ashp® MIDYEAR 2016
Clinical Meeting & Exhibition

281-L01: Creating Positive Outcomes for Gram-Negative Infections: Deciphering Antibiograms for Best Results (Part 1)

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Disclosures

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships, except:

- **Christopher Bland** - ALK Abello: Consultant, Grant/Research Support; Merck: Speaker's Bureau

- This disclosure does not relate to the content or objectives of this presentation topic:
  - Consultant: BioQ® Pharma
    - Specialty pharmaceutical company focused on infusible drugs

Objectives

- By the end of the session, the audience should be able to:
  - Identify markers of Gram-negative resistance based on current antibiogram
  - Compare Gram-negative resistance rates with underlying mechanisms of resistance

My level of knowledge regarding bacterial resistance is:

A. Mastery
B. Confident
C. Somewhat confident
D. Limited/None

AmpC resistance in E. coli results in resistance to all the following agents EXCEPT:

A. Amoxicillin

B. Amoxicillin-clavulanate

C. Aztreonam

D. Ceftriaxone

My level of knowledge regarding antibiograms

A Mastery

B Confident

C Somewhat confident

D Limited/None

Are you involved in creating your institution's antibiogram?

A YES

B NO

Which of the following contributes to antimicrobial resistance

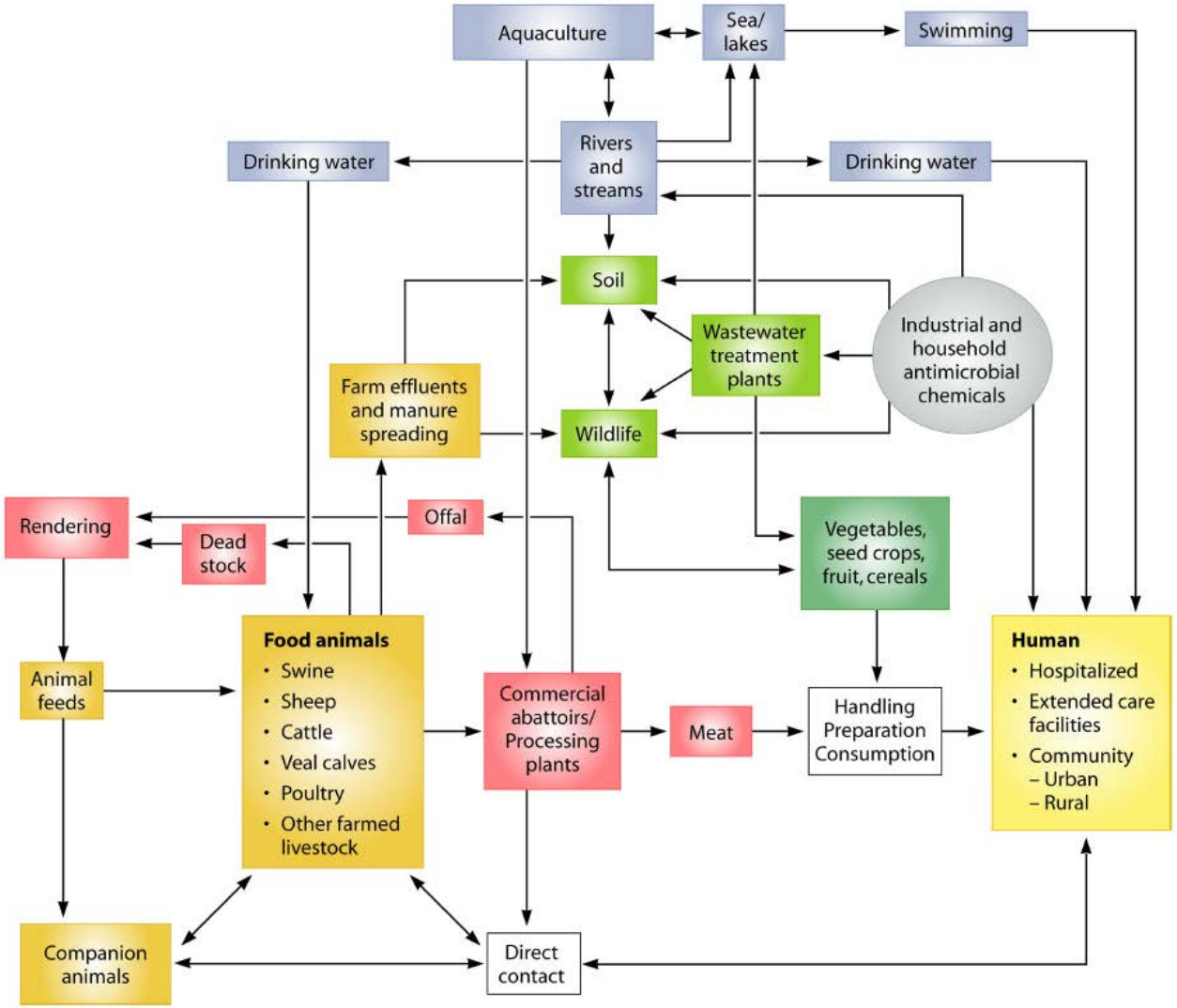
A. Human use of antibiotics

B. Use of antibiotics in livestock

C. Bacterial survival in nature

D. New antibiotic discovery

Antibiotics



Davies J. Microb and Molec Bio Rev 2010;74(3):417-433 Figure 4

History

- Oldest traces of tetracycline dates back to 350 AD found in the skeleton remains from an ancient Sudanese Nubian
- 1885, Escherichia coli first discovered
- 1930 sulfonamide resistance was first discovered

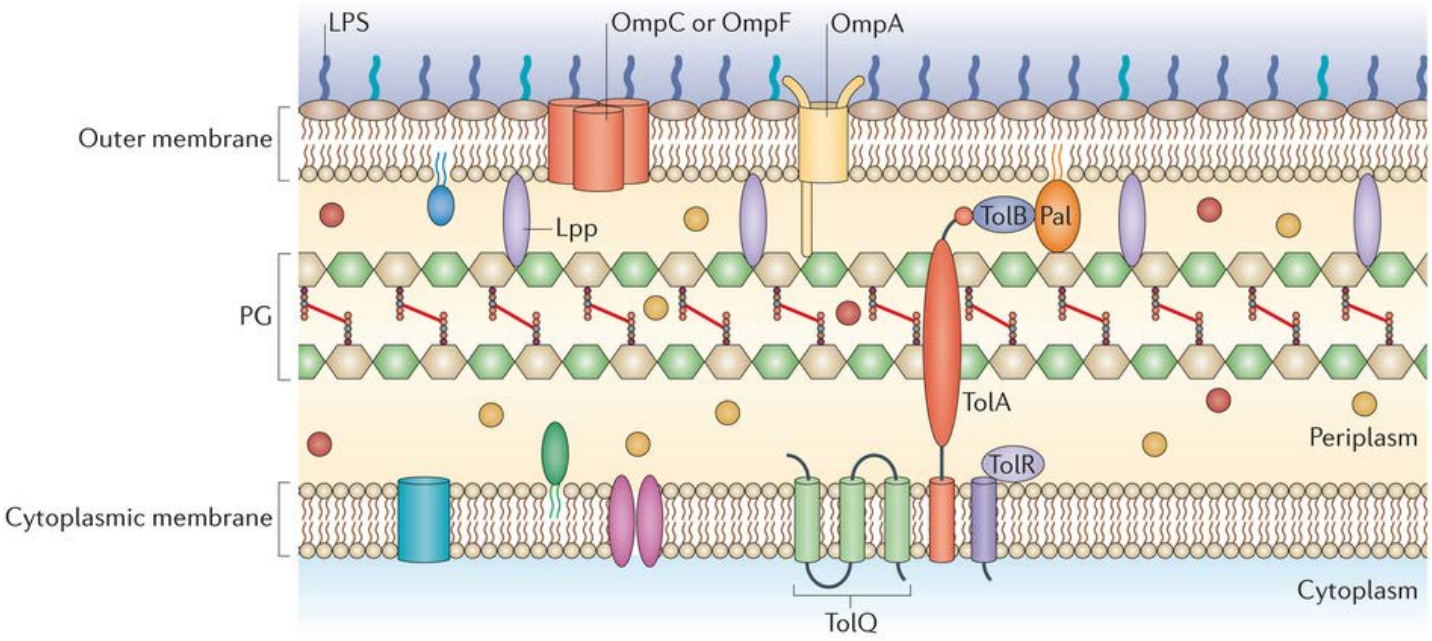
Davies J. Microb and Molec Bio Rev 2010;74(3):417-433
Jacoby Clin Micro Rev 2009;22(1):161-182

Bacterial Resistance - Review

- 4 major mechanisms of bacterial resistance:
  - Cell wall permeability
  - Enzymatic degradation
  - Alteration of the target binding site
  - Efflux pumps

Bacterial Resistance - Review

- Cell Wall Permeability:
  - Outer-membrane
    - Lipopolysaccharides (LPS)
    - phospholipid



Nature Reviews | Microbiology

Bacterial Resistance Review
Entry

- Antibiotics enter via one or both methods:
  - Diffusion through the membrane
    - Aminoglycosides, macrolides, fluoroquinolones, and tetracyclines
  - Porin mediated
    - Beta-lactams, Fluoroquinolones, Tetracyclines, aztreonam, Cephalosporins, and Carbapenems

Du. Trends in Micro 2015;23(5): 311-319
Iredell J. BMJ. 2016 Feb 8;352

Bacterial Resistance Review
Entry

- Resistance occurs due to alteration in the porins such as OprD (P. aeruginosa), OmpK37 (K. pneumoniae), and OmpN (E. coli)
- Alterations in porins may result in:
  - Absence of normal porins
  - And/or replacement with smaller porins

Du. Trends in Micro 2015;23(5): 311-319
Iredell J. BMJ. 2016 Feb 8;352

Bacterial Resistance Review
Degradation

- Enzymatic degradation via enzymes which are able to hydrolyze beta-lactams and altered binding sites
- Beta-lactamases are believed to be derived from Penicillin-Binding-Proteins (PBPs)
  - Penicillinase/Beta-lactamase
  - Extended Spectrum Beta-Lactamase (ESBL)
  - Carbapenemase
- In some cases, PBP is modified to prevent binding of antibiotic to target without affecting the antibiotic agent structure

Du. Trends in Micro 2015;23(5): 311-319
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Bacterial Resistance Review
Binding Site

- Alteration of target binding site
  - Most common method of bacterial resistance
  - Alteration of PBP, topoisomerase, 70s ribosome, PABA, D-alanine D-alanine
  - Resistance to various classes of antibiotics

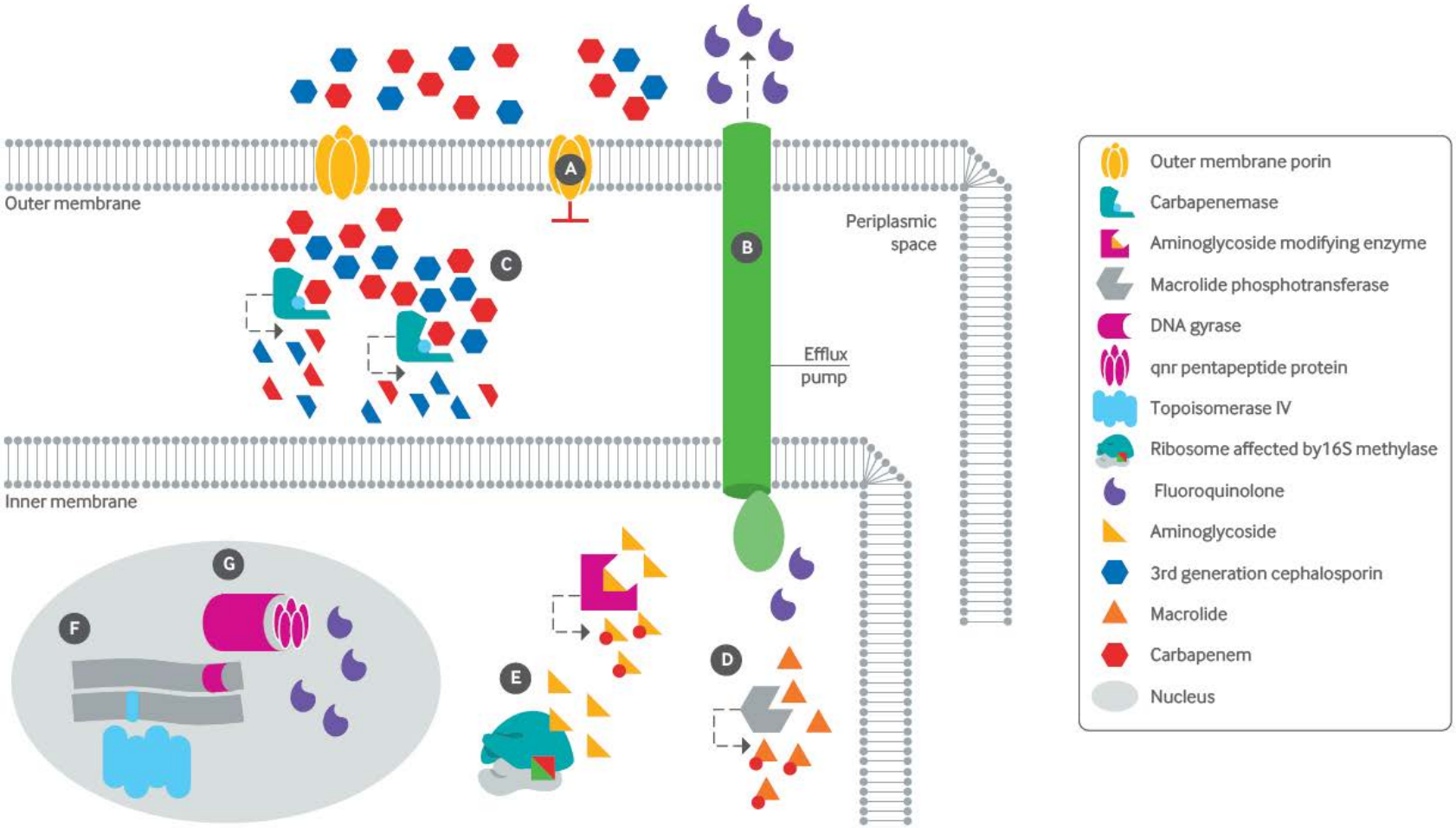
Du. Trends in Micro 2015;23(5): 311-319
Iredell J. BMJ. 2016 Feb 8;352

Bacterial Resistance Review
Efflux

- Some organisms are able to utilize efflux pumps which are able to eject antibiotics from inside the bacteria back into the environment
- 5 families of transmembrane transporters have been identified
  - ATP-Binding Cassette transporters (ABC)
  - Major facilitator (MFS)
  - Small Multidrug Resistant (SMR)
  - Resistance/Nodulation/Cell Division (RND)
  - Multidrug and Toxic-compound Extrusion (MATE)

Du. Trends in Micro 2015;23(5): 311-319
Iredell J. BMJ. 2016 Feb 8;352

Bacterial Resistance



Iredell J. BMJ. 2016 Feb 8;352 Figure 4

History of GN-Resistance

- Fleming discovered penicillin in 1928 and failed to purify it by 1940
- Florey and Chain purified penicillin in 1940
- First AmpC beta-lactamase discovered in 1940 in an E. coli isolate
  - Penicillin was mass produced in 1945

Davies J. Microb and Molec Bio Rev 2010;74(3):417-433
Jacoby Clin Micro Rev 2009;22(1):161-182

Definitions: AmpC

- Gram-negative organisms
- Chromosomally/plasmid mediated
- Serine beta-lactamase
- Resistance genes: CMY, FOX, ACC, LAT, MIR
- Confers resistance to:
  - Penicillin and penicillin derivatives
  - Cephalosporins 1st-3rd generations (including Cephalomycins)
  - Beta-lactamase inhibitors (clavulanate>sulbactam> tazobactam)

Doi Y. Semin Resp Crit Care Med 2015;36(1):74-84

Definitions: AmpC

- AmpC remain susceptible to:
  - 4th generation cephalosporins (cefepime)
  - Carbapenems
  - Aztreonam
- Inducers of AmpC:
  - Penicillins, aminopenicillins, cephalosporins, and Carbapenems
  - Clavulanate (especially with P. aeruginosa)

Doi Y. Semin Resp Crit Care Med 2015;36(1):74-84

History of Gram-negative Resistance

- 1960, TEM-1 discovered in E. coli bacteremia in patient in Greece
  - TEM-1, TEM-2, and SHV-1 encode for beta-lactamase production
    - Resistance to penicillins, aminopenicillins, and 1-2 generation cephalosporins
- 1988, TEM-3 discovered which encodes for ESBLs
  - 2 amino-acid substitution compared to TEM-2
  - Additional resistance to 3rd generation cephalosporins

Datta 1965 Nature 208:239-244
Sougakoff 1988 FEMS Microbiol Lett. 56:343-348

History of Gram-negative Resistance

- 1989, CTX-M discovered in E. coli from a cancer patient
  - Resistant to 3rd generation cephalosporins especially cefotaxime
- 1992, inhibitor resistant TEM beta-lactamase were discovered
  - Resistance to clavulanate and sulbactam
  - Found in various Enterobacteriaceae including E. coli and K. pneumoniae

