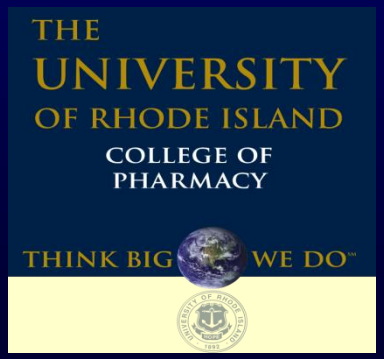
Fighting "Superbugs": A focus on the epidemiology and treatment of ESBLs

Haley J Morrill, Pharm.D.
Antimicrobial Stewardship Fellow

Rhode Island Infectious Diseases (RIID) Research Program of the Providence Veterans Affairs Medical Center and University of Rhode Island College of Pharmacy



Disclaimer

- The information disseminated in this lecture is given in my personal capacity and not in my capacity as a VA employee nor does it necessarily reflect the views of the United States Department of Veterans Affairs

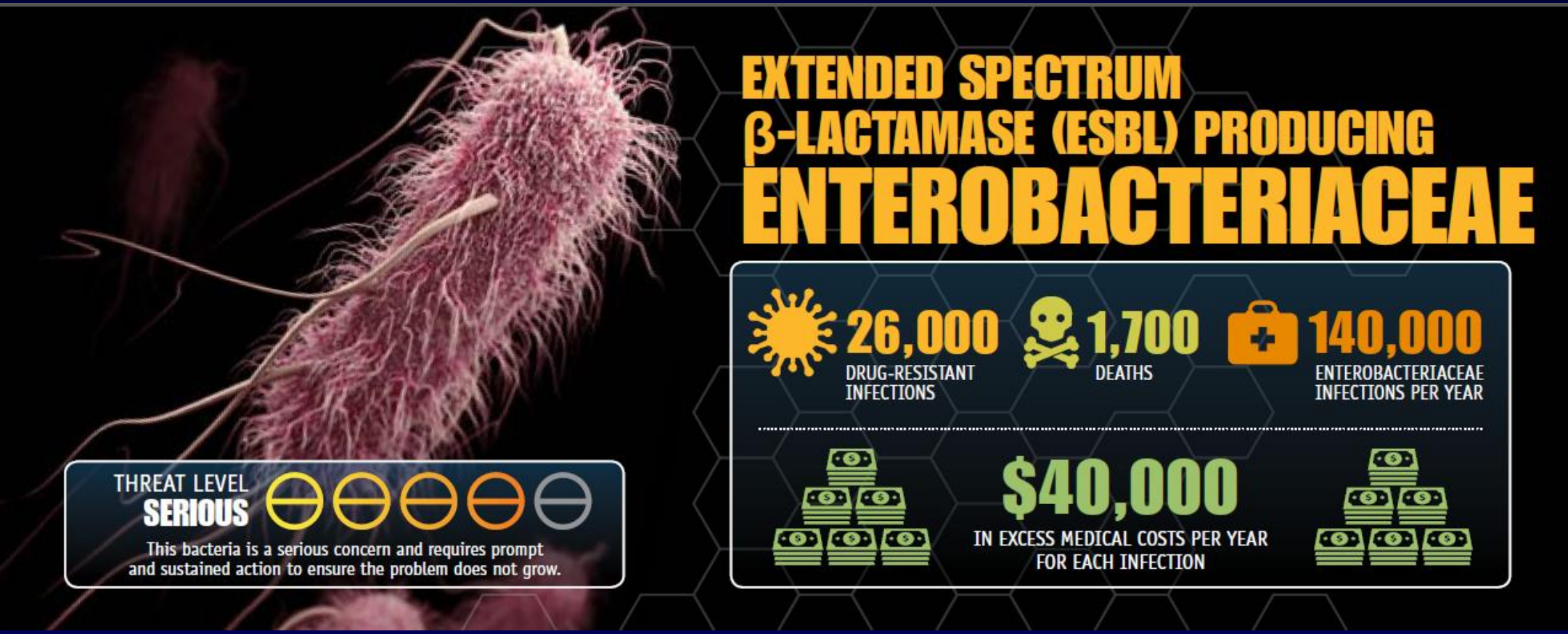
Objectives

- Define extended-spectrum beta-lactamases (ESBL)
- Outline the various spectrums of resistance of different ESBL types
- Discuss treatment options for ESBL infections

Introduction

- Extended-spectrum beta-lactamases (ESBL)
  - Enzymes that break down many common antibiotics, making the antibiotics ineffective, including:
    - Penicillins, cephalosporins, and aztreonam (monobactam)
- Carbapenems constitute the best treatment option for infections caused by ESBL producing organisms
- Treatment of serious infections is complicated
  - Resistant to a broad range of antibiotics
- Infections with ESBLs have been associated with poor outcomes

Serious Public Health Threat



"This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow."

