Widespread Fosfomycin Resistance in Gram-Negative Bacteria Attributable to the Chromosomal *fosA* Gene

The Role of *fosA* in Challenges with Fosfomycin Susceptibility Testing of Multispecies Klebsiella pneumoniae Carbapenemase-Producing Clinical Isolates

Ito R, Mustapha MM, Tomich AD, Callaghan JD, McElheny CL, Mettus RT, Shanks RMQ, Sluis-Cremer N, Doi Y. Widespread Fosfomycin Resistance in Gram-Negative Bacteria Attributable to the Chromosomal fosA Gene. mBio. 2017 Aug 29;8(4):e00749-17. doi: 10.1128/mBio.00749-17. PMID: 28851843; PMCID: PMC5574708.
Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

Pyelonephritis Treatment

Primary treatment	• SMX/TMP, levofloxacin, ciprofloxacin
Secondary therapy	• Ertapenem, meropenem, imipenem-cilastatin
Alternative therapy	• Full course aminoglycosides

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

ESBL Outside the GU System

Preferred treatment	• Meropenem, imipenem-cilastatin, ertapenem
Step-down therapy	• SMX/TMP, levofloxacin, ciprofloxacin

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

Ertapenem Pearl

- Ertapenem should be used with caution in patients with hypoalbuminemia or who are critically ill
- Ertapenem is extremely protein bound which greatly increases its half-life
- This study shows that patients had a 5-times higher risk of mortality when using ertapenem compared to meropenem or imipenem/cilistatin
- Odds Ratio difference was 4.6 in ertapenem compared to 1.2 in imipenem/meropenem
- Significant correlation between ertapenem mortality and low albumin with Odds Ratio 2.45

Association between hypoalbuminemia and mortality among subjects treated with ertapenem versus other carbapenems: prospective cohort study

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.
Zusman O, Farbman L, Tredler Z, Daitch V, Lador A, Leibovici L, Paul M. Association between hypoalbuminemia and mortality among subjects treated with ertapenem versus other carbapenems: prospective cohort study. Clin Microbiol Infect. 2015 Jan;21(1):54-8. doi: 10.1016/j.cmi.2014.08.003. Epub 2014 Oct 12. PMID: 25636928.

Piperacillin-Tazobactam – Merino Trial

- Compared Pip/Tazo to meropenem for bloodstream infections
- Differences between susceptibilities and clinical results
- Not recommended for use over other agents
- Controversy around results of trial

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

Harris PNA, Tambyah PA, Lye DC, Mo Y, et al; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). 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. JAMA. 2018 Sep 11;320(10):984-994. doi: 10.1001/jama.2018.12163. Erratum in: JAMA. 2019 Jun 18;321(23):2370. PMID: 30208454; PMCID: PMC6143100
Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

Merino Controversy

- Secondary analysis findings
  - Possibly more resistant pathogens in the pip/tazo group
  - Updated breakpoints where initially susceptible pathogens were actually resistant
  - Findings showed there may not be a difference between treatments, but it is questionable whether the study's power was enough
- Deemed pip/tazo to still be clinically inferior to meropenem based on available evidence

Harris PNA, Tambyah PA, Lye DC, Mo Y, et al; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). 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. JAMA. 2018 Sep 11;320(10):984-994. doi: 10.1001/jama.2018.12163. Erratum in: JAMA. 2019 Jun 18;321(23):2370. PMID: 30208454; PMCID: PMC6143100
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Cefepime and Cephamycins

Cefepime

- May show susceptibilities but not recommended for use
- Studies have shown high failure rates
- More data may be needed to assess true efficacy

Cephamycins

- Not enough data
- Many cephamycins being studies are not available in the US
- Cefoxitin and cefotetan are the most common
- Not recommended

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

β-Lactam-β-Lactamase Inhibitor Combinations and Cefiderocol

- Reserved for carbapenem resistant organisms
  - Meropenem-vaborbactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol
- Ceftolozone-tazobactam should be avoided as treatment

