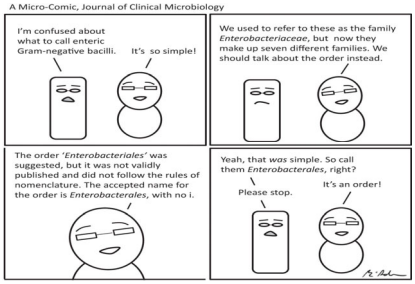
Presentation Outline

- Clinical and economic burden of antimicrobial resistance
- Trends in antimicrobial resistance prevalence
  - USA versus Worldwide
    - Extended-Spectrum Beta-Lactamases (ESBL)
    - Carbapenem-Resistant Enterobacteriaceae (CRE)
    - Multidrug-Resistant *(MDR) Pseudomonas aeruginosa*
- Growing diversity of resistance mechanisms
- Role of local / unit-based antibiograms

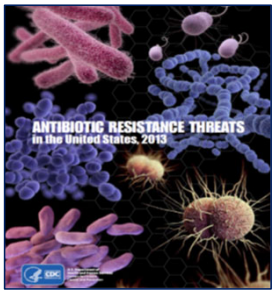
Antimicrobial Resistance: What is the Cost?

Enterobacteriaceae and Enterobacterales



McAdam AJ. *J Clin Microb.* 2020; 58: e01888-19.

Antibiotic Resistance Threats Report



https://www.cdc.gov/drugresistance/biggest-threats.html

CDC's Antibiotic Resistance Threats in the United States, 2019

- Latest national death and infection estimates that underscore the continued threat of antibiotics resistance in the U.S.
- >2.8 million antibiotic-resistant infections in the U.S. each year
- More than 35,000 people die as a result
- In addition, 223,900 cases of *Clostridioides difficile* occurred in 2017 and at least 12,800 people died
- Lists 18 antibiotic-resistant bacteria and fungi into three categories (5 urgent, 11 serious, 2 concerning) based on level of concern to human health

Antibiotic Resistance Threats in the United States, 2019.
www.cdc.gov/DrugResistance/Biggest-Threats.html

CDC Priority Lists – *2019*

Urgent Threats
Carbapenem-resistant Enterobacteriaceae
Carbapenem-resistant *Acinetobacter baumannii*
Candida auris
Clostridioides difficile
Drug-resistant *Neisseria gonorrhoeae*

Serious Threats
DR *Campylobacter*
DR *Candida*
ESBL-producing Enterobacteriaceae
Vancomycin-resistant *Enterococci*
MDR *Pseudomonas aeruginosa*
DR nontyphoidal *Salmonella*
DR *Salmonella* serotype Typhi
DR *Shigella*
MRSA
DR *Streptococcus pneumoniae*
DR Tuberculosis

Concerning Threats
Erythromycin-resistant group A *Streptococcus*
Clindamycin-resistant group B *Streptococcus*

Watch List
Azole-resistant *Aspergillus fumigatus*
DR *Mycoplasma genitalium*
DR *Bordetella pertussis*

DR: Drug-resistant
ESBL: Extended-spectrum beta-lactamase
MDR: Multidrug-resistant
MRSA: Methicillin-resistant *Staphylococcus aureus*

Antibiotic Resistance Threats in the United States, 2019.
www.cdc.gov/DrugResistance/Biggest-Threats.html

CDC's Antibiotic Resistance Threats in the United States, 2019

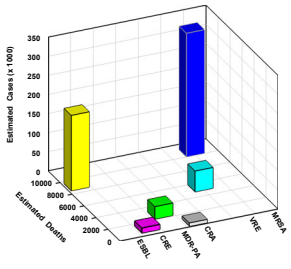
- Like the 2013 report, the 2019 report assesses threats according to seven factors:
  - Clinical impact
  - Economic impact (when available)
  - Incidence
  - 10-year projection of incidence
  - Transmissibility
  - Availability of effective antibiotics
  - Barriers of prevention

Name the three germs that had their ranking shifted since the 2013 report?