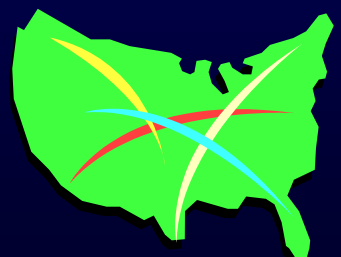
CDC. 2013. Antibiotic resistance threats in the United States, 2013.
Available from: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

Introduction

- Reliable identification of ESBL producing organisms in clinical laboratories can be challenging
  - Some isolates have MICs that have minimum inhibitory concentrations (MICs) that are high but remain in the susceptible range
  - Likely that prevalence is underestimated!!

Epidemiology

- ESBL producing organisms have been increasingly reported worldwide
- Most often found in hospital specimens, but have also been reported from the community
- Community clinics and nursing homes have been identified as reservoirs for producing *K. pneumoniae* and *E. coli*
- Prevalence rates vary from hospital to hospital and country to country



ESBL Risk Factors

- Patients with ANY previous antibiotic use
  - Especially those who've recently had recent 3rd generation cephalosporins or quinolones
- Institutionalized patients
  - Especially ICU patients
  - Risk increases with length of stay
- Prior residence in a long-term care facility (eg, nursing home)
- Patients with indwelling devices
  - Catheters, GI tubes
- Other risk factors
  - Abdominal surgery
  - Gut colonization
  - Ventilator assistance
  - Hemodialysis

Jacoby et al. NEJM. 2005; 352 (4): 380-288.

Extended Spectrum Beta-Lactamase Production in Gram Negative Bacteria

Evolution of Resistance

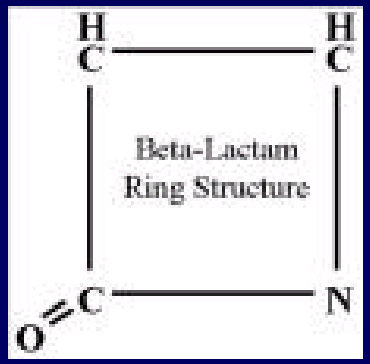
What are beta-lactams?

What are beta-lactamases?

What are extended spectrum beta-lactamases?

Beta-Lactam's

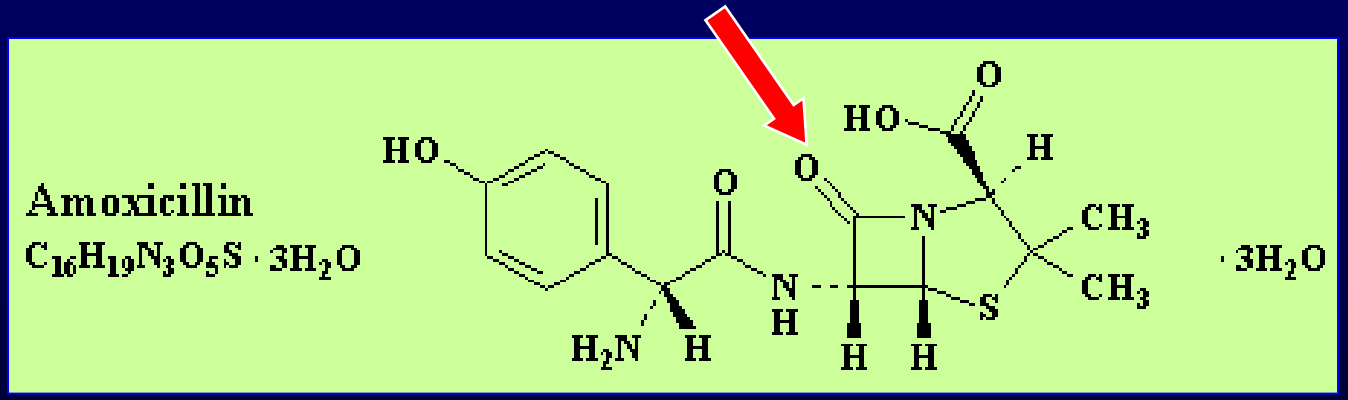
4 major classes of antibiotics



1. Penicillin's (natural and semi-synthetic)
2. Cephalosporins
3. Monobactam (aztreonam)
4. Carbapenems (meropenem, imipenem, ertapenam and doripenem)