Rodriguez-Bano Expert Rev ov Anti-infective Ther 2008;671-688
http://www.lahey.org/studies/ Last Accessed 10/1/2016
Megged Pediatr Nephrol 2014;29(9)1583-7

Definitions: ESBL

- Extended Spectrum Beta-lactamase (ESBL)
  - Gram-negative organisms (most commonly Enterobacteriaceae, Pseudomonas spp, and Acinetobacter spp)
  - Plasmid mediated
  - Serine beta-lactamase
  - Resistance genes: TEM, SHV, CTX-M, and OXA
  - Confer resistance to most beta-lactams including:
    - Penicillins and penicillin-derivatives
    - Cephalosporins (except cephalomycins)
    - Monobactams (aztreonam)

Doi Y. Semin Resp Crit Care Med 2015;36(1):74-84

Definitions: ESBL

- ESBLs can also be resistant other antibiotic classes through concurrent resistance genes presence:
  - Aminoglycosides
  - Fluoroquinolones
  - Sulfamethoxazole/trimethoprim
- ESBLs may remain susceptible to:
  - Cephalomycins
  - Beta-lactamase inhibitors/Beta-lactams
- ESBLs are usually susceptible to:
  - Carbapenems

Rodriguez-Bano Expert Rev of Anti-infective Ther 2008;671-688
http://www.lahey.org/studies/ Last Accessed 10/1/2016
Megged Pediatr Nephrol 2014;29(9)1583-7

History of Gram-negative Resistance

- 1996, first Carbapenemase detected in K. pneumoniae in a patient in NC
- 1997, KPC spread to NYC
- 2001, OXA-48 Carbapenemase first discovered in a K. pneumoniae isolate in Turkey
- 2008 detection of new form of Carbapenemase called New Delhi metallo-beta-lactamase detected in E. coli and K. pneumoniae in a patient in Sweden from India
- 2011, first report of gram-negative resistance to colistin and tigecycline combination

Rodriguez-Bano Expert Rev ov Anti-infective Ther 2008;671-688
http://www.lahey.org/studies/ Last Accessed 10/1/2016
Megged Pediatr Nephrol 2014;29(9)1583-7
Mediavilla Antimicrob. Agents Chemother. 2011;55(2):593-9

Definitions - CRE

- Carbapenemase Resistant Enterobacteriaceae (CRE)
  - Most commonly associated with Enterobacteriaceae (especially K. pneumoniae), P. aeruginosa, and A. baumannii
  - Plasmid mediated resistance
  - Genes involved include: OXA, IMP, VIM, NDM

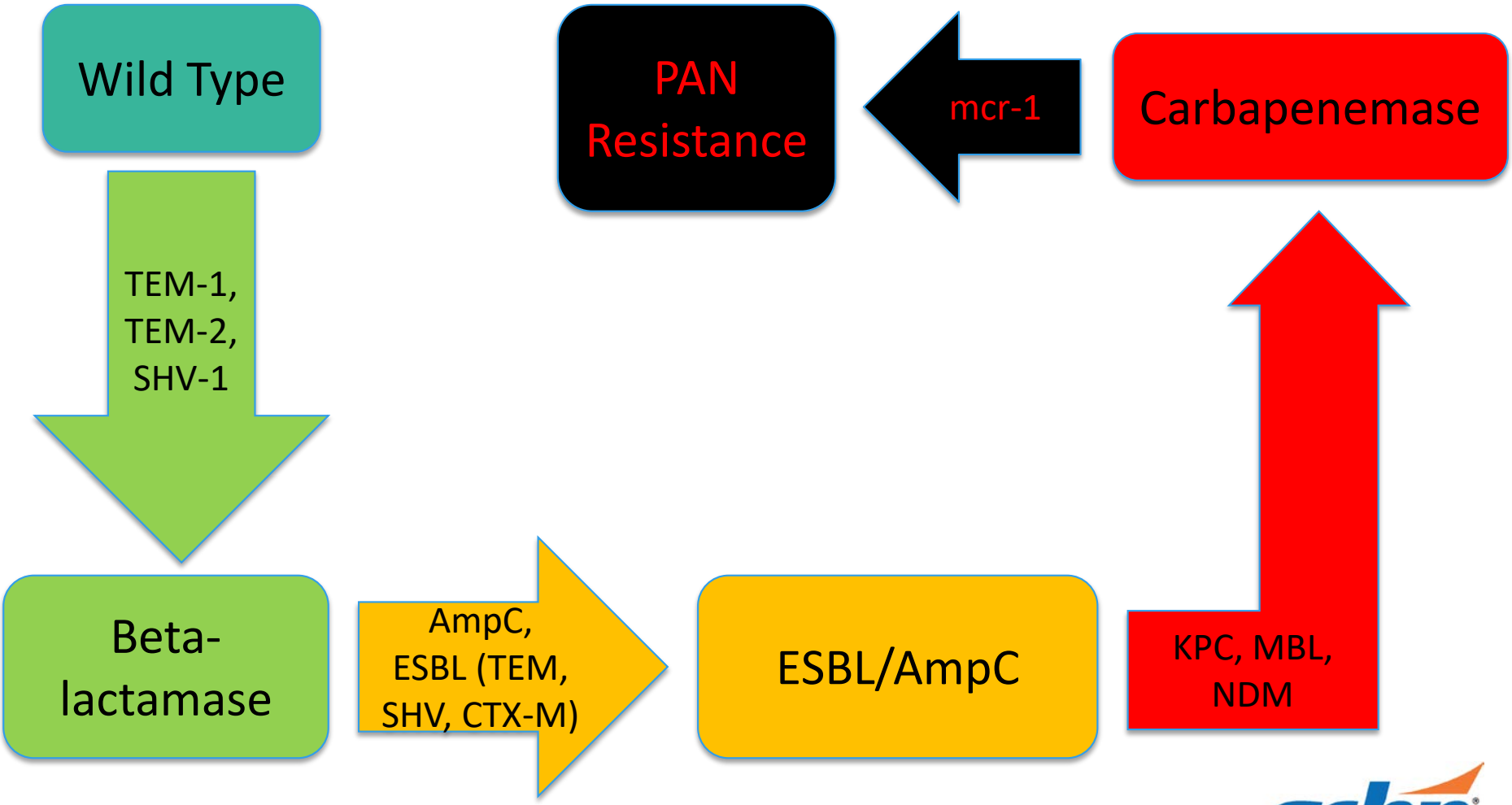
Doi Y. Semin Resp Crit Care Med 2015;36(1):74-84

Definition - CRE

- Confers resistance to:
  - Penicillins and penicillin-derivatives
  - Cephalosporins
  - Carbapenems
  - BLBLI combinations
- Also associated with resistance to:
  - Fluoroquinolones
  - Aminoglycosides
- CRE susceptible to:
  - Colistin
  - Polymixin E

Doi Y. Semin Resp Crit Care Med 2015;36(1):74-84

History of Gram-negative Resistance



ESKCAPE Organisms

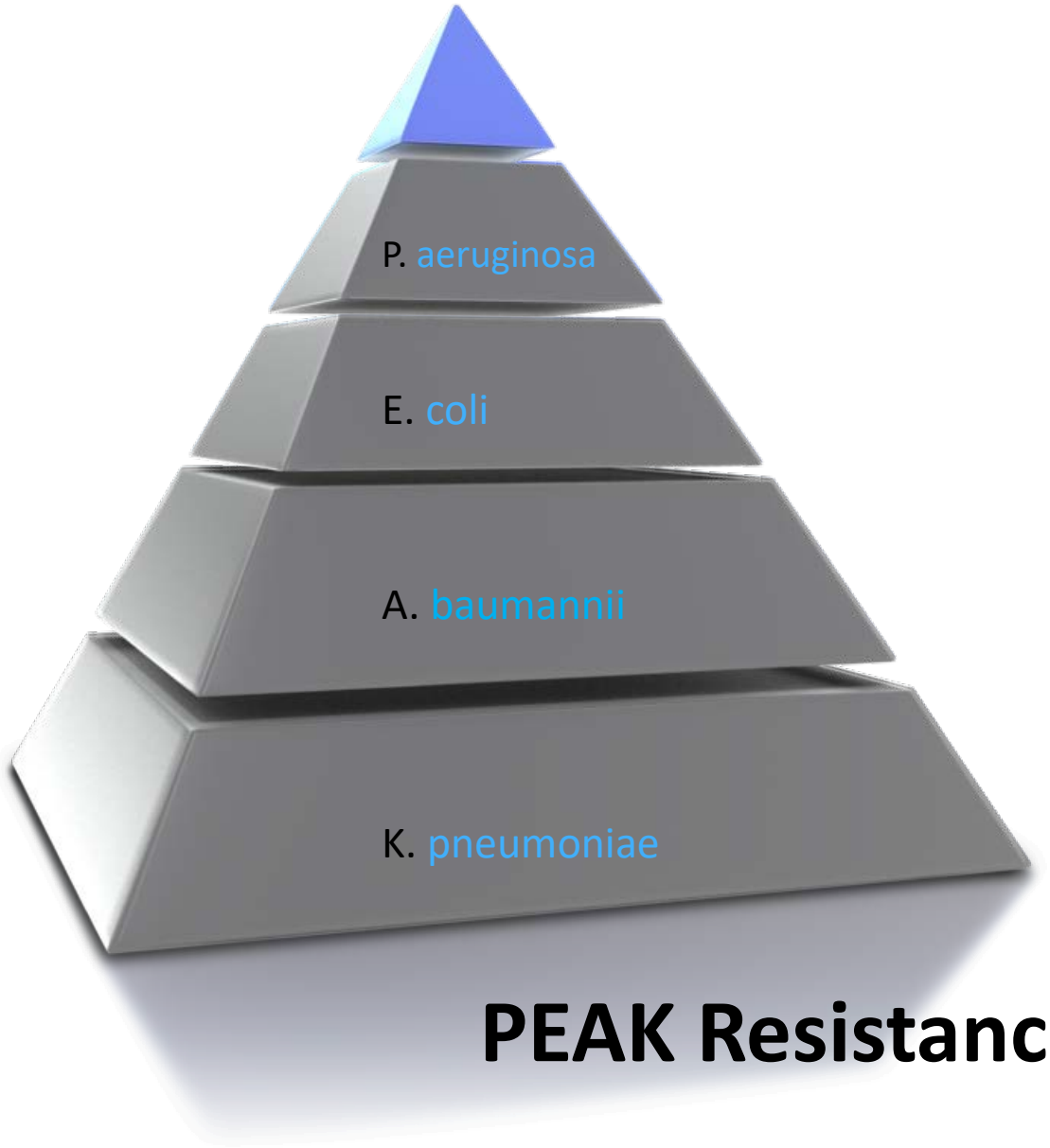
Acinetobacter baumannii

Pseudomonas aeruginosa

Enterobacteriacea

Klebsiella pneumoniae

Escherichia coli



PEAK Resistance

PEAK Organisms

- CDC resistance Rates

http://gis.cdc.gov/grasp/PSA/MapView.html (US)
http://resistancemap.cddep.org/DRI.php (international)

- CDC classification and recommendation

http://www.cdc.gov/drugresistance/biggest_threats.html

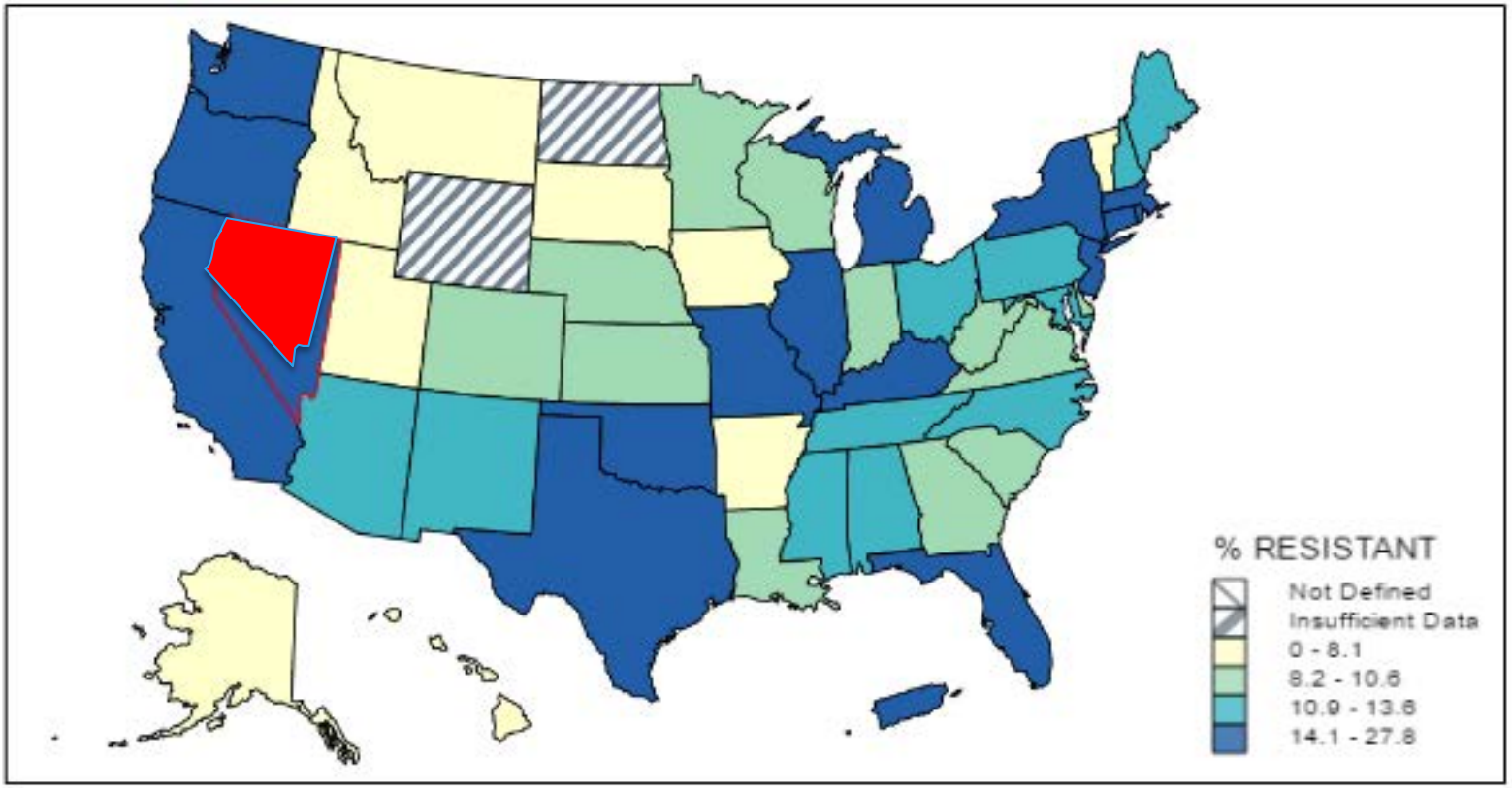
- Resistance Patterns
- Risk factors
- Infection control measures and recommendations

E. coli

- Escherichia coli (E. coli) is a Gram-negative rod
- Member of the Enterobacteriaceae group
- Predominant GN organism in the GI tract
- Implicated in:
  - Urinary tract infections
  - Gastroenteritis
  - Intra-abdominal infections
  - Bacteremia
  - Other

E. coli – Statewide (NV)

Extended-Spectrum Cephalosporin-Resistant *E.coli* | All HAIs | 2014



Note: HAIs include CAUTI, CLABSI, AND SSI; these account for about 25% of HAIs in acute care hospitals; values excludes some facility types (nursing homes) All data current as of 12/16/2015

Footnotes

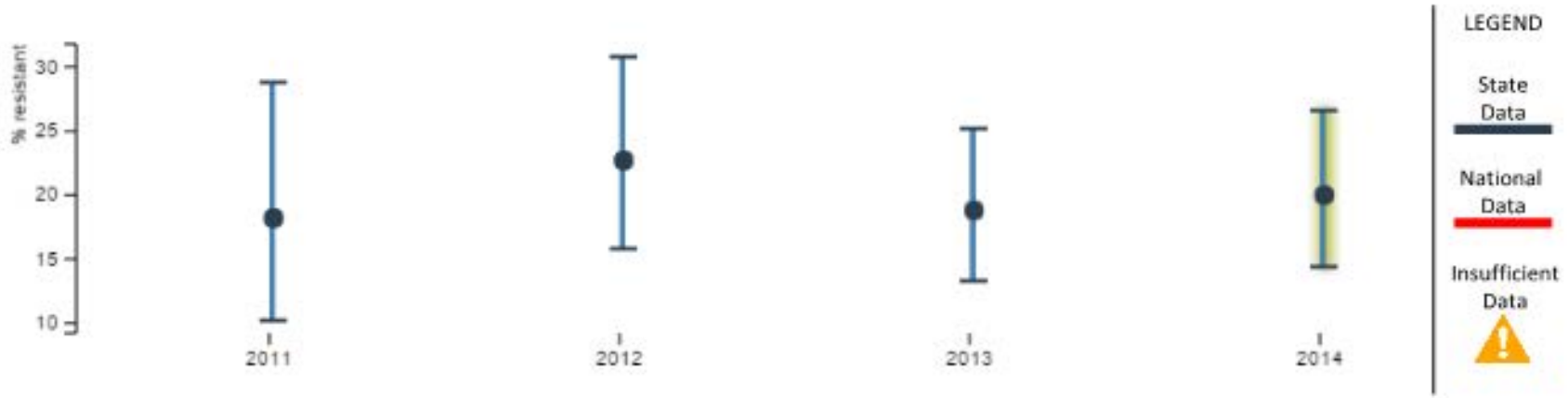
Insufficient Data - Between 1 and 19 isolates were tested for susceptibility. The percent resistance and accompanying data points cannot be calculated when the number of tested isolates is less than 20