- Carbapenem-resistant *A. baumannii*
  - Moved to Urgent Threat
- *Candida auris*
  - Added as an Urgent Threat
- Vancomycin-resistant *S. aureus*
  - Removed as a threat

Antibiotic Resistance Threats in the United States, 2019.
www.cdc.gov/DrugResistance/Biggest-Threats.html

Estimate of Cases and Deaths in USA – 2017

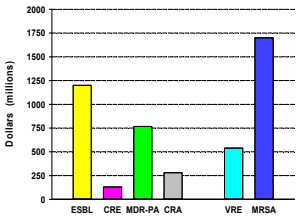


Pathogen	Estimated Cases in Hospitalized Patients	Estimated Deaths
ESBL	197,400	9,100
CRE	13,100	1,100
MDR-PA	32,600	2,700
CRA	8,500	700
VRE	54,500	5,400
MRSA	323,700	10,600

ESBL: Extended-spectrum β-lactamase-producing Enterobacteriaceae
CRE: Carbapenem-resistant Enterobacteriaceae
MDR-PA: Multidrug-resistant *Pseudomonas aeruginosa*
CRA: Carbapenem-resistant *Acinetobacter*
VRE: Vancomycin-resistant *Enterococcus*
MRSA: Methicillin-resistant *Staphylococcus aureus*

Antibiotic Resistance Threats in the United States, 2019.
www.cdc.gov/DrugResistance/Biggest-Threats.html

Attributable Costs in USA – 2017



Pathogen	Estimated Attributable Healthcare Costs	Estimated Healthcare Costs / Hospitalized Patients
ESBL	$ 1.2 Billion	$ 6,079
CRE	$ 130 Million	$ 9,924
MDR-PA	$ 767 Million	$ 23,859
CRA	$ 281 Million	$ 33,059
VRE	$ 539 Million	$ 9,890
MRSA	$ 1.7 Billion	$ 5,252

ESBL: Extended-spectrum β-lactamase-producing Enterobacteriaceae
CRE: Carbapenem-resistant Enterobacteriaceae
MDR-PA: Multidrug-resistant *Pseudomonas aeruginosa*
CRA: Carbapenem-resistant *Acinetobacter*
VRE: Vancomycin-resistant *Enterococcus*
MRSA: Methicillin-resistant *Staphylococcus aureus*

Antibiotic Resistance Threats in the United States, 2019.
www.cdc.gov/DrugResistance/Biggest-Threats.html

Bloodstream Infections Caused by Multidrug-Resistant Gram-Negative Bacteria

- 891 patients with monomicrobial MDR BSI at Duke University
  - 292 patients (33%) had BSI due to MDR pathogens and more likely to have:
    - History of transplant (19% versus 13%; *P* = 0.02)
    - Prior Gram-negative infection (46% versus 33%; *P* = 0.0003)
    - Hospital-acquired infection (35% versus 28%; *P* = 0.05)
- Most commonly isolated Gram-negative bacteria were:
  - *Escherichia coli* (37%; 330/891)
  - *Klebsiella pneumoniae* (19%; 166/891)
  - *Pseudomonas aeruginosa* (13%; 119/891)
- MDR phenotype was most common in *Escherichia coli* (50%) and *Citrobacter freundii* (44%)

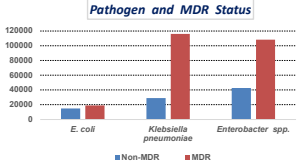
MDR, multidrug resistant (nonsusceptible to at least one agent in greater than or equal to 3 antimicrobial categories)
BSI, bloodstream infections

Thaden JT, et al. *Antimicrob Agents Chemother.* 2017; 61: e01709-16.

Increased Costs Associated with Bloodstream Infections Caused by MDR Gram-Negative Bacteria

- In patients with hospital-acquired BSI (n = 296), mean inpatient costs higher in patients with MDR BSI ($ 136,945 versus $ 89,197, *P* = 0.02)

Inpatient Costs by Pathogen and MDR Status



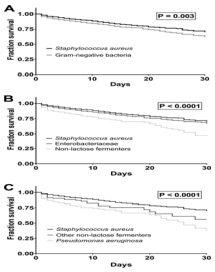
MDR, multidrug resistant (nonsusceptible to at least one agent in greater than or equal to 3 antimicrobial categories)
BSI, bloodstream infections

- MDR BSI relative to non-MDR BSI were associated with increased mean inpatient costs ($ 59,266 versus $ 36,452)
  - Significant even after adjustments for patient demographics, medical comorbidities, and treatment factors
- Increased cost of MDR BSI stemmed primarily from increased length of hospital stay
- Patients with hospital-acquired infections were the primary drivers of the increased costs associated with the MDR phenotype
- MDR BSI were associated with recurrent BSI during the same hospital stay

Thaden JT, et al. *Antimicrob Agents Chemother.* 2017; 61: e01709-16.