Beta-Lactamases

- Beta-lactamases are enzymes that hydrolyze the beta-lactam ring, thus inactivating the antibiotic



Classification of ESBLs

- Over 1,000 different types of ß-lactamase enzymes have been identified and this number is progressively increasing
- There are a number of different classification systems for these ß-lactamase enzymes
  - Ambler - based on molecular structure
  - Bush-Jacoby - based on function
- The resistance profiles of ß-lactamase enzymes vary greatly dependent on the specific enzyme type of the organism

ESBL Classification

- Ambler Classification - Four classes; easily labeled in the order they were identified in (A, B, C, and D)
- Classes A, C, and D all share the same amino acid (serine) in the active site and are known as "serine ß-lactamases“
  - Class A and C ß-lactamases most common in the United States
  - Class D ß-lactamases are less common in the US and are mainly found in Europe.
- Class B enzymes require a metal (usually zinc) for activity and are known as "Metallo-beta-lactamases (MBLs)”
  - Class B mostly found in countries in Southern Asia

Background of Resistance

- Greece (1960s) - First plasmid-mediated beta lactamase in Gram negative bacteria
  - Named **TEM** after the patient from which it was isolated (Temoniera)
- Later a closely related enzyme was discovered and named TEM-2 and another SHV 1
  - Similar biochemical properties, but differs by a single amino acid

TEM-related ESBLs were discovered in France in 1984 and the USA in 1988

Plasmid - Mediated BETA-LACTAMASES

- TEM-1 and TEM-2 enzymes are among the most common plasmid-mediated beta-lactamases in Gram negative bacteria (Enterobacteriaceae, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae*).

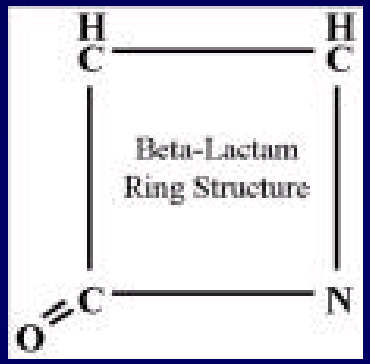
- TEM-1, TEM-2 and SHV 1- hydrolyze penicillins and narrow spectrum cephalosporins, such as cefazolin (Ancef).

- Not effective against higher generation cephalosporins (i.e., cefotaxime, ceftazidime, ceftriaxone, or cefepime)

- All are inhibited by beta lactamases inhibitors

TEM-1, TEM-2 and SHV-1 Beta-Lactams

4 major classes of antibiotics



Penicillins

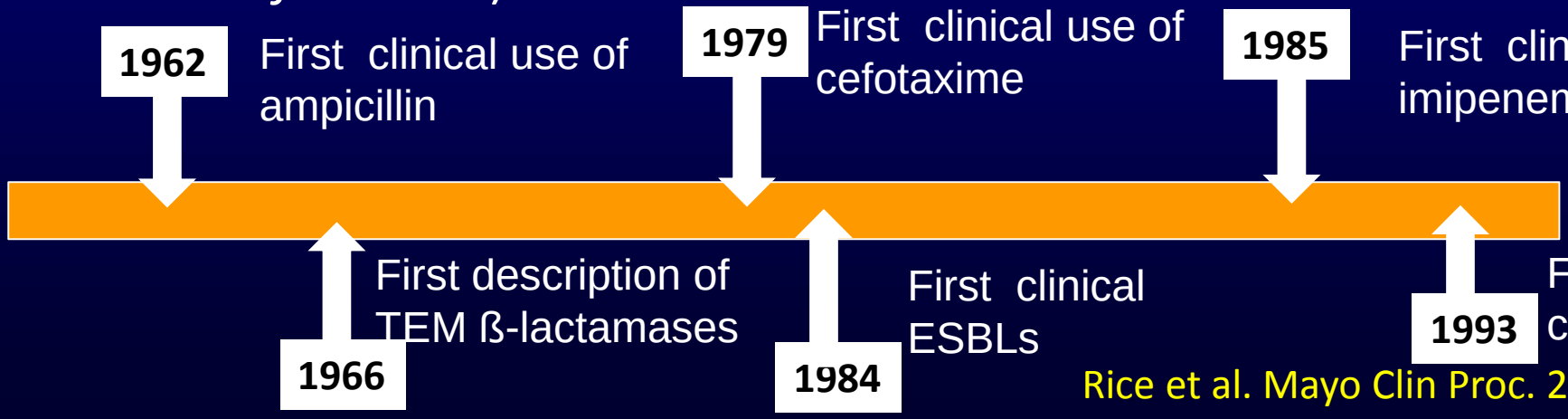
Cephalosporins (1^{st}, 2^{nd} 3^{rd} 4^{th})