Not Defined - Zero isolates were tested. The percent resistance and accompanying data points cannot be calculated when the

E. coli – Statewide (NV)

Extended-Spectrum Cephalosporin-Resistant *E.coli* | All HAIs | 2014

Nevada % Resistance Over Time



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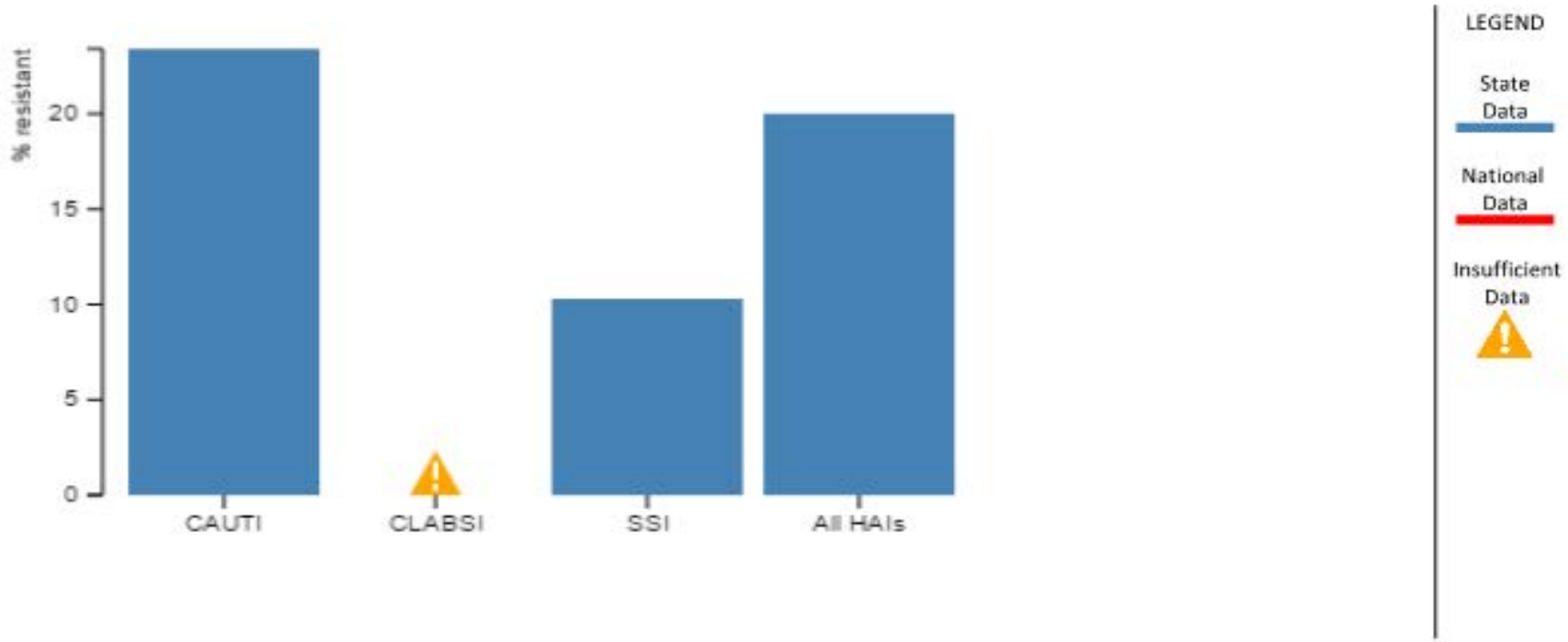
E. coli – Statewide (NV

Extended-Spectrum Cephalosporin-Resistant *E.coli* | All HAIs | 2014

Nevada % Resistance by Event Type



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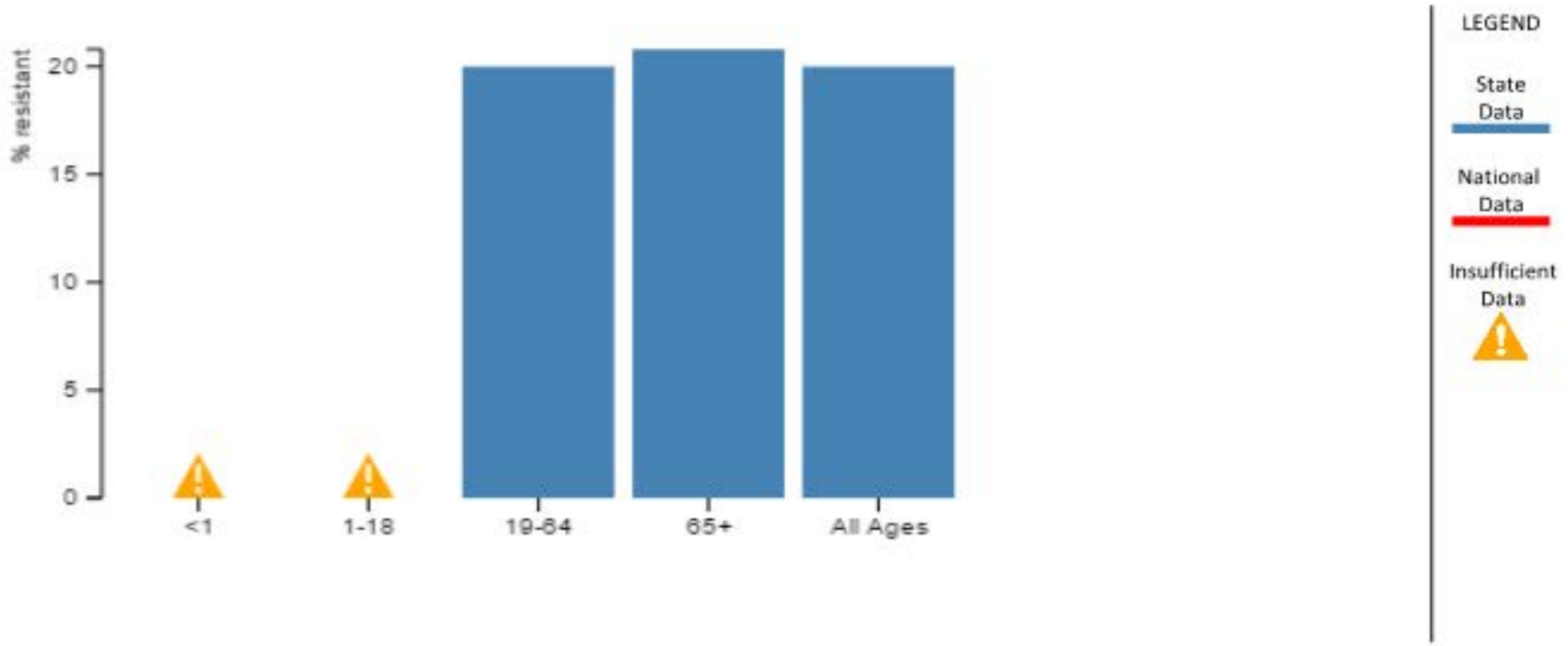
E. coli – Statewide (NV)

Extended-Spectrum Cephalosporin-Resistant *E.coli* | All HAIs | 2014

Nevada % Resistance by Age Group



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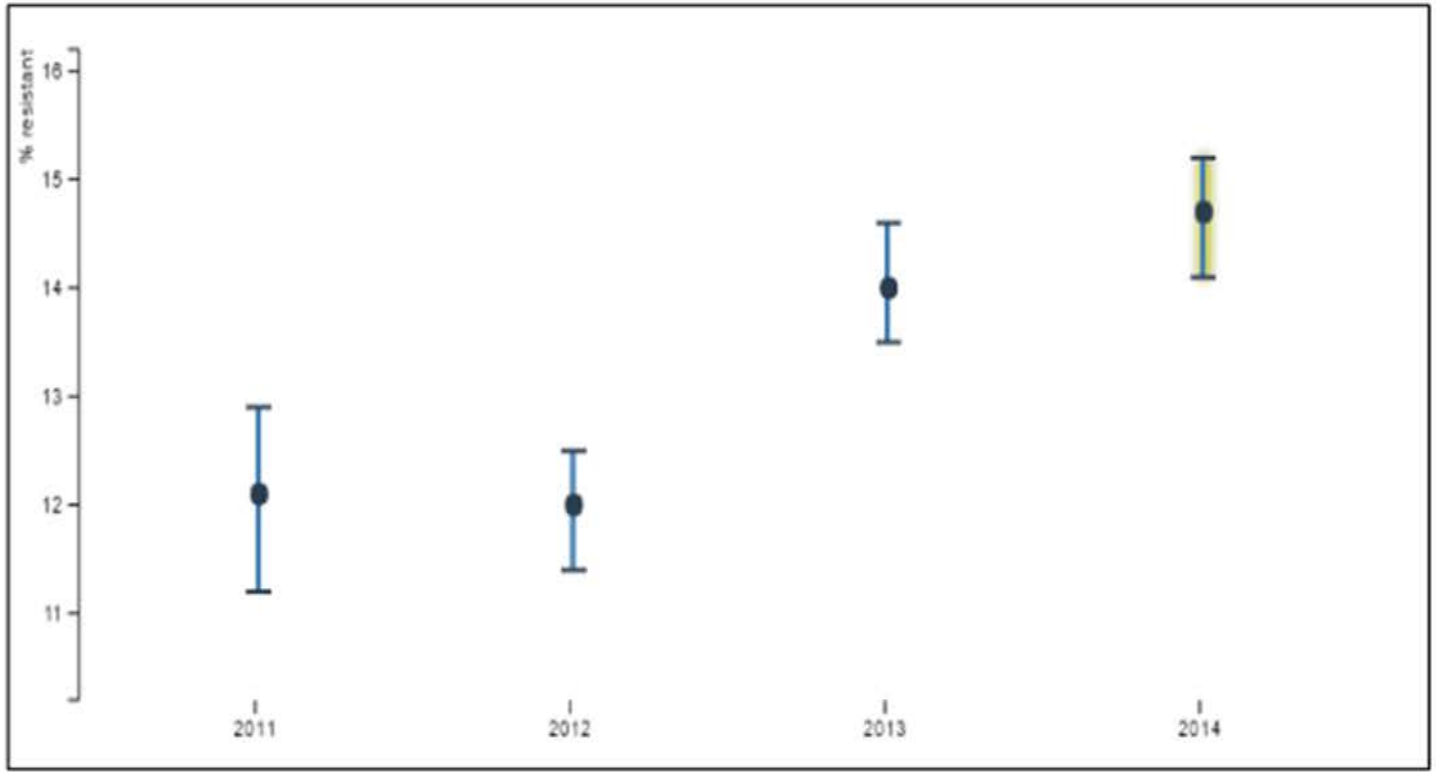
All data current as of 12/16/2015

E. coli - US

Extended-Spectrum Cephalosporin-Resistant *E.coli* | All HAIs | 2014

National % resistance over time



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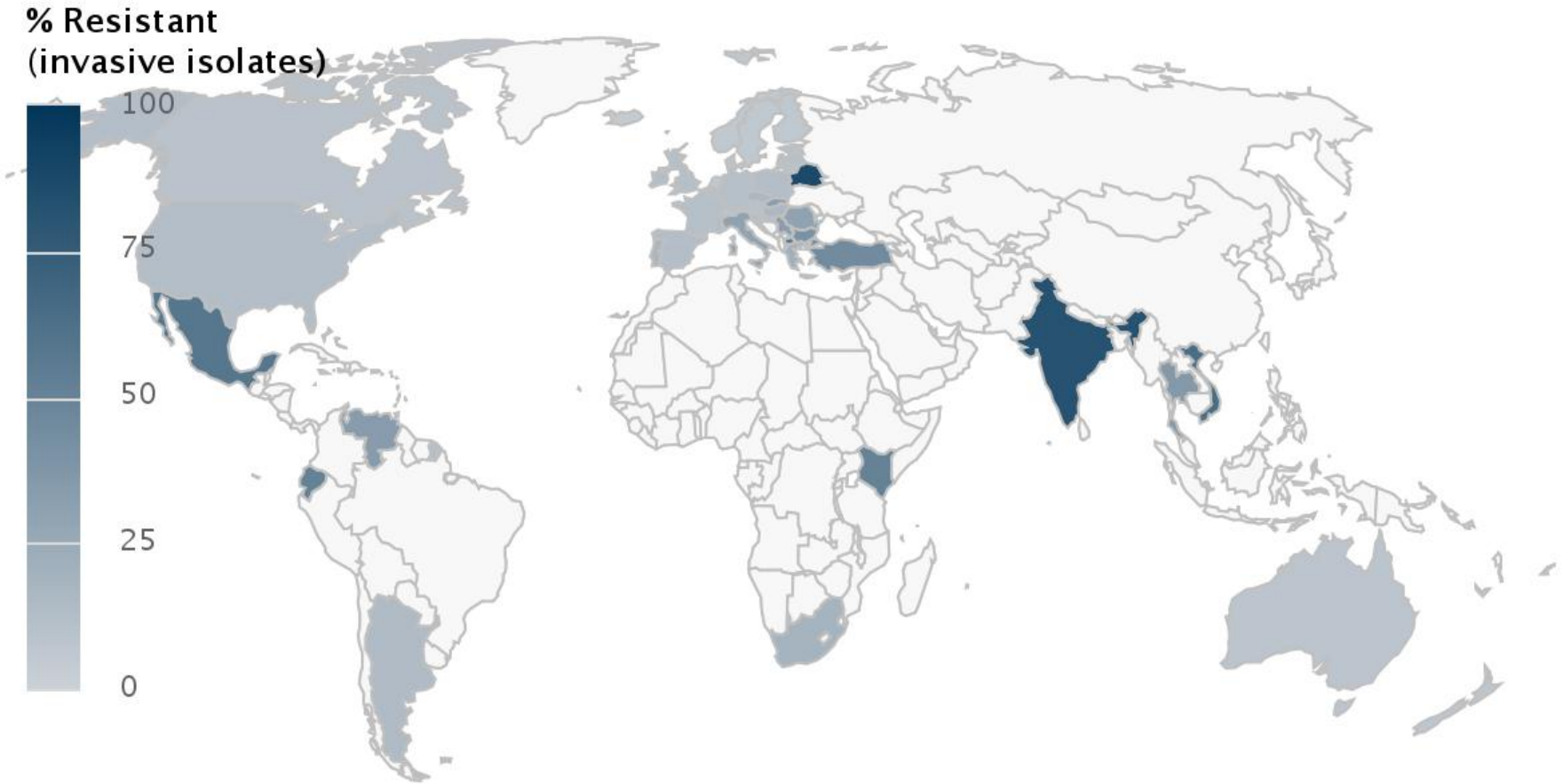
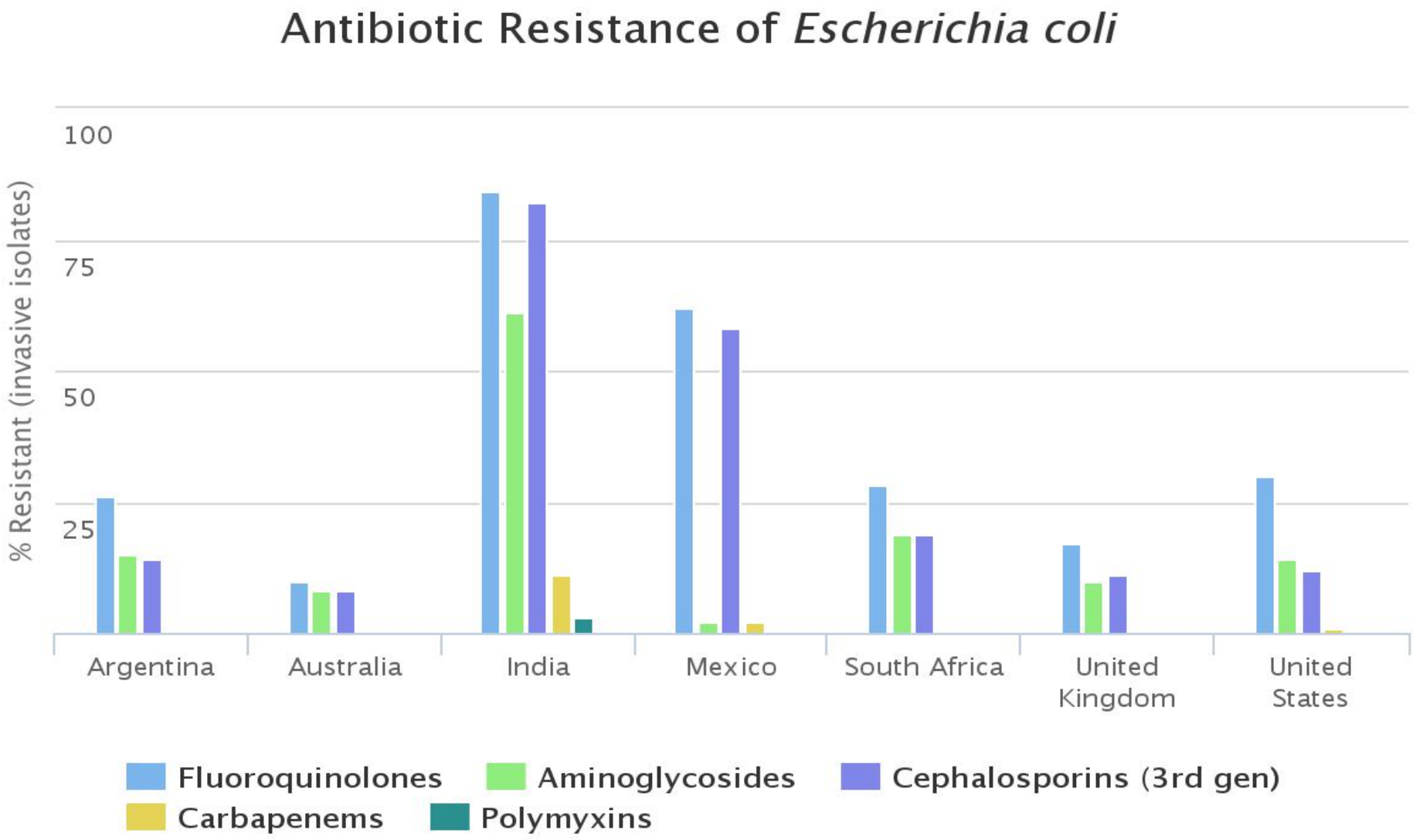
E. coli - Worldwide