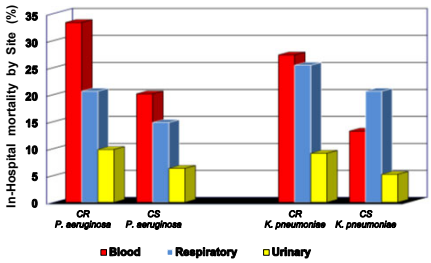
Increased Mortality Associated with Bloodstream Infections Caused by Pseudomonas aeruginosa

- 2,659 patients with bloodstream infections (BSI)
  - 999 (38%) *Staphylococcus aureus* (51% MRSA)
  - 1,660 (62%) Gram-negative bacteria
    - 81% Enterobacteriaceae
    - 16% Non-lactose-fermenting
- Cohort study using unadjusted time-to-mortality
- *Pseudomonas aeruginosa* BSI was associated with increased mortality relative to other Gram-negative or *Staphylococcus aureus* BSI
- This effect persisted after adjustments for patient, bacterial, and treatment factors



Thaden JT, et al. *Antimicrob Agents Chemother.* 2017; 61: e02671-16.

In-Hospital Mortality by Each Site
Carbapenem-Resistant (CR) vs -Susceptible (CS) Infections



- Patients with CR pathogens were more likely to receive more than 1 systemic antibiotic
- Patients with pathogens from the blood and respiratory were more likely to receive 2 or more antibiotics
- Fewer different antibiotic combinations were used to treat patients with CS versus CR infections

Cai B, et al. *Open Forum Infect Dis.* 2017; 4: ofx176.

Increased Mortality, Length of Stay, and Costs
Inappropriate Empiric Treatment of CRE

- Retrospective cohort study among 40,137 patients presenting to the hospital with Enterobacteriaceae infections (UTI [>50%], pneumonia, sepsis); 1227 (3.1%) were carbapenem-resistant (CRE)
- Patients with CRE tended to be slightly younger, more likely African-American than non-CRE patients
- Chronic and acute illness (by day 2: ICU and mechanical ventilation) burden were higher among CRE patients
- CRE patients were 3x more likely to receive inappropriate empiric treatment (IET)
- IET was associated with an adjusted mortality rate of 12% and an excess length of stay of 5.2 days and $ 10,312 in costs

Zilberberg MD, et al. *BMC Infect Dis.* 2017; 17: 279.

New Tools to Advance Pathogen-specific Therapy

Keith A. Rodvold, PharmD

The Prevalence of Gram-Negative Resistance: United States and Globally

United States Estimates of Multidrug-Resistant Bacterial Infections Associated with Healthcare


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

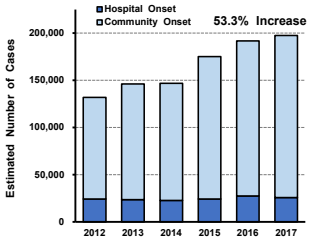
Multidrug-Resistant Bacterial Infections in U.S. Hospitalized Patients, 2012–2017

John A. Jernigan, M.D., Kelly M. Hatfield, M.S.P.H., Hannah Wolford, M.S.P.H., Richard E. Nelson, Ph.D., Babatunde Olubajo, Ph.D., Sujan C. Reddy, M.D., Natalie McCarthy, M.P.H., Prabasaj Paul, Ph.D., L. Clifford McDonald, M.D., Alex Kallen, M.D., Anthony Fiore, M.D., Michael Craig, M.P.P., and James Baggs, Ph.D.

- New analysis methods to provide more robust national burden estimates and allow tracking of recent incidence trends
- Used 3 electronic health databases to calculate national burden estimates:
  - Premier Healthcare Database
  - Cerner Health Facts
  - BD Insights Research Database
- Served as the basis for the updated CDC report *"Antibiotic Resistant Threats in the United States, 2019"*

Jernigan JA, et al. *N Engl J Med.* 2020; 382: 1309-19.
https://www.cdc.gov/drugresistance/biggest-threats.html

ESBL-Producing Enterobacteriaceae
United States Hospitalized Patients, 2012 - 2017

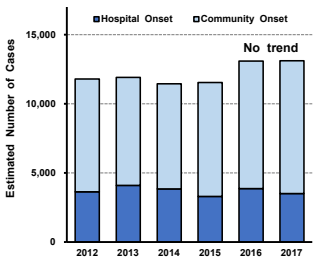


- Increase in incidence was from 37.55 to 57.12 cases per 10,0000 hospitalizations