Carbapenems

Monobactams

History of ESBL Resistance

- In the 1960s, first wave of narrow spectrum ß-lactamases (early TEM and SHV type) in association with the first clinical use of ampicillin
  - Prompted development of newer ß-lactam classes
- In the 1980s, not long after cefotaxime came into use the first mobile plasmid-mediated ESBL enzymes arose from mutations in the genes for the narrow spectrum TEM- and SHV- type ß-lactamases
  - Mutations resulted in enzymes with broader spectrum of action by opening up the active site to allow access to bulky 3rd generation oxyimino cephalosporins (e.g. *ceftazidime*, *cefotaxime*, and *ceftriaxone*).



Rice et al. Mayo Clin Proc. 2012;87 (2): 198-208.

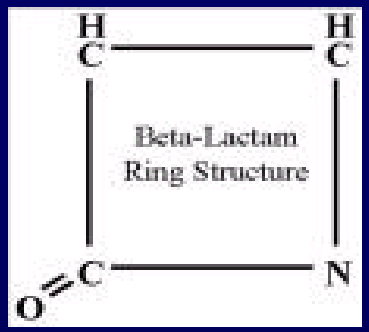
ESBL Varieties

1. TEM beta-lactamases (TEM-10, 12 and 26)
   - More than 200 TEM-type enzymes
   - In the US until recently ESBLs were primarily of the TEM- and SHV- variety
2. SHV beta-lactamases (SHV-5 and 12)
   - More than 180 SHV varieties known
3. CTX-M beta-lactamases (CTX-M-14 and 15)
   - More than 130 CTX-M varieties known
   - Replacing TEM- and SHV- type ESBLs worldwide; prevalence rising sharply
   - **CTX-M- type ESBLs are now the most common group in the US**
4. OXA beta-lactamases
   - More than 100 OXA varieties known
   - Found mainly in *Pseudomonas aeruginosa* isolates from Turkey and

ESBLs are heterogeneous

ESBLs Spectrum of Resistance

- Break down penicillins and 1st , 3rd, 4th generation cephalosporins
- Not effective against 2nd generation cephalosporins (e.g., cefoxitin and cefotetan) or carbapenems



Penicillins

Cephalosporins (1st, **2nd**, 3rd,4th)

Carbapenems (meropenem and imipenem)

Monobactams (aztreonam)

Varying Hydrolytic Activity by Enzyme Type

Ambler Class (active site)	Group example	Host Organism	Substrates	Inhibition by BLI	Region
Broad Spectrum ß-lactamases					
A (serine)	TEM-1 TEM-2 SHV-1	Enterobacteriaceae and non-fermenters (NFs)	**Narrow spectrum penicillins** (benzylpenicillin [penicillin G], aminopenicillins [amoxicillin, ampicillin], carboxypenicillins [carbenicillin, ticarcillin], uridopenicillin [piperacillin], **narrow-spectrum cephalosporins** [cefazolin, cephalothin, cefamandole, cefuroxime, and others])	Yes	US and world-wide
D (serine)	OXA-1 OXA-2	Enterobacteriaceae and NFs	Same as above **PLUS** cloxacillin, methicillin, and oxacillin	Variable	Europe