Resistance of *Escherichia coli* to Cephalosporins (3rd gen)



Center for Disease Dynamics, Economics & Policy (cddep.org) © Natural Earth

E. coli - Worldwide



E. coli Resistance

- E. coli resistance in the US (2014)
  - ESBL: 14.7%
  - Fluoroquinolones: 34%
  - Multi-drug resistant (3 or more classes): 8%
  - Carbapenemase: 0.6%

E. coli

- E. coli can express some resistance through
  - TEM-1/2 and SHV-1 genes
    - Resistance to penicillin-derivatives, amino-penicillins, and 1-2 generation cephalosporins
    - Susceptible to beta-lactamase inhibitors such as clavulanate and sulbactam
  - OXA-1
    - Resistance to penicillin-derivatives, amino-penicillins, 1-2 generation cephalosporins, and beta-lactamase inhibitors
      - OXA-10 weakly hydrolyzes 3rd generation CS and aztreonam

Paterson Clin Microbiol Rev 2005;18(4):657-686

E. coli

- Can present as an ESBL or CRE
- ESBL genes:
  - CTX-M14/15
    - Resistance to 1-3rd generation cephalosporins
    - CTX-14: resistance to Cefotaxime>ceftazidime
    - CTX-15 belongs to international sequence type 13 (ST13): resistance to all 3rd generation CS
    - AmpC (CMY-13)
      - Resistance to all CS in addition to aztreonam

Bajaj Front of Microbiol 2016;7:1-14

E. coli

- NDM-1
  - Metallo-beta-lactamase resulting in Carbapenemase production
  - Resistance to all Carbapenems
  - Unable to hydrolyze aztreonam
  - Remains relatively rare in the US (<1% of all E. coli)

Bajaj Front of Microbiol 2016;7:1-14
Doi Y. Semin Respir Crit Care Med 2015;36(1):74-84

K. pneumoniae

- Gram-negative aerobic bacilli
- Member of the Enterobacteriaceae group
- Results in:
  - Pneumonia
  - Sepsis
  - Intra-abdominal infections
  - Others

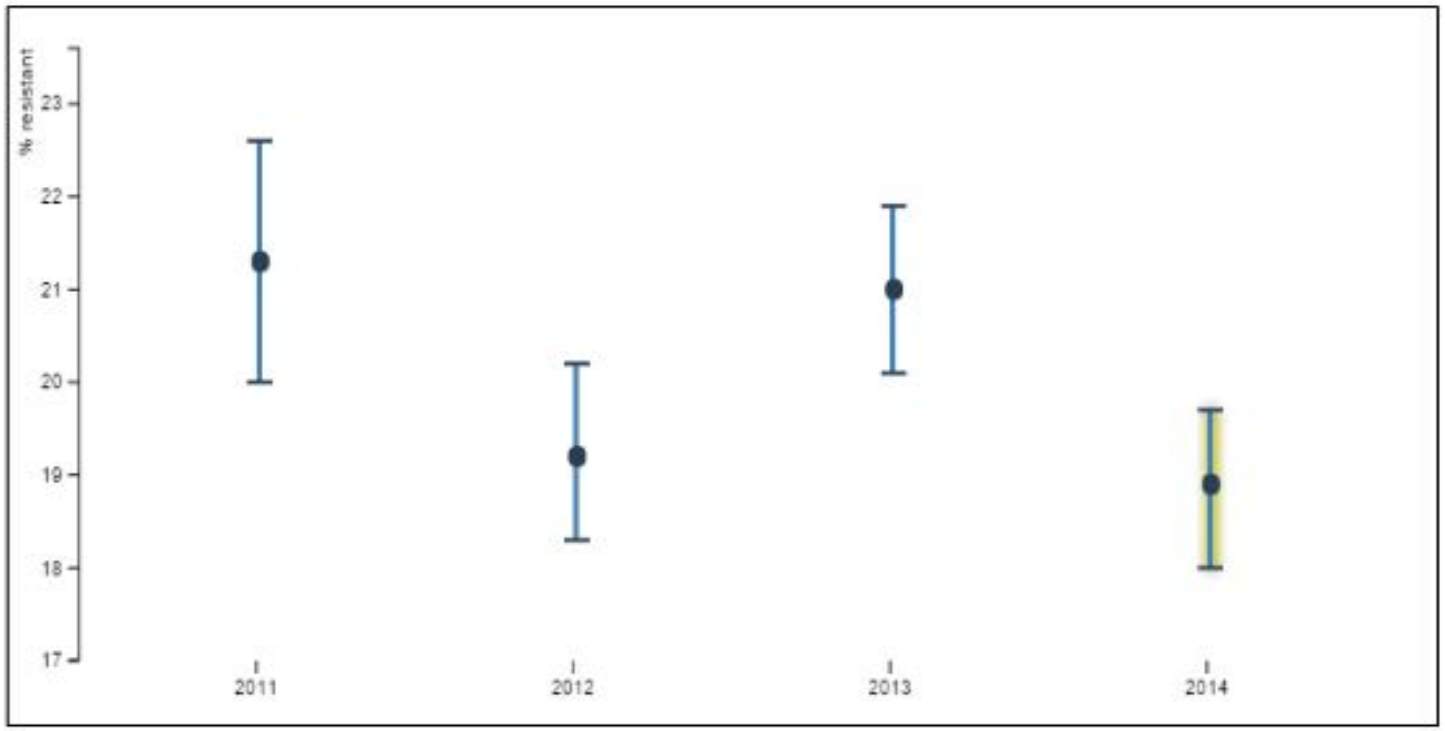
K. pneumoniae – ESBL US

Centers for Disease Control and Prevention

AR PATIENT SAFETY ATLAS

Extended-Spectrum Cephalosporin-Resistant *Klebsiella* spp. | All HAIs | 2014

National % resistance over time



NHSN

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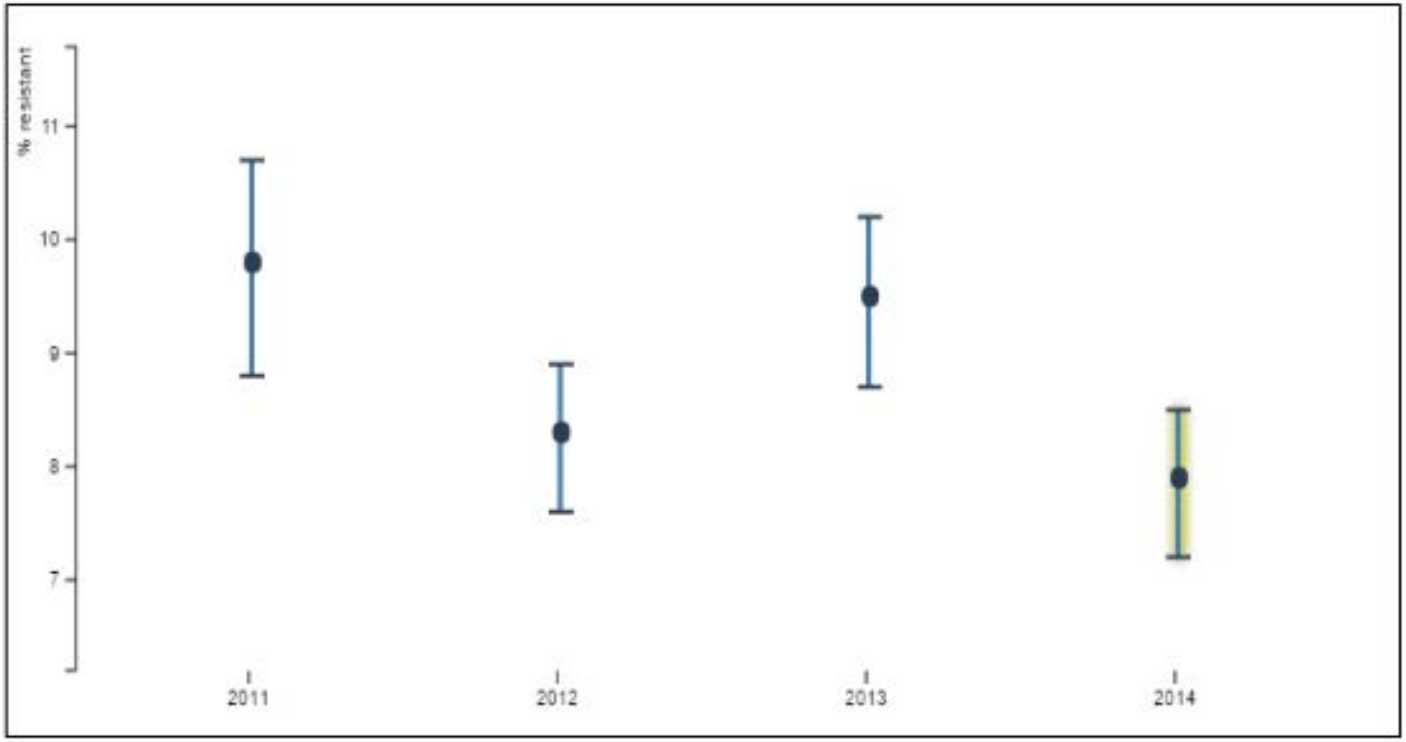
K. pneumoniae – CRE US

Carbapenem-Resistant *Klebsiella* spp. | All HAIs | 2014

National % resistance over time



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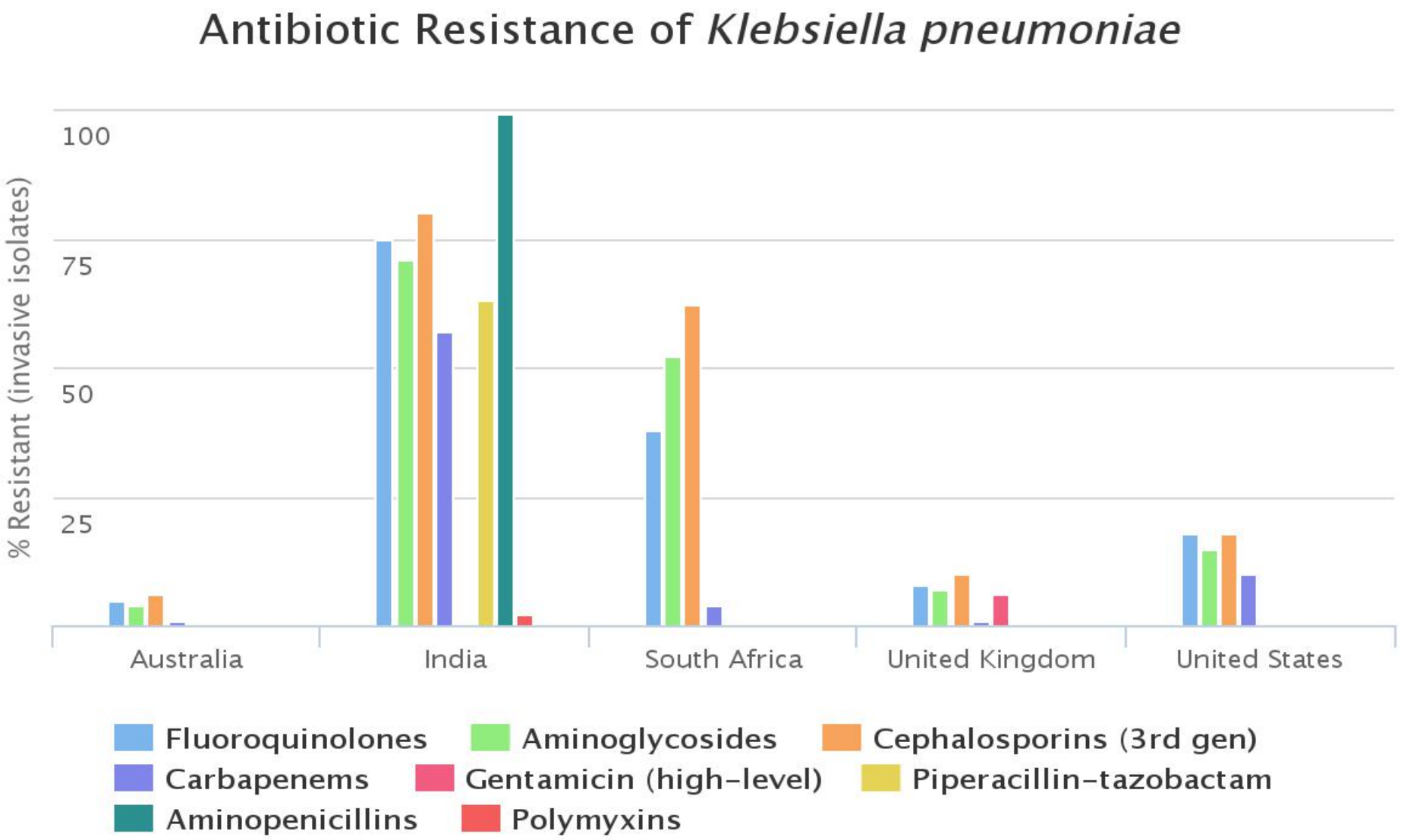
K. pneumoniae - Worldwide



K. pneumoniae Resistance

- Associated with ESBLs and Carbapenemase (KPC)
- ESBL:
  - Most commonly associated SHV-2
  - Resistance to penicillins, aminopenicillins, 1-3rd generation CS, aztreonam
  - Resistance pattern can mimic ESBLs with E. coli

Doi Y. Semin Resp Crit Care Med 2015;36(1):74-84

K. pneumoniae Resistance

- Carbapenemase:
  - Associated with KPCs, **NDM**, and OXA-48
  - KPC
    - Resistance to all penicillin-derivatives, cephalosporins, and Carbapenems, and aztreonam
    - ST258 predominates among KPC-producing K. pneumoniae in the US
    - KPC is mainly spread in healthcare settings
  - NDM
    - NDM is able to hydrolyze carbapenems but not aztreonam
    - NDM is spread in within healthcare settings and in the community