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

Review

- Bacteria & Resistance:
  - E. coli, Klebsiella pneumoniae, Klebsiella oxytoca, Proteus mirabilis
  - CTX-M, TEM, SHV, OXA
- Susceptibility:
  - Ceftriaxone MIC > 2
  - Multi-resistance
- Treatment:
  - Cystitis - Nitrofurantoin or SMX/TMP
  - Pyelonephritis - SMX/TMP, levofloxacin, ciprofloxacin
  - Other sources - Meropenem, imipenem-cilastatin, ertapenem

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

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Carbapenem-Resistant Enterobacterales

(CRE)

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Background

- On CDC urgent threats list
- 13,100 cases in 2017
- 8.4% mortality rate based on their 2017 data
- Multiple potential enzymes involved including KPC, NDM, VIM, OXA-48

2019 antibiotic resistance threats report. Centers for Disease Control and Prevention. November 23, 2021. Accessed August 20, 2023. https://www.cdc.gov/drugresistance/biggest-threats.html#extend.

Identification

- Enterobacterales with evidence of carbapenem resistance
  - Resistant to a carbapenem
  - Confirmed carbapenemase gene

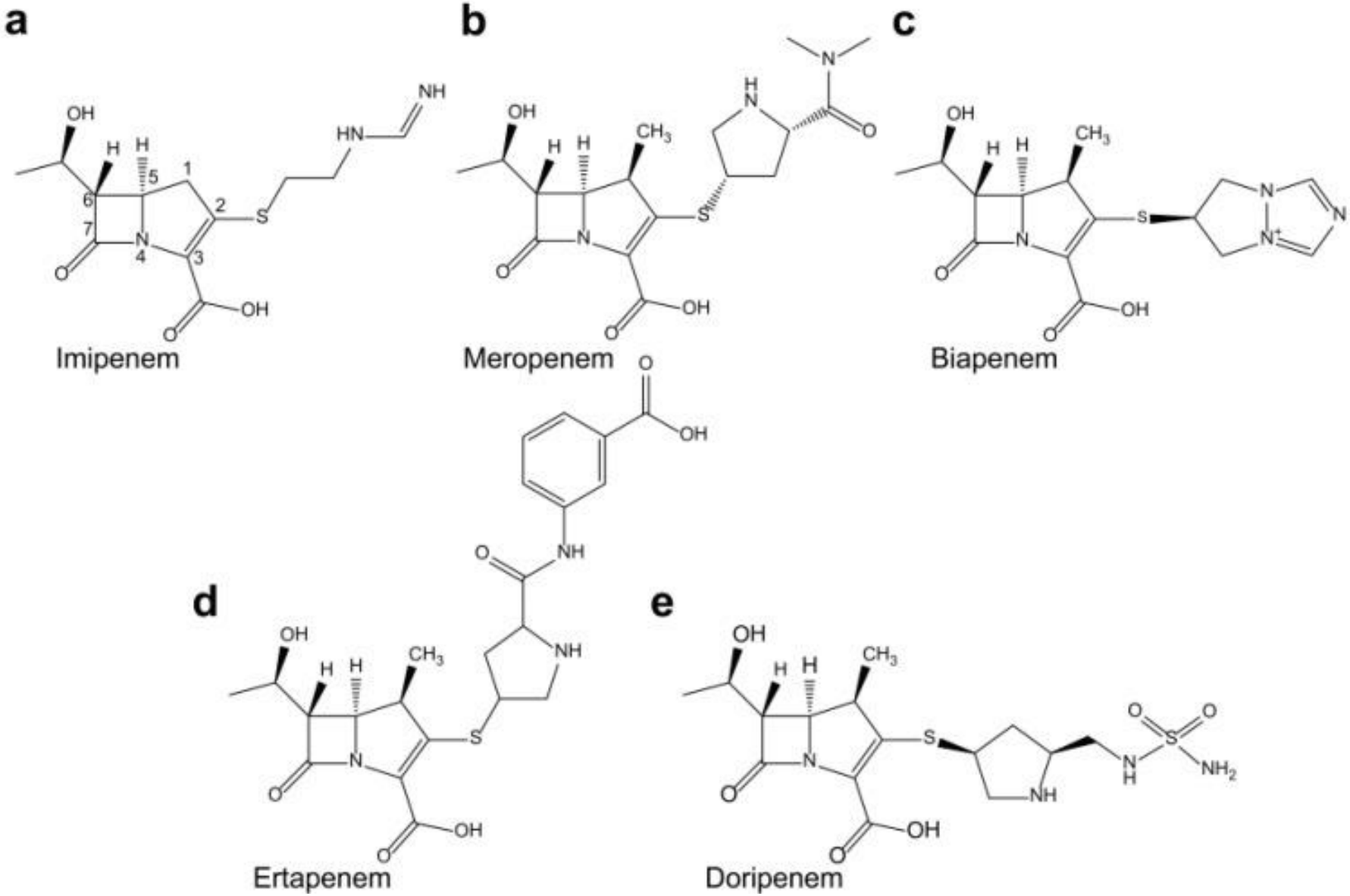
- Most common bacteria
  - Enterobacterales
    - Klebsiella spp.
    - Serratia marcescens
    - E. coli