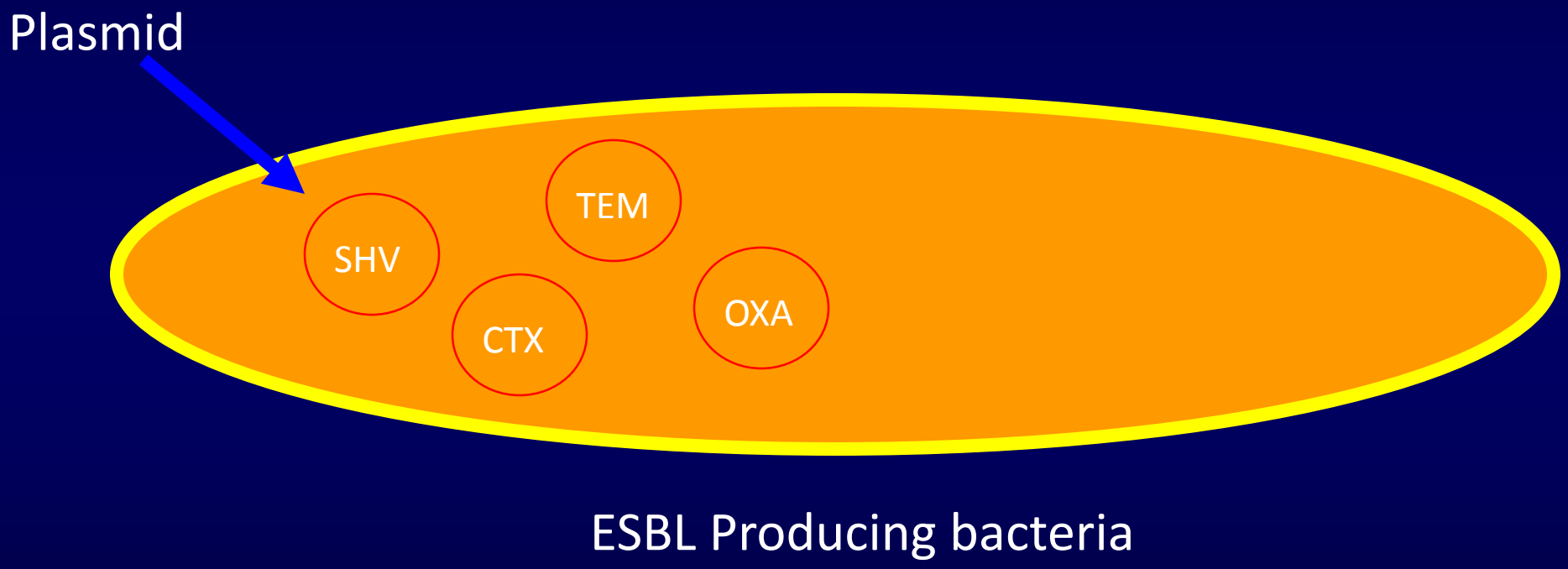
Ambler Class (active site)	Group example	Host Organism	Substrates	Inhibition by BLI	Region
Extended spectrum ß-lactamases					
A (serine)	TEM-10 TEM-12 TEM-26 SHV-5 SHV-12	Enterobacteriaceae and non-fermenters	Same as broad spectrum ß-lactamases **PLUS** and **3rd generation** oxyimino-cepahlosporins (cefotaxime, cefpodoxime, ceftazidime, and ceftriaxone) and **monobactam** (aztreonam)	Yes	US and worldwide
A (serine)	CTX-M-15	Enterobacteriaceae and non-fermenters	Same as above (variable activity against aztreonam) **PLUS 4th generation oxyimino-cepahlosporin** (cefepime; for some enzymes)	Yes	US and worldwide

NOTE: CTX-M-15 typically also co-express fluoroquinolone resistance

Ambler Class (active site)	Group example	Host Organism	Substrates	Inhibi-tion by BLI	Region
C (serine)	AmpC	Mainly found it *Enterobacter* spp., *Citrobacter* spp., *P. aeruginosa* (can also be found in other enterobacteriaceae and NFs)	Same as CTX-M- ESBL **PLUS 2nd generation cephamycin cepahlosporins** (cefotetan, cefoxitin, and others)	No	US and worldwide
D (serine)	OXA-10 OXA-11	Mainly found in *P. aeruginosa* (can also be found in other enterobacteriaceae and NFs)	Same as CTX-M- ESBL group	Vari-able	Europe