Doi Y. Semin Respir Crit Care Med 2015;36(1):74-84

A. baumannii Resistance

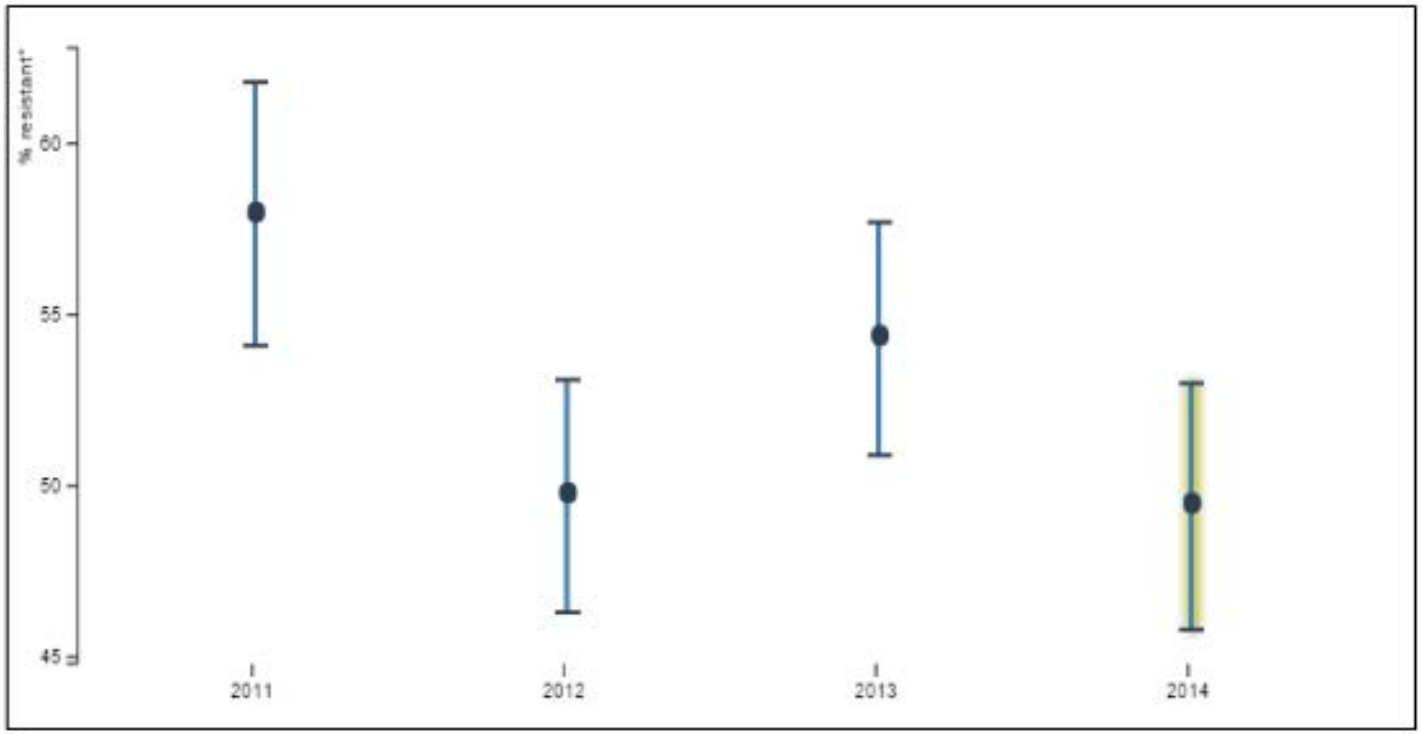
- Aerobic Gram-negative non-fermenting coccobacillus/rod
- Present in the environment such as water, soil, catheters, lotions, and AC systems
- Considered an opportunistic organism infecting patients with immunosuppression
- Infections:
  - Pneumonia
  - Catheter associated infections
  - UTIs
  - Sepsis

A. baumannii Resistance

Centers for Disease Control and Prevention

AR PATIENT SAFETY ATLAS

Carbapenem-Resistant *Acinetobacter* spp. (Resistant or Intermediate) | All HAIs | 2014
National % resistance over time



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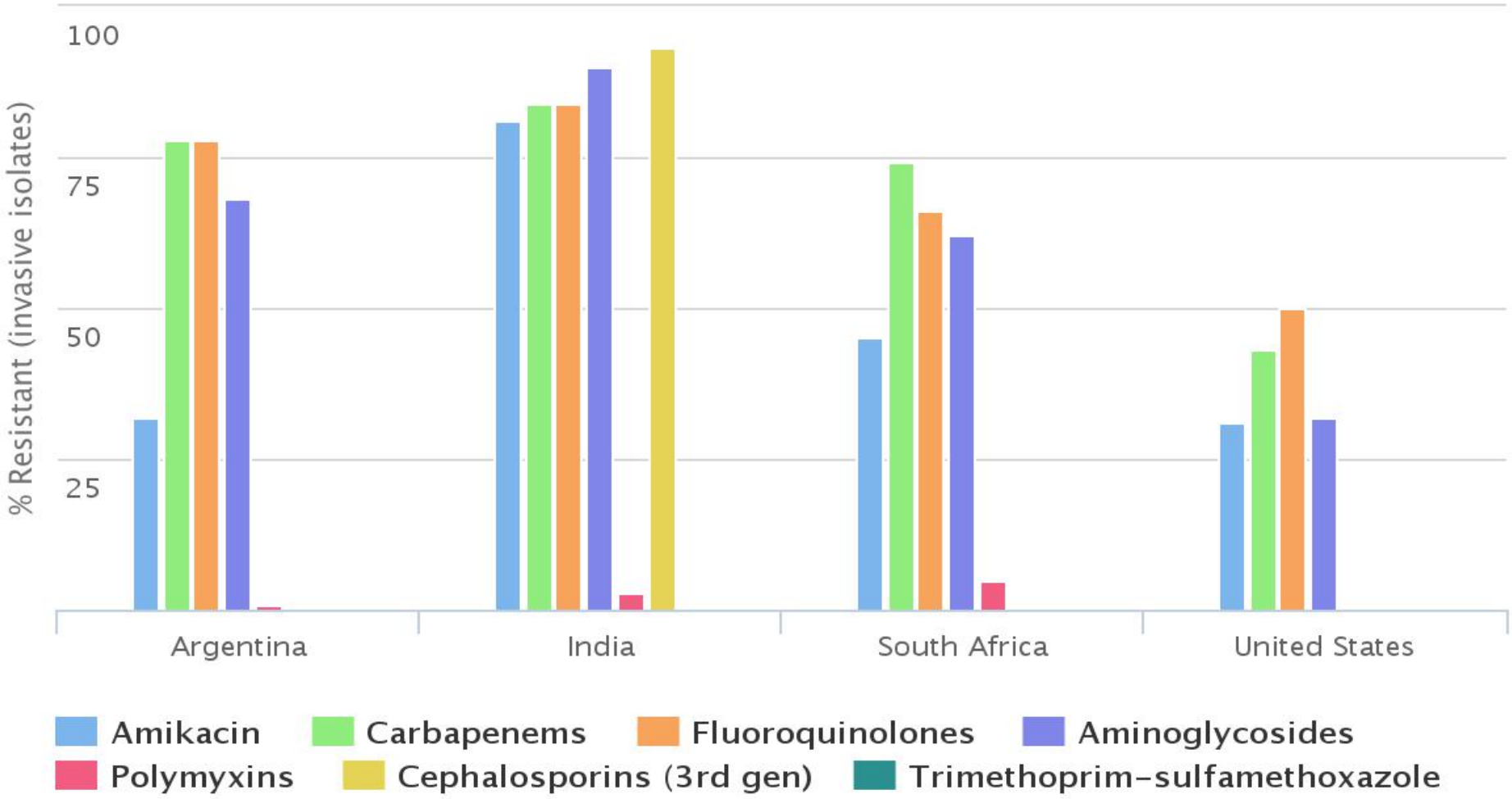
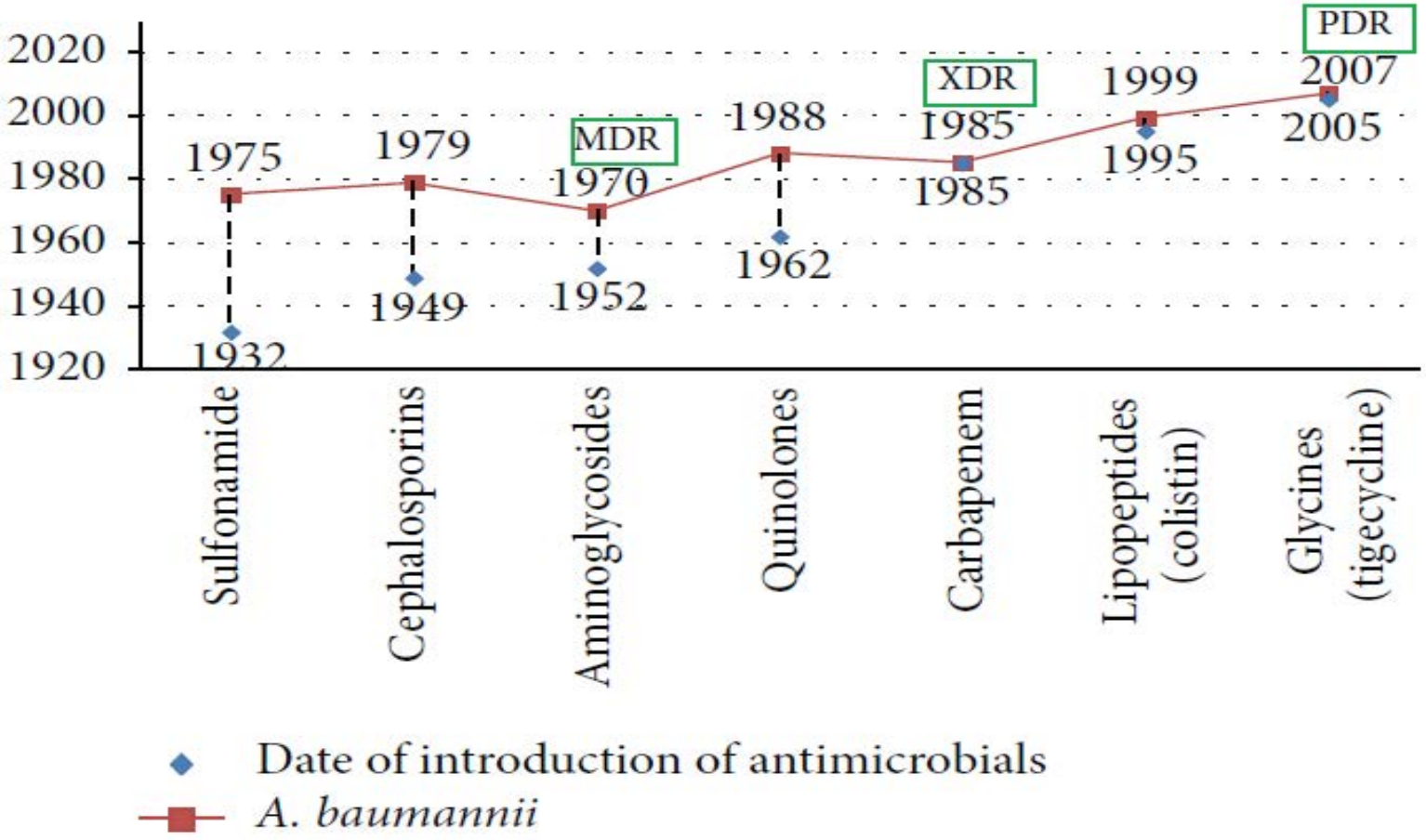
A. baumannii Resistance



A. baumannii Resistance



Gonzalez-Villoria, A. J of Pathogens 2016;2016:article 7318075. Figure 1

A. baumannii Resistance

- Resistance developed in hospitals prior to identifying it as an virulent organism and multi-drug resistant
- A. baumannii presents as either wild-type or Carbapenem-Resistant A. baumannii (CRAB)
- OXA-beta-lactamase encodes for the CRAB
- NDM-1 has more recently been associated with CRAB

Gonzalez-Villoria, A. J of Pathogens 2016;2016:article 7318075

Pseudomonas aeruginosa

P. aeruginosa

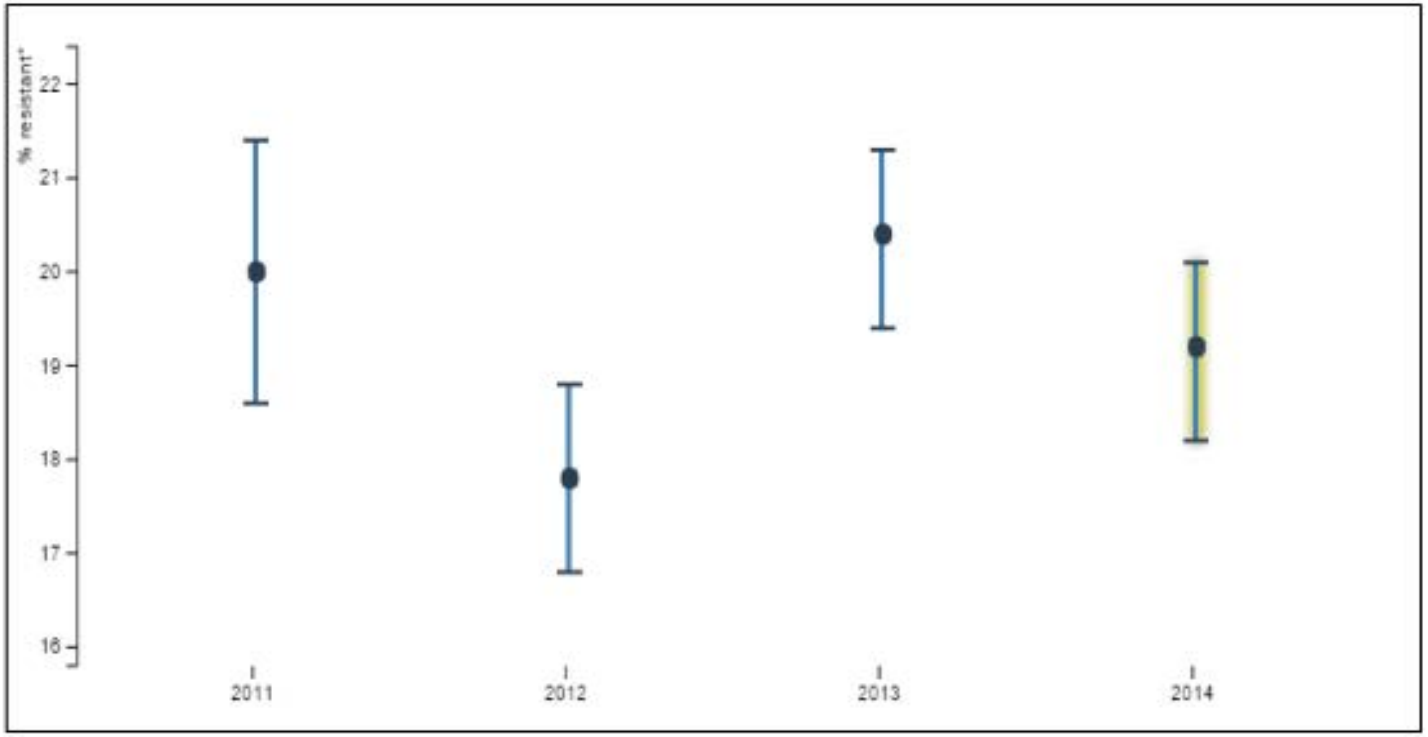
- Gram-negative non-fermenting motile bacillus
- Results in blue-green pus (pyocyanin/pyoverdin)
- Inhabits natural environments such as water and soil but can also live in hot tubs, water heaters, and petroleum
- Infection types:
  - Pneumonia
  - Sepsis
  - SSTI
  - UTI
  - other

Gniadek TJ. J Clin Microbiol 2016;54(7): 1700-1710

P. aeruginosa Resistance

Carbapenem Resistant *Pseudomonas aeruginosa* (Resistant or Intermediate) | All HAIs | 2014

National % resistance over time



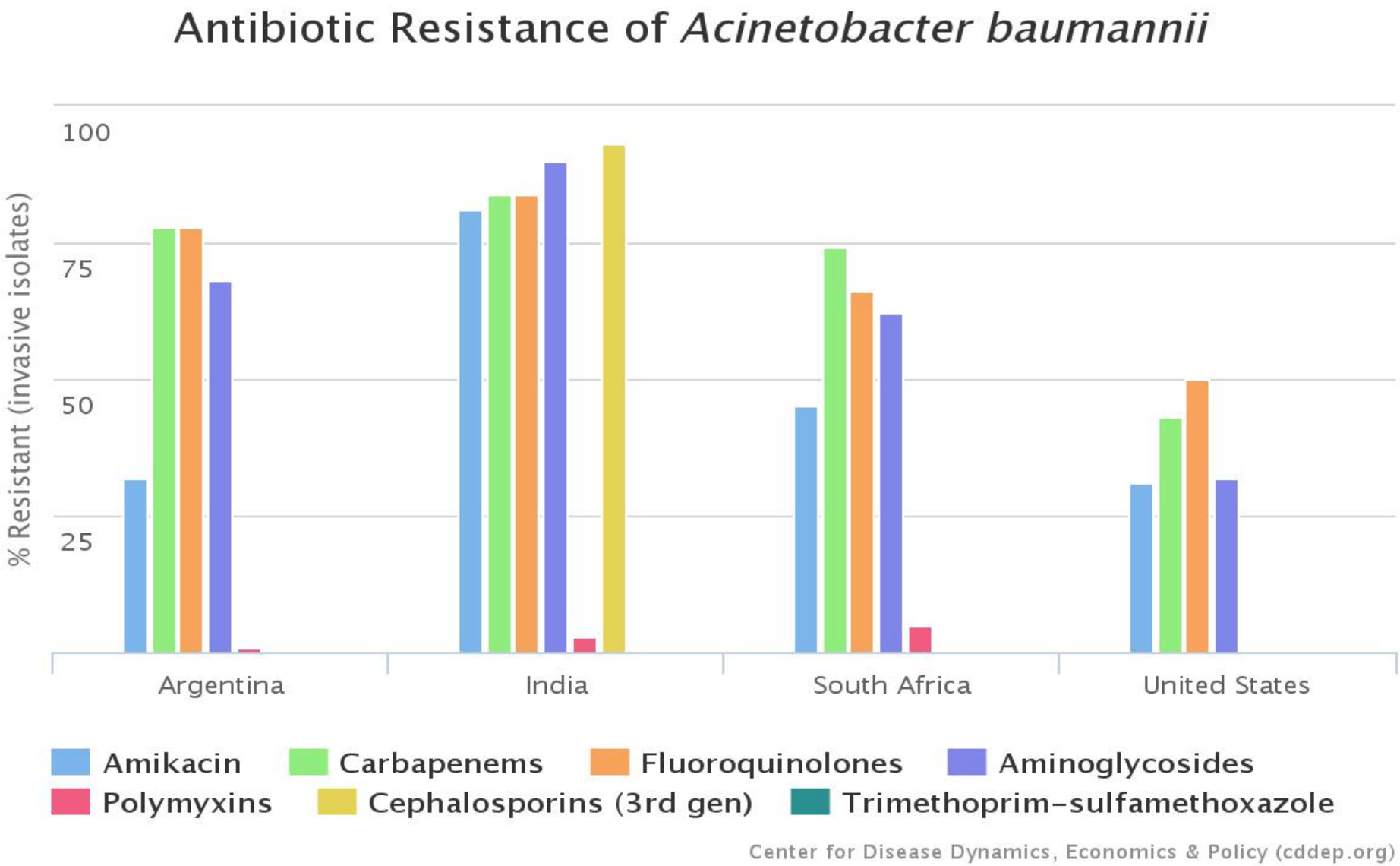
Note: HAIs include CAUTI, CLABSI, AND SSI; these account for about 25% of HAIs in acute care hospitals; values excludes some facility types (nursing homes) All data current as of 12/16/2015