- Emergence of *E. coli* clonal group ST131
  - Enhanced virulence characteristics
  - Colonize for longer periods of time
  - Strongly associated with ESBL phenotype
- Greater proportion of cases likely result from community-based transmission

Jernigan JA, et al. *N Engl J Med* 2020; 382: 1309-19.
https://www.cdc.gov/drugresistance/biggest-threats.html

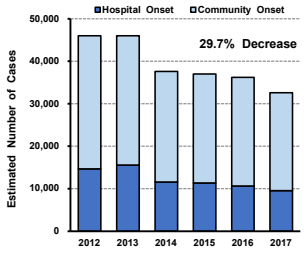
Carbapenem-Resistant Enterobacteriaceae
United States Hospitalized Patients, 2012 - 2017



- No significant change in the incidence, from 3.36 to 3.79 cases per 10,0000 hospitalizations
- Proportion of healthcare-associated Enterobacteriaceae resistant to carbapenems decreased sharply in the United States between 2007 and 2012
- Reductions subsequently plateaued and remained at low, stable levels since 2012
- Further progress may be needed in high-risk populations and better regional surveillance and prevention activities

Jernigan JA, et al. *N Engl J Med.* 2020; 382: 1309-19.
https://www.cdc.gov/drugresistance/biggest-threats.html

MDR Pseudomonas aeruginosa
United States Hospitalized Patients, 2012 - 2017



- Decrease in incidence was from 13.10 to 9.43 cases per 10,0000 hospitalizations
- Decreases in incidence are very likely attributable to a change in transmission in health care settings rather than in the community
- MDR *P. aeruginosa* are identified almost exclusively among patients with substantial health care exposure
- Appear to be rarely acquired in the community

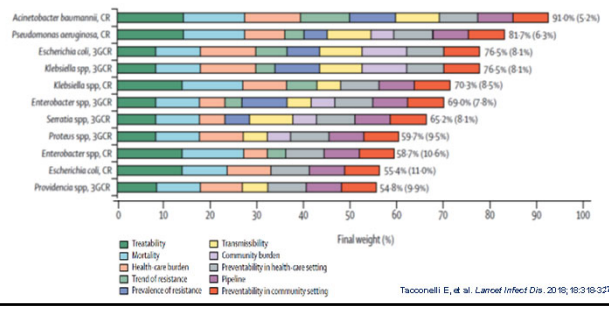
Jernigan JA, et al. *N Engl J Med.* 2020; 382: 1309-19.
https://www.cdc.gov/drugresistance/biggest-threats.html

WHO Priority Pathogen List
for R&D of New Antibiotics

- **Priority 1: Critical**
  - ***Enterobacteriaceae*, carbapenem-resistant, ESBL-producing**
  - ***Pseudomonas aeruginosa*, carbapenem-resistant**
  - ***Acinetobacter baumannii*, carbapenem-resistant**
- Includes multidrug-resistant bacteria that pose a particular threat in hospitals, nursing homes, and among patients whose care requires devices such as ventilators and blood catheters
- Can cause severe and often deadly infections such as bloodstream infections and pneumonia
- Resistant to a large number of antibiotics, including the best available antibiotics for treating multi-drug resistant bacteria

Released February 27, 2017
http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/

WHO Priority List
Final Ranking of Antibiotic-Resistant Bacteria



Tacconelli E, et al. *Lancet Infect Dis*. 2018; 18:318-327.

WHO Priority Pathogen List
for R&D of New Antibiotics

- **Priority 2: HIGH**
  - ***Enterococcus faecium*, vancomycin-resistant**
  - ***Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate or resistant**
  - ***Helicobacter pylori*, clarithromycin-resistant**
  - ***Campylobacter* spp., fluoroquinolone-resistant**
  - ***Salmonellae*, fluoroquinolone-resistant**
  - ***Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant**
- **Priority 3: MEDIUM**
  - ***Streptococcus pneumoniae*, penicillin-non-susceptible**
  - ***Haemophilus influenzae*, ampicillin-resistant**
  - ***Shigella* spp., fluoroquinolone-resistant**

Released February 27, 2017
http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/

Which geographic region has had the highest increase in the prevalence rate of carbapenem-resistant *Klebsiella pneumoniae* during the past 20 years ?