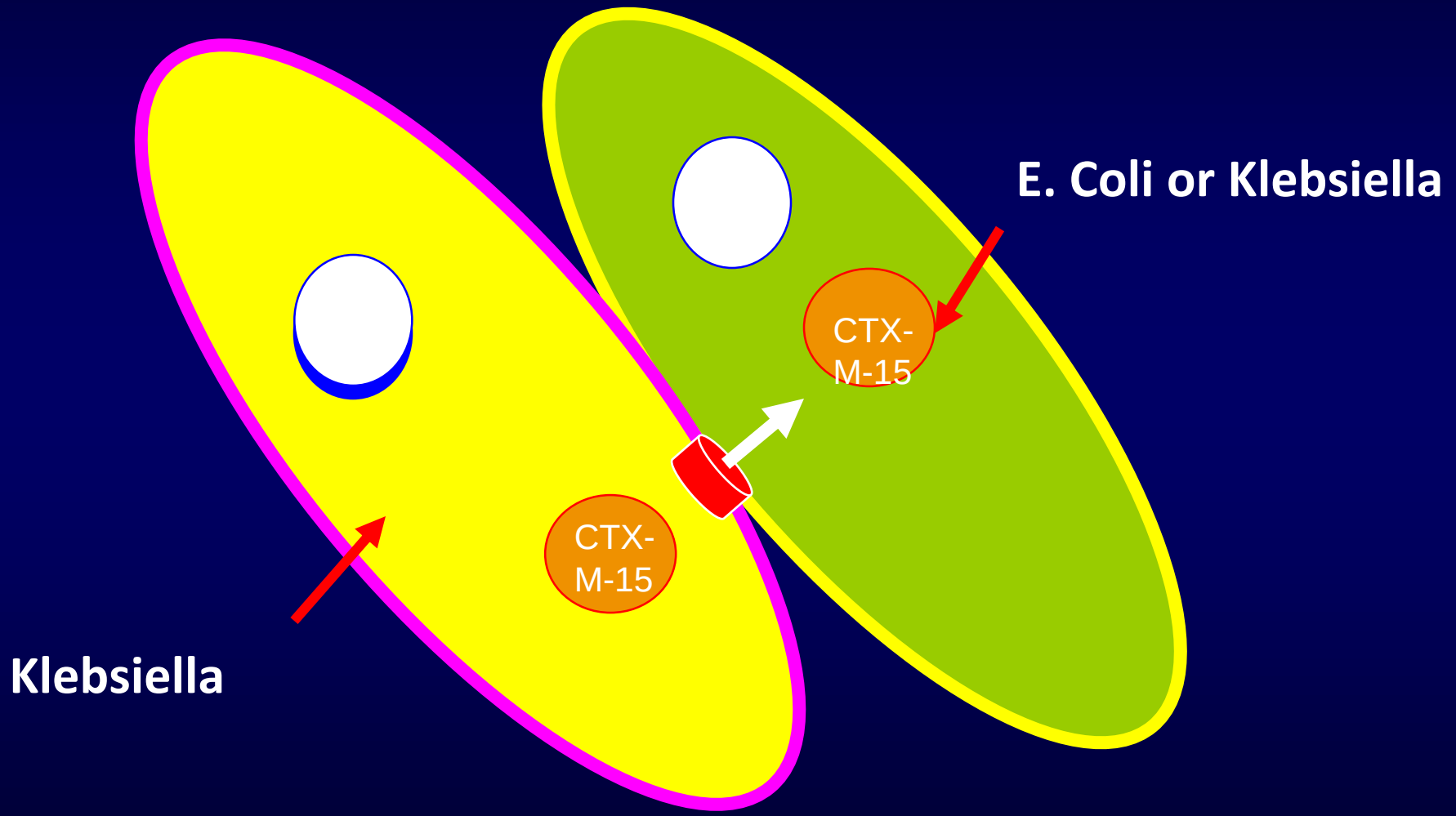
Table adapted from:
Kanj et al.Mayo Clin Proc. 2011; 86(3):250-259.
Jacoby et al. NEJM. 2005; 352 (4): 380-288.

Heterogeneous in Nature



Difficult to detect in a clinical laboratory!!

Plasmid Transfer



Who Can Carry ESBLs?

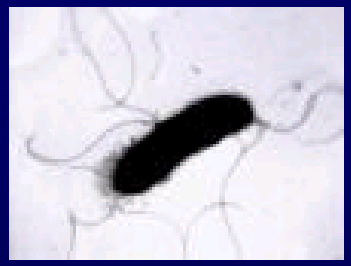
ESBLs found exclusively in **Gram Negative Organisms**

ESBLs with Clinical and Laboratory Standards Institute (CLSI) recommended screening tests:

Klebsiella pneumoniae

Klebsiella oxytoca

Escherichia coli



Found in many other gram negatives, including:

Salmonella, Proteus, Enterobacter, Citrobacter, Serratia, and Pseudomonas spp.

Treatment Options
and
Human Trials

Limited Clinical Data

- There is limited clinical data on treatment options for infections caused by ESBL producers
- To date, no randomized, controlled trials have been conducted to determine the optimal treatment for patients with serious infections
- Much of the evidence currently available stems from small studies that compile and compare cases, mostly from outbreak settings, treated with different antibiotic agents

ESBL Treatment

- Treating an ESBL infection can be very challenging
- Options for treatment are very limited
- ESBL infections associated with poor outcomes

Treatment decisions should be based on based on local antimicrobial resistance patterns and consult of local infectious diseases specialists!!