Footnotes

Insufficient Data - Between 1 and 19 isolates were tested for susceptibility. The percent resistance and accompanying data points cannot be calculated when the number of tested isolates is less than 20

Not Defined - Zero isolates were tested. The percent resistance and accompanying data points cannot be calculated when the number of observations in the denominator is zero

P. aeruginosa Resistance



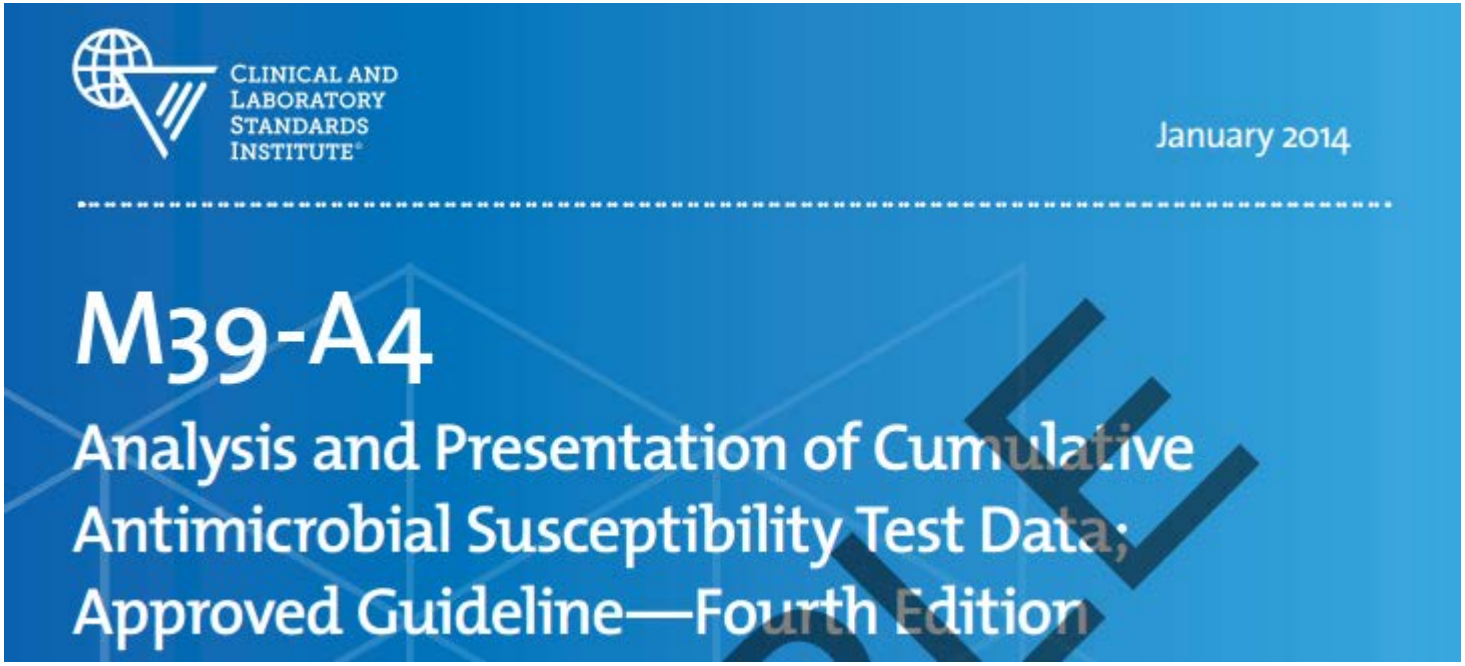
P. aeruginosa Resistance

- Unlike other Gram-negative bacteria, P. aeruginosa can utilize all 4 methods of resistance to antibiotics
- Unlike other Gram-negative bacteria, P. aeruginosa can utilize all ESBL and Carbapenem-resistant genes

Antibiogram Tools

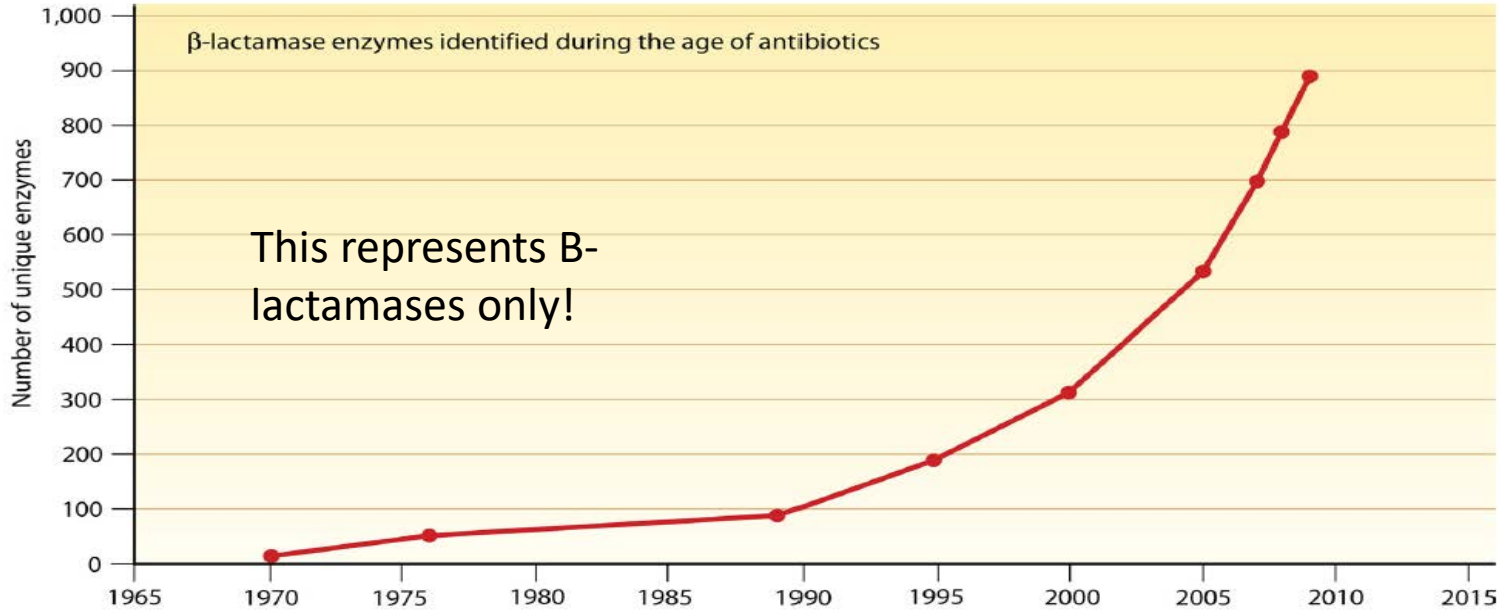
Antibiogram Tools

- Use of CLSI M39 as a guide to create your antibiogram



Antibiogram Tools

- Spend to the time to review trends in resistance such as AmpC, ESBL, and CREs



Davies J. Microb and Molec Bio Rev 2010;74(3):417-433 Figure 2

Antibiogram Tools

- Use various forms of antibiograms to detect bug-drug %S more specific to your institution
  - Ward specific antibiogram
  - Outpatient antibiogram
  - Organism specific antibiogram (P. aeruginosa/A. baumannii)
  - Patient population specific (transplant, oncology, immunosuppressed)
  - Nursing home specific

	Amik	Aztreo	Cefep	Ceftaz	Cipro	Gent	Imip	Levo	Mero	Tobra	Zosyn
Amikacin	96										
Aztreonam	98	76									
Cefepime	98	88	85								
Ceftazidime	NR	91	91	88							
Cipro	98	89	95	97	78						
Gentamicin	95	94	96	98	94	80					
Imipenem	NR	96	98	NR	96	99	94				
Levofloxacin	97	87	94	96	80	93	96	74			
Meropenem	100	99	99	99	99	100	97	98	97		
Tobramycin	99	99	99	99	99	99	99	99	100	99	
Zosyn	99	91	92	91	96	98	96	96	99	99	89

Represents combinations which are not recommended

Represents monotherapy use of one agent

E. Grace

Key Takeaways

- Resistance is increasing
  - Decreased use of antibiotics (amount and spectrum) is needed in order to control bacterial resistance
- E. coli is not just E. coli….
  - Every isolate of PEAK organisms needs to be examined closely to determine resistance mechanism(s) and most appropriate therapy to prevent further resistance
- Antibiograms are not perfect but a great tool
  - Resistance rates by country, state, city, and institution are important for each patient and each antimicrobial therapy regimen

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Clinical Meeting & Exhibition

Special Thanks:

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Creating Positive Outcomes for Gram-Negative Infections: Developing Optimal Treatment Regimens
Part 2

Christopher M. Bland, Pharm.D., FCCP, FIDSA, BCPS
Clinical Associate Professor
University of Georgia College of Pharmacy
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Savannah, GA

Objectives

- Formulate empiric and streamlined antibiotic regimens for patients with suspected Gram-negative infections
- Develop an antibiotic regimen with specific doses based on suspected/known organism and resistance patterns

When was the last time you saw a CRE infection treated at your institution?

- A In the past month
- B In the past 6 months
- C In the past year
- D Fortunately have not had to treat one yet

How many patients have you personally seen treated with polymyxin therapy at your institution?

A 0-50

B 51-100

C 101-150

D >150

Which polymyxin product do you typically use at your institution?

A. Polymyxin B (systemic)

B. Colistin (systemic)

C. Polymyxin B (inhaled)

D. Colistin (inhaled)

How many patients have you treated with ceftolozane/tazobactam at your institution?

A 0-50

B 51-100

C 101-150

D >150

How many patients have you treated with ceftazidime/avibactam at your institution?

A 0-50

B 51-100

C >100

D We would treat more but cannot get from supplier

What is the primary organism that ceftolozane/tazobactam is used against in your institution?

A. MDR *Pseudomonas aeruginosa*

B. ESBL-producing *E. coli*

C. ESBL-producing *K. Pneumoniae*

D. We don't currently test susceptibilities for ceftolozane/tazobactam in our facility so don't use it

What is the primary organism that ceftazidime/avibactam has been used against in your institution?

A. MDR *Pseudomonas aeruginosa*

B. ESBL-producing *E. coli/K.Pneumoniae*

C. KPC-producing organisms

D. We don't currently test susceptibilities for ceftazidime/avibactam in our facility so don't use it

Antibiotic Resistance

- Definition
  - Acquired or intrinsic ability of a pathogen to withstand an antibiotic that kills off its sensitive counterparts
- Multidrug-resistant (MDR) bacteria
  - No consensus definition
  - ≥ 3 antimicrobial classes
- ~ 70% of bacteria causing hospital-acquired infections are resistant to ≥ 1 antibiotic

	Pandrug Resistant	Extensively Drug Resistant
Antipseudomonal cephalosporins	Resistant	Resistant
Antipseudomonal carbapenems	Susceptible	Resistant
Piperacillin/ tazobactam	Resistant	Resistant
Ciprofloxacin Levofloxacin	Resistant	Resistant
Ticarcillin/ clavulanate	Resistant	Resistant
Aminoglycosides	Susceptible	Resistant

Potential MDR GNR Treatment Options

- Aminoglycosides
- Carbapenems
- Cefepime
- *Ceftazidime/Avibactam*
- *Ceftolozane/Tazobactam*
- *Colistin/Polymyxin B*
- *Fosfomycin*
- Piperacillin/Tazobactam
- *Tigecycline*

Polymyxins

- Most active in vitro vs. CRE
- Good activity vs. Pseudomonas species and ESBL strains
- Polymyxin B and Colistin commercially available
  - Colistin preferred for UTI
- Administered intravenously and inhaled
- International units vs. mg Colistin Base Activity (CBA)
- Nephrotoxicity and Neurotoxicity
- Caution resistance development as monotherapy
- Narrowest of therapeutic indices
  - 2.5mg/L therapeutic "goal" often nephrotoxic
  - Vitamin C "nephroprotective"?

Morrill HJ et al. *Open For Infect Dis.* 2015;2:ofv050.
Dalfino L et al. Clin Infect Dis. 2015;61:1771-7.

Polymyxins

	Colistin	Polymyxin B
Dosage Form Administered	Prodrug	Active moeity
Units	mg CBA (US); International Units (Europe)	International Units
Dosing Equiv.	30mg CBA=80mg CMS=1 MU CMS	10,000 IU=1mg
Loading Dose	5mg CBA/kg (Required)	20-25,000 IU (2-2.5mg/kg): Recommended
Time to maintenance dose	12-24 hours	12 hours
Maintenance Dose	Highly variable	25-30,000 IUs daily (2.5-3mg/kg/day)
Dosing intervals	Q8-q12h depending on renal function	q12h
Renal dose adjustment	Yes	No
Maximum approved dose	300mg CBA	2 million IU (200mg)

Morrill HJ et al. Open For Infect Dis. 2015;2:ofv050.

Polymyxins: Obesity Dosing

- Data Limited
- Package Insert Dose Dated
- Recent paper used fixed dosing of 9 MU LD followed by 4.5MU q12h-48h based on renal function
  - Weights of patients not included in study
- Colistin associated with nephrotoxicity when actual body weight used
- Garonzik et al. gives recommendations up to 106kg (Cautions against LD > 300mg CBA)
- Movement toward Polymyxin B due to potential less nephrotoxicity

1. Dalfino L et al. Clin Infect Dis 2012;54:1720-6.
2. Garonzik SM et al. Antimicrob Agents Chemother 2011;55:3284-94.
3. Gauthier TP et al. Antimicrob Agents Chemother 2012;56:2392-6.

TABLE 3. Suggested loading dose and daily maintenance doses of CMS[a]

Dose	Category of critically ill patient	Dosing suggestions
Loading dose	All patient categories	Equation 9: Loading dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × 2.0 × body wt (kg).[c] See caveat in footnote *c*. First maintenance dose should be given 24 h later.
Maintenance dose	Not on renal replacement	Equation 10: Daily dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × (1.50 × CrCL + 30).[d] Recommended dosage intervals based on CrCL: <10 ml/min/1.73 m^2, every 12 h, 10-70 ml/min/1.73 m^2 every 12 (or 8) h, and >70 ml/min/1.73 m^2 every 12 (or 8) h. See important caveat in footnote *d*.
	Receiving intermittent hemodialysis	Daily dose of CBA on a non-HD day to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target[b] = 30 mg[e]. Supplemental dose of CBA on a HD day[f]: add 50% to the daily maintenance dose if the supplemental dose is administered during the last hour of the HD session, or add 30% to the daily maintenance dose if the supplemental dose is administered after the HD session. Twice-daily dosing is suggested.
	Receiving continuous renal replacement	Daily dose of CBA to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target = 192 mg.[g] Doses may be given every 8-12 h.

[a] Expressed as mg of colistin base activity (CBA) for various categories of critically ill patients. The suggested maintenance daily dose would commence 24 h after administration of a CMS loading dose. Example: To target a colistin $C_{ss,avg}$ of 2.5 mg/liter, a 55-kg patient with a CrCL of 40 ml/min/1.73 m^2 would receive a loading dose of 275 mg CBA followed in 24 h by commencement of a maintenance regimen of 225 mg CBA/day in 2 to 3 equally divided doses.

[b] Colistin $C_{ss,avg}$ target is expressed in mg/liter. This target should be based on MIC, site, and severity of infection.