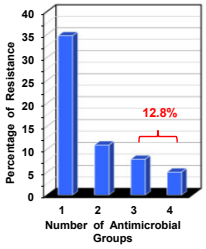
1. Latin America
2. Asia – Pacific
3. Northern Europe
4. North America

Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)

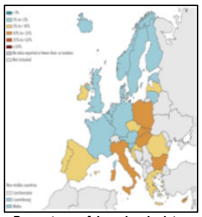
- Based on antimicrobial resistance data from invasive isolates reported to EARS-Net by 30 European Union (EU) and European Economic Area (EEA) countries in 2019 (data referring to 2018)
- Trend analyses of data reported by the participating countries for the period 2015 to 2018
- For most Gram-negative bacterial species–antimicrobial group combinations, changes in resistance percentages between 2015 and 2018 were moderate, and resistance remained at previously reported high levels

https://www.ecdc.europa.eu
European Centre for Disease Prevention and Control. Surveillance of Antimicrobial Resistance in Europe 2018. Stockholm: ECDC; 2019.

Escherichia coli
Surveillance of Antimicrobial Resistance in Europe



- 58.3% of isolates were resistant to at least one of the antimicrobial groups
- Population-weighted mean resistance percentage:
  - 57.4% - Aminopenicillins
  - 25.3% - Fluoroquinolones
  - 15.1% - 3rd-Generation Cephalosporins
  - 11.1% - Aminoglycosides
  - Rare - Carbapenems
- Large inter-country variations
- Higher resistance reported from southern and eastern Europe than northern Europe

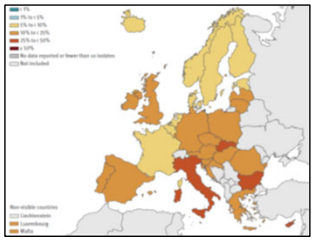


Percentage of Invasive Isolates with Combined Resistance to 3rd GC, FQ, and AG

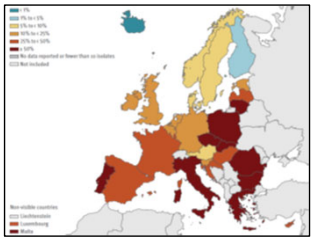
https://www.ecdc.europa.eu

Resistance to 3rd-Generation Cephalosporins
Survey on Epidemiological Situation in Europe, July 2018

Escherichia coli

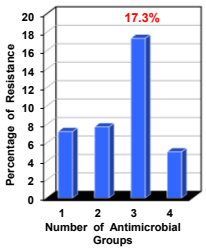


Klebsiella pneumoniae

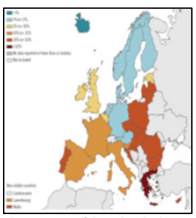


https://www.ecdc.europa.eu

Klebsiella pneumoniae
Surveillance of Antimicrobial Resistance in Europe



- 37.2% of isolates were resistant to at least one of the antimicrobial groups
- Population-weighted mean resistance percentage:
  - 31.7% - 3rd-Generation Cephalosporins
  - 31.6% - Fluoroquinolones
  - 22.7% - Aminoglycosides
  - 7.5% - Carbapenems
- Between 2015 and 2018, significantly increasing trends in population-weighted mean percentages of fluoroquinolone and carbapenem resistance

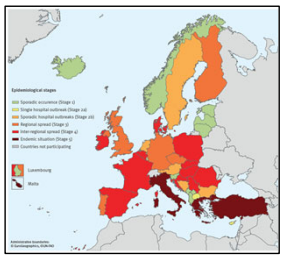


Percentage of Invasive Isolates with Combined Resistance to 3rd GC, FQ, and AG

https://www.ecdc.europa.eu

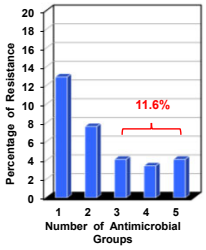
Carbapenemase-Producing Enterobacteriaceae
Survey on Epidemiological Situation in Europe, July 2018

- CPE in healthcare systems in Europe disseminated further between 2015 and 2018
- In 2018, 20 of 37 countries reported inter-institutional spread of CPE within the country (epidemiological stages 3 - 5)
- Compared to 2015, 11 countries reported a worsened epidemiological situation
- The general situation for carbapenem-resistant Enterobacteriaceae (CRE), including *E. coli*, worsened in many EU/EEA countries between 2010 and 2018
- Reports of the occurrence of CR *E. coli* in several bordering non-EU/EEA countries