Resistance

- Various mechanisms of resistance
  - Carbapenemase production
  - Membrane permeability alterations
  - Efflux pumps
  - Enhanced ESBL production

- Majority of resistance is carbapenemase producing bacteria
  - 60% of all CRE cases

Carbapenem Structure



KPC

- Klebsiella pneumonia carbapenamse (KPC)
  - Can be more organisms that just K. pneumonia
- Class A carbapenamase
- Most common carbapenemase in US and worldwide
- Preferred therapy
  - Meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam
- Alternative therapy
  - Cefiderocol

NDM

- New Delhi metallo-B-lactamase (NDM)
- Class B carbapenemase
- Commonly in China, Pakistan, India, and Bangladesh
- Preferred therapy
  - Ceftazidime-avibactam in combination with aztreonam
  - Cefiderocol monotherapy

OXA-48

- Oxacillinase (OXA)
- Class D carbapenemase
- Commonly found in Acinetobacter spp. or Pseudomonas aeruginosa
- Commonly in Saudi Arabia, Turkey, Morocco, Egypt, and EU
- Preferred therapy
  - Ceftazidime-avibactam
- Alternative therapy
  - Cefiderocol

VIM

- Verona integron-encoded metallo-B-lactamase (VIM)
- Class B carbapenemase
- Commonly in Japan, Taiwan, and China
- Preferred therapy
  - Ceftazidime-avibactam in combination with aztreonam
  - Cefiderocol monotherapy

Primary Treatments

Cystitis	• Nitrofurantoin, SMX/TMP, ciprofloxacin, or levofloxacin
Pyelonephritis	• SMX/TMP, ciprofloxacin, or levofloxacin
All other sources	• Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam • Alternative – cefiderocol

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Review

- Bacteria:
  - Klebsiella spp., Serratia marcescens, Enterobacterales, E. coli
  - KPC, NDM, OXA-48, VIM
- Identification:
  - Carbepenem resistance
  - Carbapenemase gene
- Treatment:
  - Cystitis - Nitrofurantoin, SMX/TMP, fluoroquinolone
  - Pyelonephritis - SMX/TMP, levofloxacin, ciprofloxacin
  - Other sources - Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam

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IDSA Guidance Document on Gram-negative Resistance

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IDSA 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Published by IDSA on 6/7/2023. Document is current as of 12/01/22, 7/1/2023

A Focus on Extended-spectrum β-lactamase-Producing Enterobacterales, AmpC β-Lactamase-Producing Enterobacterales, Carbapenem-Resistant Enterobacterales, *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance, Carbapenem-Resistant Acinetobacter *baumannii*, and *Stenotrophomonas maltophilia*

This updated document replaces previous versions of the guidance document.

Essentia Health

Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van DCuin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed September 1st 2023.

Key Topics of this Document

- ESBL
- AMP-C
- CRE
- Pseudomonas
- CRAB
- Stenotrophomonas

GUIDANCE DOCUMENT CONSIDERATIONS

Applicable in pediatrics

Contains a dosing & MIC guide

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Duration of Therapy

- The duration of therapy should remain the same as a normal infection
  - Resistant bacteria do not require more time to eliminate
- Duration of therapy should begin once appropriate therapy is initiated
  - Exception in cystitis

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Transitioning to Oral Therapy

Should not be delayed because of resistance, especially when:

- Susceptibility to an appropriate oral agent is demonstrated
- The patient is hemodynamically stable
- Reasonable source control measures have occurred
- Concerns about insufficient intestinal absorption are not present

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IV to PO

Inferred Susceptibility
Ampicillin → Amoxicillin
Ampicillin/Sulbactam → Amoxicillin/Clavulanate
Cefazolin → Cefadroxil, Cephalexin
Ceftriaxone → Cefpodoxime, Cefuroxime
Cefepime → No oral conversion
Carbapenems → No oral conversion

Most treatments discussed do not have inferred susceptibility because oral products are not available. Cefepime, Pip/Tazo, and carbapenems are examples of this along with our broader β-lactam + β-lactamase inhibitor combinations

Utilization of medications that have both formulations may be helpful i.e. ciprofloxacin, levofloxacin, SMX/TMP

We are called to make a healthy difference in people's lives.

Summary & Closing Remarks

Essentia Health

Review

1. Understand what are ESBL enzymes
2. Recognize how to detect ESBL organisms
3. Understand what makes ESBL organisms more difficult to treat

Patient Case #1

HPI: TR is a 64-year-old male who presents with flank pain and urinary frequency. His urinary analysis and culture are shown below

URINALYSIS, REFLEX TO CULTURE
Collection Time: 08/30/23 11:27 PM
Specimen: Urine CVMS

Result	Value	Ref Range
Urine Color	Yellow	Straw, Yellow, Amber
Urine Appearance	Turbid (A)	Clear
Urine Specific Gravity	1.019	1.003 - 1.035
Urine pH	5.0	5.0 - 8.0
Urine Glucose	Negative	Negative
Urine Ketones	Negative	Negative
Urine Protein	>=500 (A)	Negative, Trace mg/dL
Urine Nitrites	Positive (A)	Negative
Urine Leukocyte Esterase	Large (A)	Negative
Urine WBC's	>182 (A)	0 - 8 /HPF
Urine RBC's	>182 (A)	0 - 3 /HPF
Urine Squamous Epithelial Cells	None Seen	/HPF
Urine Bacteria	Occasional (A)	None Seen /HPF

Specimen: Urine
Organism: > 100,000 CFU/mL *E. coli*

Antimicrobial	MIC	Interpretive category
Nitrofurantoin	<32	Sensitive
SMX/TMP	<2/38	Sensitive
Ceftriaxone	>2	Resistant
Cefepime	<2	Sensitive
Pip/Tazo	<16/4	Sensitive
Meropenem	<1	Sensitive

ESBL Resistance CTX-M Gene Detected!

Question #1

What would be the most appropriate choice of antibiotic for TR?

1. Pip/Tazo
2. Cefepime
3. Nitrofurantoin
4. Meropenem
5. SMX/TMP

Antimicrobial	MIC	Interpretive category
Nitrofurantoin	<16	Sensitive
SMX/TMP	<2/38	Sensitive
Ceftriaxone	>2	Resistant
Cefepime	<2	Sensitive
Pip/Tazo	<8/4	Sensitive
Meropenem	<1	Sensitive

ESBL Resistance CTX-M Gene Detected!

Question #1 Rationale

ESBL

Pyelonephritis Treatment

Primary treatment	• SMX/TMP, levofloxacin, ciprofloxacin
Secondary therapy	• Ertapenem, meropenem, imipenem-cilastatin
Alternative therapy	• Full course aminoglycosides

Organism: > 100,000 CFU/mL *E. coli*

Antimicrobial	MIC	Interpretive category
Nitrofurantoin	<16	Sensitive
SMX/TMP	<2/38	Sensitive
Ceftriaxone	>2	Resistant
Cefepime	<2	Sensitive
Pip/Tazo	<8/4	Sensitive
Meropenem	<1	Sensitive

ESBL Resistance CTX-M Gene Detected!