[c] Use the lower of ideal or actual body weight, expressed in kg. At this time, we suggest caution in the use of a loading dose greater than 300 mg CBA (see the text for more details).

[d] Based upon the population PK analysis for 101 critically ill patients not on continuous renal replacement therapy. Colistin $C_{ss,avg}$ target expressed in mg/L. Creatinine clearance (CrCL) expressed in ml/min/1.73 m^2. Although the Jelliffe equation was used to estimate CrCL in this study, other means (e.g., Cockcroft and Gault equation) may be used to estimate CrCL which would then be normalized to a body surface area of 1.73 m^2. See text for caveat regarding use of the algorithm in patients with CrCL values > 70 ml/min/1.73 m^2 or when targeting a "high" colistin $C_{ss,avg}$, both being circumstances where the algorithm may predict daily doses of CBA substantially greater than the current upper limit in the product label.

[e] Based upon use of equation 10 and setting CrCL to zero.

[f] Supplemental dose of CMS to achieve a similar colistin $C_{ss,avg}$ on a HD day as occurs on a non-HD day. It is assumed that the hemodialysis session occurs toward the end of a CMS dosage interval.

[g] Based on the population PK analysis for 4 critically ill patients receiving continuous renal replacement therapy.

Tigecycline

- Sparce data in “sick” ESBL or CRE-infected patients
- *No* activity vs. Pseudomonas species
- Low urinary concentrations
- Bloodstream concentrations below MIC of most pathogens
- Increased mortality relative to other agents for FDA-approved indications
- Role primarily for non-septic infections with good source control
- Always “rifampin-like” in therapy of KPC infections

Bassetti M. et al. Current Opin Infect Dis. 2016;29:583-94.

Fosfomycin

- Orally available only (United States)
- Excellent activity vs. CRE, ESBL-producing organisms (*E. coli*>*K. pneumoniae*), and NDM-1 isolates
- Limited clinical data primarily in use for UTIs
- Avoid in systemic infections (Again…in United States)

Bassetti M. et al. Current Opin Infect Dis. 2016;29:583-94.
Morrill HJ et al. Open For Infect Dis. 2015;2:ofv050.

Ceftazidime/Avibactam

- Broad Gram-negative activity
- Addition of avibactam
  - Activity in the presence of certain resistance mechanisms
  - Inhibition of a broader class of ESBLs
- Active against:
  - Class A (TEM, SHV, CTX-M ie ESBLs)
  - Some Class C (AmpC)
  - Some Class D (e.g., OXA 48)
  - ***Active against certain carbapenemases (KPC)***
- FDA-approved for IAI(with metronidazole) and cUTI
- ***Not*** active against:
  - the metallo-beta-lactamases (NDM-1, IMP, VIM)

Liscio JL et al. IJAA. 2015;46:266-71.

Ceftazidime/Avibactam

- REPRISE
  - Phase 3 open label
  - CAZ/AVI vs best available therapy for complicated UTI or intra-abdominal infection caused by ceftazidime-resistant Enterobacteriaceae or *Pseudomonas aeruginosa*
  - 96% of patients in the best available therapy group received carbapenem monotherapy
  - Clinical cure at test-of-cure visit was 91% in both groups for the microbiologically modified intention-to-treat population

Carmeli Y et al. Lancet Infect Dis 2016;16:661-73.

Alphabet Soup: Focus for Today

- Extended spectrum beta-lactamase (ESBL) producing organisms
  - *E. coli* and *K. pneumoniae* most common
- Carbapenem-resistant enterobacteriaceae (CRE)
  - Klebsiella pneumoniae carbapenemase (KPC)
  - New Delhi Metallo-beta-lactamase (NDM)
- Multidrug-resistant (MDR) *Pseudomonas aeruginosa*
  - Typically resistant to 3 or more classes of antimicrobials

Urgent Threat: CRE

- Carbapenem-resistant Enterobacteraciae (CRE)
- Estimated 9,000 infections, 600 deaths yearly
- Primarily Klebsiella spp. (KPC)
- Resistant to nearly all or all antibiotics in many patients

http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

KPC-Producing *Enterobacteriaceae*

1. Susceptibility of KPC-positive *K. pneumoniae* (N = 113)	
Agent	% Susceptible
Colistin	84.1
Tigecycline	97.3
Amikacin	41.6

2. Susceptibility of KPC-positive Enterobacteriaceae (N = 170)	
Agent	% Susceptible
Polymyxin	92
Tigecycline	81
Aminoglycoside (gent, tobra, amikacin)	88

1. Kaiser RM, et al. Diagn Microbiol Infect Dis 2013;76:356-60.
2. Lin YM et al. Clin Infect Dis 2013;57:1246-52.

Clinical Case

- 65 year-old NH female resident presents to ED with pyelonephritis. The patient has received multiple courses of antimicrobials over the past 6 months including ciprofloxacin, TMP-SMX, and amoxicillin/clavulanate. She is hemodynamically stable after 2L NS and will be admitted to the medicine ward. She has normal renal function and NKDA.

You make the call!

- What empiric therapy would you start for this patient if they were admitted to your facility?

A. Ceftolozane/Tazobactam

B. Cefepime

C. Piperacillin/Tazobactam

D. Meropenem

Is Help on the Way?

- Would you add a second agent that is active against Gram-negatives, and if so, what?

A. I wouldn't add a second agent

B. A fluoroquinolone

C. An aminoglycoside

D. A polymyxin

Uh oh…

- You get a call from the microbiology lab. You recently implemented multiplex PCR on your blood cultures. Her blood cultures are demonstrating a *Klebsiella pneumoniae* that is positive for KPC.

Now what…

- What empiric therapy would you start for this patient?

a. Meropenem
b. Meropenem + colistin
c. Meropenem + colistin + tigecycline
d. Meropenem + ertapenem
e. Ceftolozane/tazobactam
f. Ceftazidime/avibactam +/- Polymyxin
g. No idea

Role of Combination Treatment

- Retrospective data of patients with bacteremia caused by KPC producing *K. pneumoniae* indicated lower mortality in patients who receive combination therapy (usually carbapenem with colistin and/or tigecycline) versus monotherapy
- Triple therapy of colistin, tigecycline, and meropenem decreased mortality even with inappropriate empiric therapy
- Carbapenems play an important, MIC-dependent role in combination therapy
  - Even when "resistant"

Qureshi ZA, et al. AAC 2012;56:2108-13
Dalkos GL et al. AAC 2014;58:2322-8
Tumbarello M, et al. Clin Infect Dis 2012;55:943-50
Petrosillo N et al. Expert Rev Anti Infect Ther 2013;11:159-77.

Role of Dual Carbapenem Therapy

- Ertapenem is the most readily hydrolyzed by KPC enzymes
- Synergy demonstrated when ertapenem is given with meropenem or doripenem
- Clinical success seen in 7/18 (39%) of patients with carbapenem-resistant *K. pneumoniae* and microbiologic success in 11/14 (79%) of the evaluable patients

Bulik CC. AAC 2011;55:3002-4.
Cprek JB. AAC 2015;60:669-73.

Role of Ceftazidime/Avibactam

- Ceftazidime/Avibactam has activity vs. CRE including KPCs
- Clinical success/survival 59%/76% in recent single center retrospective study
- Recent manuscript shows 99% susceptibility in US hospitals
  - Need to still manually test to gain susceptibilities
- Resistance reported without prior exposure
- Monotherapy?
- Combination therapy? Which agent?
- Currently in shortage (early 2017 for release)

Shields RK et al. *Clin Infect Dis* 2016. Ahead of Print.
Sader HS et al. *AAC*. 2016;60:4355-60.

Serious Threat: ESBL-producing organisms

-Increased tremendously in past 10 years, often driven by community CTX-M strains

Patient Case

- A 35 year old-female reports to her primary care provider with her 3rd UTI in the past six months. Patient traveled to India several months ago on a mission trip. She presents with fever to 103.4F, shaking chills, and heart rate of 120 BPM (sinus tachycardia). She is actively resuscitated and diagnosed with septic shock upon transfer to the ICU. Her previous culture one month ago demonstrated an ESBL-producing *E. coli* (susceptibilities unavailable).

Empiric Therapy Options

- A Piperacillin/Tazobactam
- B Colistin (systemic)
- C Meropenem
- D Cefepime

Extended-Spectrum β-Lactamases

- First discovered in 1980's
- Initially confined to nosocomial settings
- ESBL often implies only beta-lactamase resistance
  - FQ resistance
  - Aminoglycoside resistance
  - TMP/SMX resistance
  - Tetracycline resistance
  - Therefore often MDR!
- Now found in community settings
  - Especially for UTIs

Trecharichi EM et al. *Future Microbiol* 2012;7;1173-89.

β-Lactamases and Medications Affected

Table 1

Bush-Jacoby-Medeiros Group	Molecular class (Ambler)	Preferred substrates	Representative enzymes	Resistance or susceptibility to β-lactamase inhibitors
1	C	Cephalosporins	AmpC	Resistant
2b	A	Penicillins, Cephalosporins	TEM, SHV	Susceptible
2be	A	Penicillins, extended-spectrum cephalosporins, monobactams	TEM, SHV	Susceptible
2d	D	Penicillins, cloxacillin	OXA	Resistant
2e	A	Cephalosporins	Inducible cephalosporinases from *Proteus vulgaris*	Susceptible
2f	A	Penicillins, cephalosporins, carbapenems	NMC-A from *Enterobacter cloacae*	Resistant
3	B	Most β-lactams including carbapenems	L1 from *Stenotrophomonas maltophilia*	Resistant

Amended from original Bush-Jacoby-Medeiros classification scheme for bacterial β-lactamases.

Dhillion R et al. *Crit Care Research and Practice* 2012;1-11.

Differences in ESBLs

Table 2

	Community onset	Hospital onset, particularly ITU
Organism	*E. coli*	*Klebsiella spp*
Type of ESBL	CTX-M	SHV,TEM
Type of infection	Usually UTIs, but also bacteraemia and GI infection	Bacteraemia, intra-abdominal, and respiratory and urinary infection
Molecular epidemiology	Isolates not always related	Isolates usually related, that is, outbreak

Dhillion R et al. *Crit Care Research and Practice* 2012;1-11.

Prevalence of ESBL worldwide is increasing

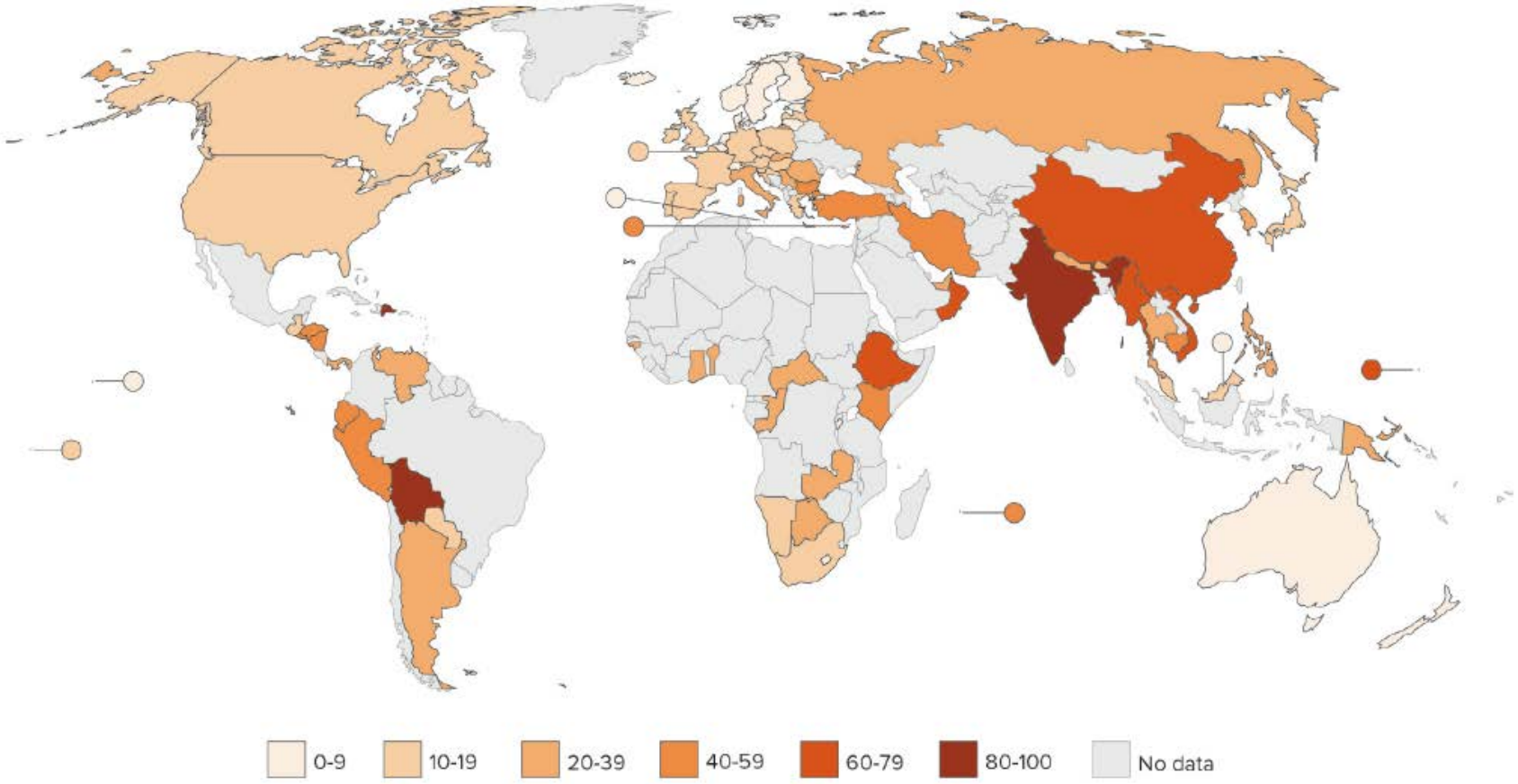


FIGURE 1-2: Percentage of extended-spectrum beta-lactamase producing *Escherichia coli, by country (most recent year, 2011–2014)**

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Center for Disease Dynamics, Economics and Policy. 2015. State of the World's Antibiotics, 2015. CDDEP: Washington, D.C.

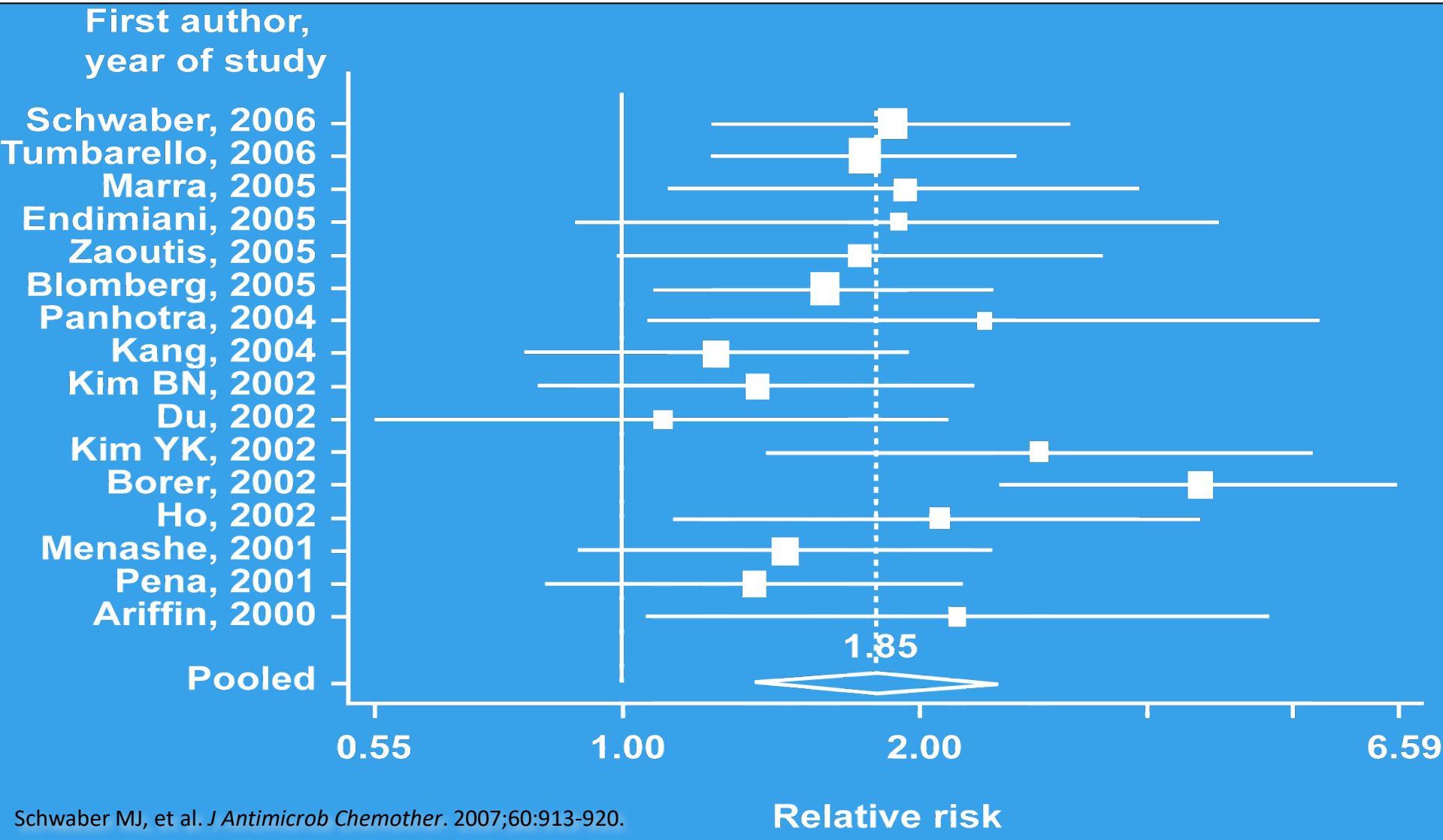
Risk Factors For ESBL Infections

TABLE 3

Factor	Odds ratio (95% CIs)
ICU admission	1.67 (1.16–2.40)
Renal failure	1.92 (1.21–3.04)
Burns	2.78 (1.92–4.01)
TPN	1.72 (1.18–2.49)
Urinary catheter	1.88 (1.25–2.83)
3rd Gen cephalosporin	2.99 (1.6–4.0)

Dhillion R et al. *Crit Care Research and Practice* 2012;1-11.