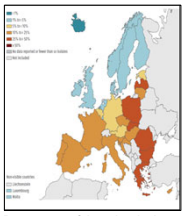


Brolund A, et al. *Euro Surveill.* 2019;24(9):pii=1900123.
https://doi.org/10.2807/1560-7917.ES.2019.24.9.1900123

Pseudomonas aeruginosa
Surveillance of Antimicrobial Resistance in Europe



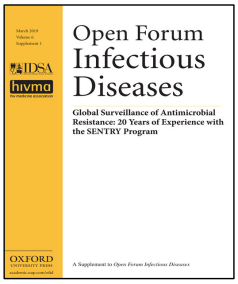
- 32.1% of isolates were resistant to at least one of the antimicrobial groups
- Population-weighted mean resistance percentage:
  - 19.7% - Fluoroquinolones
  - 18.3% - Piperacillin-Tazobactam
  - 17.2% - Carbapenems
  - 14.1% - Ceftazidime
  - 11.8% - Aminoglycosides
- Large inter-country variations
- Higher resistance reported from southern and eastern Europe than northern Europe



Percentage of Invasive Isolates with Resistance to ≥ 3 Groups

https://www.ecdc.europa.eu

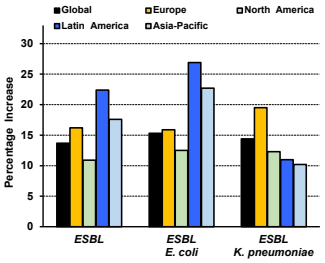
Global Surveillance of Antimicrobial Resistance



- The SENTRY Antimicrobial Surveillance Program (SENTRY Program) was designed to track AMR trends and the spectrum of microbial pathogens across various infection types on a global scale
- SENTRY Program monitors both nosocomial and community-onset infections on a global scale and uses validated reference identification and susceptibility testing methods via a central monitoring laboratory model (JMI Laboratories)
- The SENTRY Program originated from the recommendations of the American Society for Microbiology (ASM) Task Force on Antimicrobial Resistance that convened in 1994

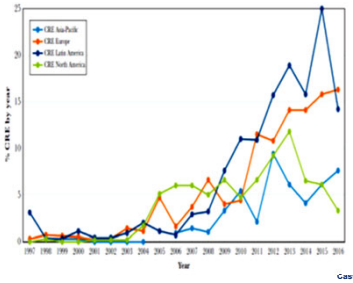
ESBL-Producing Enterobacteriaceae
20-Year SENTRY Program, 1997 - 2016

- 178,825 Enterobacteriaceae isolates, 18.0% species displayed ESBL phenotype (CLSI criteria)
- 10.3% in 1997-2000 compared to 24.0% in 2013-2016
- Greatest increase in ESBL-phenotype rate was in Latin America followed by Asia-Pacific, Europe, and USA
- ESBL-phenotype were mainly *E. coli* (47.5%) and *K. pneumoniae* (43.7%); respective occurrence increased from 3.3% to 15.8% and 7.1% to 19.4% when 1997-2000 was compared to 2013-2016



Castanheira M, et al. *Open Forum Infect Dis.* 2019; 6 (Suppl 1): S23-S33.

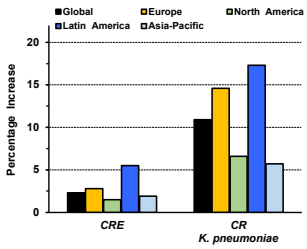
Carbapenem-Resistant Enterobacteriaceae
20-Year SENTRY Program, 1997 - 2016



- CRE prevalence in North America, rates increased from 1.7% to 5.1% from 2004 to 2005; rates stayed above 5% until 2016
- An increase in CRE prevalence among European countries was noted in 2005, with rates constantly above 5% after 2007
- CRE rates in Asia-Pacific and Latin America were above 5% after 2010 and 2008, respectively

Castanheira M, et al. *Open Forum Infect Dis.* 2019; 6 (Suppl 1): S23-S33.