Patient Case #2

- HPI: CT is 35-year-old female who presents with pain while urinating and reports that her urine has been cloudy. Her UA and culture are shown below

URINALYSIS, REFLEX TO CULTURE
Collection Time: 08/28/23 10:44 PM
Specimen: Urine CVMS

Result	Value	Ref Range
Urine Color	Yellow	Straw, Yellow, Amber
Urine Appearance	Cloudy (A)	Clear
Urine Specific Gravity	1.019	1.003 - 1.035
Urine pH	6.0	5.0 - 8.0
Urine Glucose	Negative	Negative
Urine Ketones	Trace (A)	Negative
Urine Protein	Negative	Negative, Trace mg/dL
Urine Nitrites	Positive (A)	Negative
Urine Leukocyte Esterase	Small (A)	Negative
Urine WBC's	57 (A)	0 - 8 /HPF
Urine RBC's	1	0 - 3 /HPF
Urine Squamous Epithelial Cells	Rare	/HPF
Urine Renal Epithelial Cells	Rare	None Seen, Rare /HPF
Urine Bacteria	Rare (A)	None Seen /HPF
Urine Mucous	Present (A)	None Seen

Specimen: Urine
Organism: > 100,000 CFU/mL *Klebsiella pneumoniae*

Antimicrobial	MIC	Interpretive category
SMX/TMP	>4/76	Resistant
Ceftriaxone	>2	Resistant
Cefepime	<2	Sensitive
Meropenem	<1	Sensitive

Question #2

What is a marker in this bacteria that might indicate it is ESBL?

1. Ceftriaxone MIC
2. Bactrim MIC
3. Cefepime sensitive
4. Klebsiella pneumoniae

Specimen: Urine
Organism: > 100,000 CFU/mL *Klebsiella pneumoniae*

Antimicrobial	MIC	Interpretive category
SMX/TMP	>4/76	Resistant
Ceftriaxone	>2	Resistant
Cefepime	<2	Sensitive
Meropenem	<1	Sensitive

Question #2 Rationale

ESBL

Sensitivities

- A marker to consider ESBL is if ceftriaxone MICs are greater than or equal to 2, but there can be other causes

ESBL

Most Common ESBL Producing Bacteria

- Escherichia coli
- Klebsiella pneumoniae
- Klebsiella oxytoca
- Proteus mirabilis

Antimicrobial	MIC	Interpretive category
SMX/TMP	>4/76	Resistant
Ceftriaxone	>2	Resistant
Cefepime	<2	Sensitive
Meropenem	<1	Sensitive

Organism: > 100,000 CFU/mL *Klebsiella pneumoniae*

Patient Case #3

HPI: DM is a 52-year-old female who has been in the hospital for 7 days. Over the past 6 hours she has become lethargic and pale. Her blood pressure has dropped to 72/54 and her WBC has increased to 17.2. Blood cultures were ordered, and the results are provided.

Blood Culture: Escherichia coli

Antimicrobial	MIC	Interpretive category
Levofloxacin	<1	Sensitive
SMX/TMP	<2/38	Sensitive
Ceftriaxone	>2	Resistant
Cefepime	>16	Resistant
Pip/Tazo	>32/4	Resistant
Meropenem	>4	Resistant

CRE Resistance OXA-48 Gene Detected!

Question #3

What would be the most appropriate choice of antibiotic for DM?

1. Meropenem
2. Meropenem/vaborbactam
3. Ceftazidime/avibactam
4. Levofloxacin
5. SMX/TMP

Blood Culture: Escherichia coli

Antimicrobial	MIC	Interpretive category
Levofloxacin	<1	Sensitive
SMX/TMP	<2/38	Sensitive
Ceftriaxone	>2	Resistant
Cefepime	>16	Resistant
Pip/Tazo	>32/4	Resistant
Meropenem	>4	Resistant

CRE Resistance OXA-48 Gene Detected!

Question #3 Rationale

OXA-48

- Oxacillinase (OXA)
- Class D carbapenemase
- Commonly found in Acinetobacter spp. or Pseudomonas aeruginosa
- Commonly in Saudi Arabia, Turkey, Morocco, Egypt, and EU
- Preferred therapy
  - Ceftazidime-avibactam
- Alternative therapy
  - Cefiderocol

Antimicrobial	MIC	Interpretive category
Levofloxacin	<1	Sensitive
SMX/TMP	<2/38	Sensitive
Ceftriaxone	>2	Resistant
Cefepime	>16	Resistant
Pip/Tazo	>32/4	Resistant
Meropenem	>4	Resistant

CRE Resistance OXA-48 Gene — Detected!

Resources

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Questions?

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Thank you

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