ESBL Production and Mortality



Schwaber MJ, et al. *J Antimicrob Chemother*. 2007;60:913-920.

Role of Carbapenems

- Drug of choice for serious infections
- Decreased mortality vs other treatment options

1. Decreased mortality at 14 days (OR 0.09) and 28 days (OR 0.06) in patients with ESBL *K. pneumoniae* bacteremia (n=85)
2. Meta-analysis of 21 studies – carbapenems associated with lower mortality than non-beta-lactam/beta-lactamase inhibitors (BL/BLI) for definitive and empiric treatment

Paterson DL, Clin Infect Dis 2004;39:31-7.
Vardakas KZ, J Antimicrob Chemother 2012;67:2793-803

ESBL Treatment

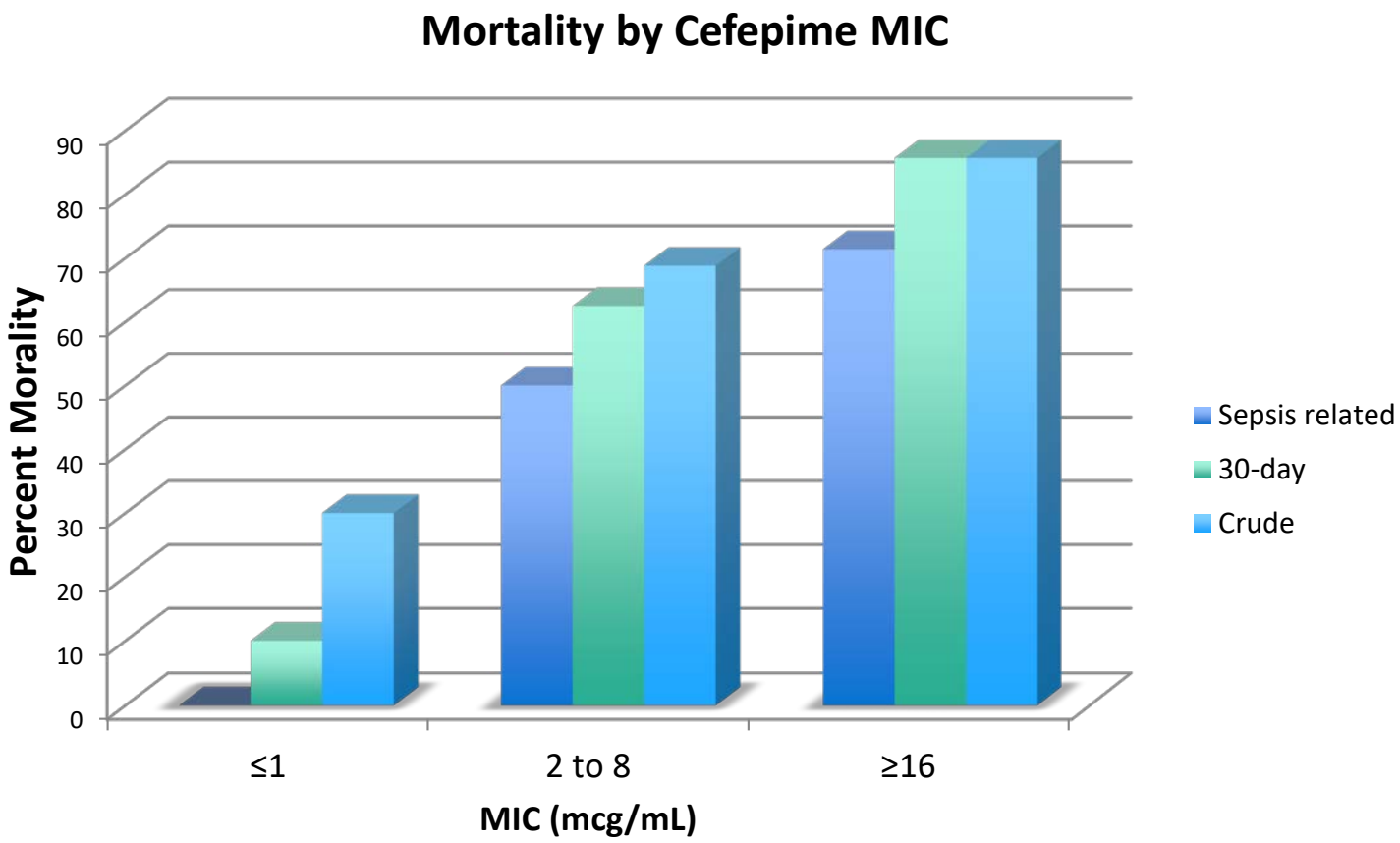
Role of Cefepime

- Cefepime vs carbapenems for ESBL-producing Enterobacteriaceae bacteremia
  - Empiric therapy: 30 day mortality rates were higher in the cefepime group (58.8% vs 17.9%)
  - Definitive therapy: higher clinical failure, microbiological failure, 30-day mortality

Lee NY. Clin Infect Dis 2013;56:488-95

ESBL Treatment

Role of Cefepime: MIC Matters



Lee NY. Clin Infect Dis 2013;56:488-95.

ESBL Treatment

Role of Beta-lactam/beta-lactamase inhibitors (BL/BLI)

- Two international retrospective analyses of carbapenems vs BL/BLIs for ESBL-producing Enterobacteriaceae bacteremias found no difference in mortality
  - One largely urine and biliary sources, one a wide variety of sources
- One US-based retrospective review of carbapenems vs piperacillin/tazobactam found increased 14-day mortality with empiric piperacillin/tazobactam vs carbapenems
  - Many patients with central line associated bacteremia or pneumonia as source

1. Rodriguez-Bano J. Clin Infect Dis 2012;54:167-74.
2. Gutierrez-Gutierrez B. AAC 2016 ;60:4159-69.
3. Tamma PD. Clin Infect Dis 2015;60:1319-25.

Role of Beta-lactam/beta-lactamase inhibitors (BL/BLI): ESBL

- One international retrospective cohort study demonstrated similar outcomes between pip/tazo and carbapenems
  - 50-70% had urinary sources
  - Less than 10% pneumonia
  - Pip/Tazo group had lower 30d acquisition of MDR and fungal infections (7.4% vs. 24.6%; $p<0.01$)
  - MICs not reported

- Variable data, definitive role unclear as most beneficial data in infections with high drug concentrations (urinary) or excellent source control (IAI)

Ng TM et al. PLoS ONE 2016 11:e0153696.

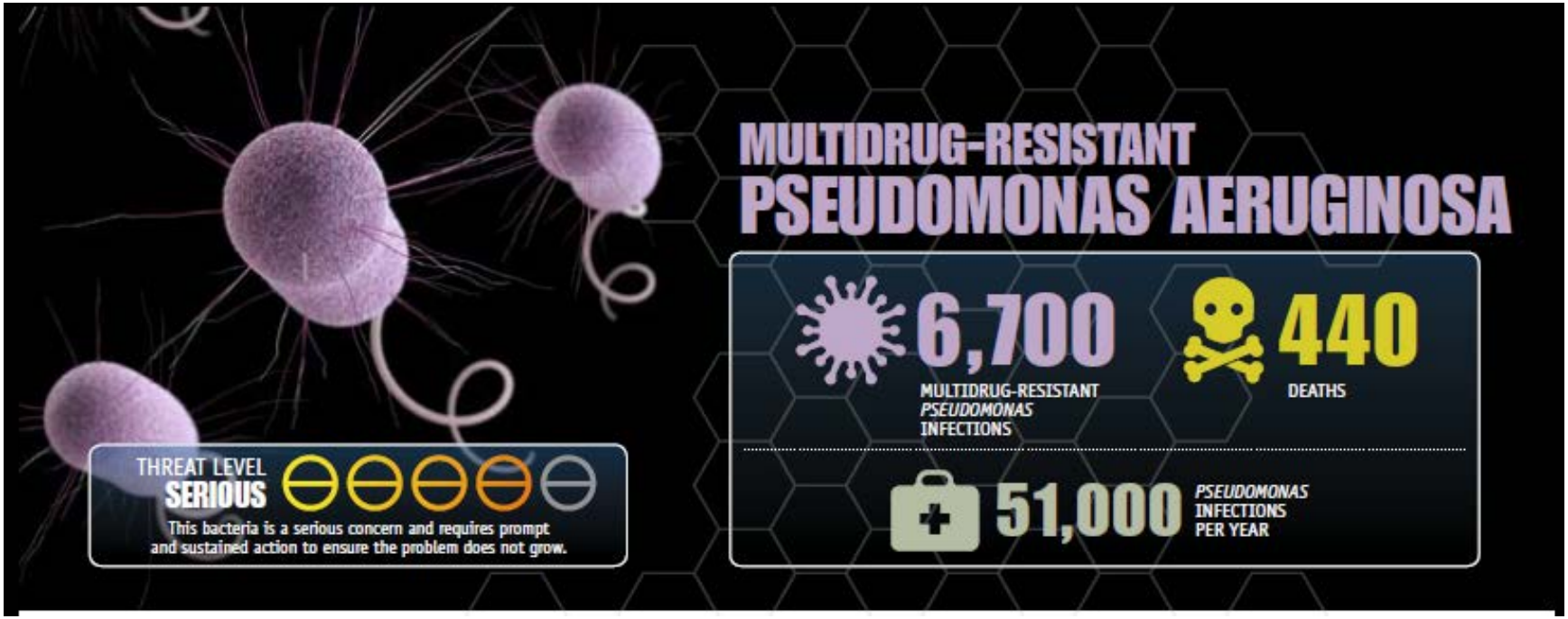
ESBL Treatment

Role of Beta-lactam/beta-lactamase inhibitors

MERINO Trial

- Meropenem versus piperacillin-tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible *Escherichia coli* and *Klebsiella* spp.

Serious Threat: MDR Pseudomonas



- 8% of all healthcare-associated infections
- 13% are multidrug resistant

Potential Treatment Options: *Pseudomonas aeruginosa*

- Empiric: Know your antibiogram!
- Double coverage not necessary for every patient
  - VAP guidelines only for prior ABX in past 90 days, units where > 10% isolates resistant, ICU susceptibilites unavailable
- Preservation of Carbapenems at a Premium!
  - Skin Testing
- Beta-lactams are core agents with best mortality data
- De-escalate when possible to monotherapy
  - Aminoglycosides okay for UTI only

Kalil AC et al. Clin Infect Dis. 2016;63:575-82.

Clinical Case

- A 44 year old female (NKDA) with a PMH significant for active Non-Hodgkins lymphoma has been hospitalized for 60 days with respiratory failure and failure to wean from the ventilator. She has received two courses of antimicrobials for septic shock over the course of her hospitalization. Three days ago she developed worsening oxygen requirement, low BP (90/50 mmHg), and fever to 102.3F. Her CXR is consistent with a new RLL infiltrate. Renal function good currently. She was placed on meropenem/vancomycin/tobramycin for her presumed VAP. Her respiratory cultures demonstrate the following:

Clinical Case-Respiratory Culture

- Pseudomonas aeruginosa

	MIC	Interpretation
Amikacin	32	I
Cefepime	16	I
Ceftazidime	>16	R
Ceftolozane/Tazo	2/4	S
Ciprofloxacin	>4	R
Imipenem	>16	R
Levofloxacin	>8	R
Meropenem	8	R
Tobramycin	>16	R
Piperacillin/Tazo	32	I

Clinical Case: Options for Therapy

- A Cefepime 2g IV q8h
- B Ceftolozane/Tazobactam 1.5g IV q8h
- C Piperacillin/Tazobactam 3.375gm IV q8h
- D Colistin 9MU X 1, followed by 4.5MU q12h

Ceftolozane/Tazobactam: Nuts and Bolts

- Antipseudomonal cephalosporin/beta-lactamase inhibitor
- Time-dependent, bactericidal agent
- Primarily renally excreted (over 90%)
- FDA-approved for IAI (with metronidazole) and cUTI
- Increased in vitro activity:
  - AmpC Beta-lactamases
  - Some ESBL organisms
  - MDR Pseudomonas species

Cho JC et al. Pharmacotherapy 2015;35:701-15.

Ceftolozane/Tazobactam: Clinical Pearls

- **No** activity vs. CRE organisms
- Staphylococcal activity very limited
- Good activity vs. MDR Pseudomonas (approx. 75% susceptible)
- Must test in house or send out (no automated test)
- Most patients in cUTI/IAI trials European with BMI ~27
- ASPECT-NP study currently recruiting
  - 3g IV q8h vs. Meropenem 1g IV q8h (8-14 days)
- Anaerobic coverage limited to certain Bacteroides species
- Worse outcomes in renal insufficient patients (IAI study)
  - 47.8% vs. 69.2% (low overall numbers)

Liscio JL et al. IJAA 2015;46:266-71.
Buehrle DJ et al. AAC 2016;60:3227-31.

Resistance Phenotypes: Beta-lactamases

	Class A (ESBL)	Class A (KPC)	Class B (MBL)	Class C (AmpC)
Aztreonam	R	R	S	R
Cefepime	I/R	R	R	S
Ceftazidime	I/R	R	R	R
Ceftazidime /Avibactam	S	S	R	S
Meropenem	S	R	R	S
Pip/Tazo	S	R	R	I/R?

Potential MDR GNR Treatment Options

- Tigecycline
  - Low plasma levels
  - Bacteriostatic
  - Black box warning for increased mortality
- Colistin/Polymyxin B
  - Nephrotoxicity
  - Neurotoxicity
  - Limited data on dosing in critically ill?
  - Ability to reach therapeutic concentrations safely?
  - Which agent is the preferred?

- Carbapenems
  - Optimal dosing?
  - Inoculum effect?
- Aminoglycosides
  - Nephrotoxicity
- Fosfomycin
  - Only available PO in the United States – limited use outside of UTI

Falagas ME. Antimicrob Agents Chemother 2014;58:654.
Queenan AM. Clin Microbiol Review 2007;20:440.
Cprek JB. Antimicrob Agents Chemother 2016;60:660.

Potential MDR GNR Treatment Options: New Kids on the Block

- Ceftolozane/Tazobactam
  - No CRE activity
  - MDR Pseudomonas
  - ESBL clinical data?
  - Indication dosing (1.5g IV q8h) vs. Off-label dosing (3g IV q8h)
- Ceftazidime/Avibactam
  - CRE activity
  - Availability
  - Appropriate Dosing?

Practice Reflection Question

- Which of the following antimicrobials does NOT have in vitro activity vs. CRE organisms?

A. Ceftazidime/Avibactam

B. Ceftolozane/Tazobactam

C. Polymyxin B

D. Tigecycline

Practice Reflection Question

- In a severely ill patient with known CRE infection, which of the following regimens would be best based on the data currently available (assume all agents are susceptible)?

A. Ceftazidime/Avibactam plus Polymyxin B

B. Meropenem plus fosfomycin

C. Colistin

D. Tigecycline

Practice Reflection Question

- Which statement best describes the role of piperacillin/tazobactam in the treatment of ESBL-producing organisms?

A. Equivalent to carbapenems in severe infections

B. Consistently worse than carbapenems across the board

C. Conflicting data with best outcomes in infections with good source control

D. Not a good option for ESBL UTIs

Practice Reflection Question

- When cultures demonstrate a MDR Pseudomonas that is susceptible to at least two agents, both of those agents should be continued for the duration of the course of therapy for most patients.

A TRUE

B FALSE

Key Takeaways

- **Key Takeaway #1**
- Severe infections with CRE organisms should be treated with combination therapy due to decreased mortality
- **Key Takeaway #2**
- For severe ESBL infections, carbapenems are a green light, pip/tazo a yellow light, cefepime a red light in most cases
- **Key Takeaway #3**
- Newer cephalosporins will have increasing role in the treatment of KPC (CAZ-AVI), ESBL, and MDR Pseudomonas infections

Questions??