Drugs with Most Reliable Activity Against ESBL-producing Enterobacteriaceae

Carbapenems –

only consistently proven tx option

Possibly

Fosfomycin, piperacillin/tazobactam (inoculum effect) , cefepime (inoculum effect) amikacin, tigecycline (not *P. mirabilis*), fluoroquinolones

Pitout JD. Lancet ID 2008 Mar; 8:159-166.

Carbapenems

- Observational study of 85 episodes of bacteremia due to ESBL-producing *K. pneumoniae*.

Results:

- 27 patients treated with carbapenem monotherapy (imipenem in 24 and meropenem in 3) Carbapenem one death (3.7%) at 14 days.
- cephalosporin monotherapy or a beta-lactam/beta-lactamases inhibitor combination such as piperacillin-tazobactam four deaths in nine patients (44%).
  - Reason for failure- Inoculum effect? Under-dosing?

Conclusion: Using a cephlosporin as to treat an infection caused by an ESBL organism was associated with extremely high mortality. Use of a carbapenem (primarily imipenem) was associated with a significantly lower 14-day mortality than was use of other antibiotics active in vitro.

Paterson et al. Clin Infect Dis 2004 Jul 1;39(1):31-7

Treatment Options

- Treatment with imipenem or meropenem has produced the best outcomes in terms of survival and bacteriologic clearance. Clinical data for the use of doripenem in infections with organisms that produce ESBL are limited but overall suggest equivalent efficacy with imipenem or meropenem.
- Clinical data for ertapenem use for ESBL infections is limited but growing.
  - In two retrospective studies patients with bloodstream infections due to Enterobacteriaceae that produced ESBLs, treatment with ertapenem was associated with similar mortality rates as treatment with meropenem and imipenem.

Collins VL et al. AAC. 2012 Apr;56(4):2173-7.
Lee NY et al. AAC. 2012;56(6):2888.

Best Options for the Treatment of ESBLs

- Imipenem 500 mg IV q6 hours to 1 g IV q8 hrs
- Meropenem at 1 g IV q8 hours
- Doripenem 500 mg IV q8 hours

- Ertapenem at 1 g IV q24h *may be* used successfully for ESBL-associated bacteremia

- No data from randomized controlled trials support their use for this purpose.

β-Lactam/β-Lactamase Inhibitor Combinations

- Tazobactam, appears to be the most potent
  - High concentrations in the urinary tract
  - May be used successfully in the treatment of UTIs and in other infections in which a low bacterial inoculum is expected
- A retrospective study of bloodstream infections due to ESBL-producing organisms showed that patients treated with piperacillin-tazobactam had the same mortality as those treated with carbapenems (Rodríguez-Baño et al CID. 2012;54(2):167)
  - Source mostly low inoculum infections (UTI or biliary tract)
- Given study limitations piperacillin-tazobactam should generally be avoided for serious infections

Tigecylcine

- First member of the glycylcyline class of antimicrobials, is a derivative of the tetracycline
- Tigecylcine has *in vitro* activity against > 95% of ESBL-producing *E. coli* and *K. pneumoniae*
- Very limited clinical data
  - Pooled data from two phase 3 studies, tigecycline was associated with a 80% (12/15) bacteriologic eradication rate for the treatment of intra-abdominal infections caused by ESBL-producing *E. coli* or *K. pneumonia*. (Stein et al; CID 2006;43(4):518-24)
  - In a systematic review of ten studies, a favorable outcome was observed in 69.7% (23/33) patients treated with tigecycline for infections caused by organisms with advanced resistance, including ESBL and carbapenemase producers. (Kelesidis et al; JAC 2008;62(5):895-904)

Tigecylcine

- Tigecycline accumulates in the intracellular and tissue compartments rapidly after intravenous infusion
  - Peak concentration of tigecycline in the blood (around 1 µg/ml) is similar to the MIC of many MDR Gram-negative organisms
  - Only 22% of tigecycline is excreted in the urine as the active drug
- AVOID as monotherapy for serious bloodstream and urinary tract infections
- Traditional dose - 100mg loading dose IV, then 50 mg IV qday
- High dose - 200 mg loading dose, then 100mg qday
- Gastrointestinal effects may be more severe at higher doses and are usually dose-limiting

Lynch. Exper Opin Pharmther. 2013;14(2):199-210.

Fosfomycin

- MOA: Cell wall & bactericidal activity against gram-positive and gram-negative pathogens
- Approval and Dose: approved by the FDA for the treatment of uncomplicated UTI at a single oral dose of 3 g
- In vitro: active against ESBL-producing *E coli* and *K pneumoniae isolates*
- Clinically: The drug appears to be useful in the oral treatment of ESBL-associated infections of the urinary tract, and initial clinical studies are promising.

Falagas JD. Lancet ID 2010 Jan; 1:43-50.

Fosfomycin

- Limited clinical data supports the use of oral fosfomycin (3 grams q48-72h for 3 doses) in the treatment of ESBL UTIs
  - Review of two clinical studies, PO fosfomycin was clinically effective in 93.8% (75/80) of patients for complicated and uncomplicated lower UTIs caused by ESBL *E. coli*. (Senol et al; 2010;22(5):355-7)
  - Prospective observational study, carbapenem and fosfomycin use for treatment of complicated lower UTIs due to ESBL *E coli* were associated with similar rates of clinical success (95.0% [19/20] vs. 77.8% [21/27]; P>0.05) and microbiological success (80.0% [16/20] vs. 59.3% [16/27]; P>0.05). (Falagas et al; 2010;65(9):1862-77).
- For systemic infections, IV formulations of fosfomycin may be effective, however IV formulation not available in the US.

Fluoroquinolones

- ESBL-producing organisms often co-express resistance to fluoroquinolones.
  - Fluoroquinolone resistance rates range from 55 to 100% among CTX-M-producing Enterobacteriaceae from different areas of the world.
- Fluoroquinolones achieve high urinary concentrations and may be an option for UTIs due to ESBL-producing organisms that remain susceptible.
- Clinical data for fluoroquinolone use for serious infections is sparse.

First Author (Year) r	Design	Infection site and organism	Findings
Endimiani et al. (2004)	Retrospective	ESBL-producing *K. pneumoniae* bacteremia (TEM-52)	**Clinical Failure:** Imipenem and meropenem: 2/10 (20%) Ciprofloxacin: 5/7 (71%) P=0.03
Kang et al. (2004)	Retrospective	ESBL-producing *E. coli* or *K. pneumoniae* bacteremia	**Mortality:** Carbapenem: 8/62 (12.9%) Ciprofloxacin: 3/29 (10.3%)
Paterson et al (2004)	Prospective Observational	ESBL-producing *K. pneumoniae* bacteremia	**Mortality:** Imipenem and meropenem: 1/27 (3.7%) Ciprofloxacin: 4/11 (36.3%)

Aminoglycosides

- Plasmids that carry genes for ESBLs frequently also have genes encoding resistance to aminoglycosides and potential for emergence of on-treatment resistance
- Susceptibility to amikacin is the highest among ESBL producers
- Aminoglycosides generally avoided and limited published clinical data.

First Author (Year)	Design	Infection site and organism	Findings
Kim et al. (2002)	Retrospective	ESBL-producing *E. coli* and *K. pneumoniae* bacteremia	**Clinical failure:** 8/15 (53%)
Kim et al. (2002)	Retrospective	ESBL-producing *K. pneumoniae* bacteremia	**Mortality:** Imipenem: 2/12 (16.7%) Aminoglycosides: 2/4 (50.0%)
Paterson et al (2004)	Prospective Observational	ESBL-producing *K. pneumoniae* bacteremia	**Mortality:** Imipenem and meropenem: 1/27 (3.7%) Amikacin: 0/2 (0%)

Clinical Outcomes

Patients with ESBL infections have shown a trend towards:

1. Higher mortality
2. Longer hospital stay
3. Greater hospital expenses
4. Reduced rates of clinical and microbiologic response

Paterson et al. Clin Infect Dis 2004 Jul 1;39(1):31-7
Lautenbach et al.Clin Infect Dis. 2001;32(8):1162
Meyer et al. Ann Intern Med. 1993;119(5):353.
Tumbarello et al. AAC. 2006;50(2):498.

How is it Spread?

Poor personal hygiene

(especially after using the washroom)

- The spread of ESBL/CREs occurs most commonly through:
  1. Direct contact with someone with ESBL/CRE
  2. A contaminated environment
  3. Hands of care providers.
- Infection Control - Careful cleaning of areas that might be touched by hands is important to reduce the spread of this organism in a facility.
  - Faucets, door handles, bedrails, bathrooms, and other surfaces that people touch must be cleaned regularly to prevent the spread of ESBL E. coli.

Fighting "Superbugs": A focus on the epidemiology and treatment of ESBLs

Haley J Morrill, Pharm.D.
Antimicrobial Stewardship Fellow

Rhode Island Infectious Diseases (RIID) Research Program of the Providence Veterans Affairs Medical Center and University of Rhode Island College of Pharmacy