Carbapenem-Resistant Enterobacteriaceae
20-Year SENTRY Program, 1997 - 2016

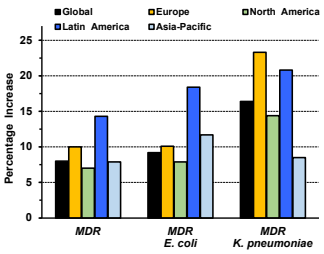


- CRE rates increased from 0.6% in 1997-2000 to 2.9% in 2013-2016
- A remarkable increase (5.6%) noted in Latin America compared to 1.5%, 1.9%, and 2.8% for North America, Asia-Pacific, and Europe, respectively
- Carbapenem-resistant *K. pneumoniae* (CR-KPN) main driver (71.1% of CRE isolates)
- CR-KPN increased varied among regions, and were higher in Latin America, followed by Europe

Castanheira M, et al. *Open Forum Infect Dis.* 2019; 6 (Suppl 1): S23-S33.

MDR Enterobacteriaceae
20-Year SENTRY Program, 1997 - 2016

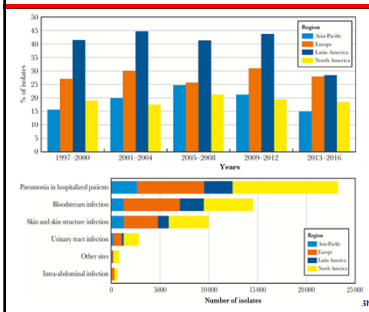
- MDR rates significantly increased from 7.3% to 15.3% in 1997-2000 compared to 2013-2016
- Variability was observed among different regions and infection sources
- Most common MDR species were *K. pneumoniae* (35.2%), *E. coli* (30.2%), *E. cloacae* (9.7%), *P. mirabilis* (6.3%), and *S. marcescens* (5.3%)
- MDR rates significantly increased over time for *K. pneumoniae* (16.4%↑) and *E. coli* (9.2%↑)



Castanheira M, et al. *Open Forum Infect Dis.* 2019; 6 (Suppl 1): S23-S33.

MDR *Pseudomonas aeruginosa*

20-Year SENTRY Program, 1997 - 2016



- The region with the highest percentage of MDR phenotypes was Latin America (41.1%)
- The MDR rates were highest in 2005 to 2008 and have decreased in the most recent period
- Colistin was the most active drug tested (99.4% susceptible), followed by amikacin (90.5% susceptible)
- Rates of MDR *P. aeruginosa* infections has decreased, particularly in Latin America

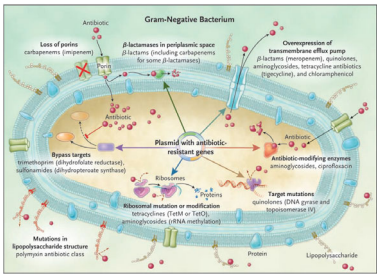
Shortridge D, et al. *Open Forum Infect Dis.* 2019; 6 (Suppl 1): S63-S68.

Common Resistance Mechanisms Used by Gram-negative Bacteria

Mechanisms of Resistance in Gram-Negative Bacteria

Mechanisms include:

- Loss of porins
- Presence of β-lactamases in the periplasmic space
- Increased expression of the transmembrane efflux pump
- Antibiotic-modifying enzymes
- Target site mutations
- Ribosomal mutations or modifications
- Metabolic bypass mechanisms
- Mutation in the lipopolysaccharide



Peleg AY & Hooper DC. *N Engl J Med.* 2010; 362: 1804-1813.

Beta-Lactamase Classifications

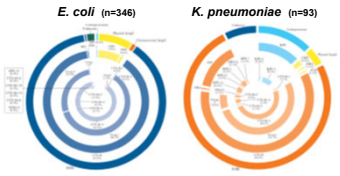
Ambler class[1]: catalytic site (spectrum)	Bush–Jacoby–Medeiros group[2]: catalytic site (spectrum)	Substrates	Inhibited by	Examples
A: serine (variable)	2a: serine (penicillinases)	Penicillins	Clavulanate, avibactam and other newer inhibitors[a]	Penicillinases from Gram-positive bacteria
	2b: serine (penicillinases)	Penicillins and narrow-spectrum cephalosporins	Clavulanate, avibactam and other newer inhibitors	TEM-1, TEM-2 and SHV-1
	2be: serine (ESBLs)	Penicillins and cephalosporins, including extended-spectrum	Clavulanate, avibactam and other newer inhibitors	SHV-2, TEM-10, CTX-M and GES-1
	2br: serine (inhibitor-resistant)	Penicillins	Avibactam and other newer inhibitors	TEM-30 and SHV-72
	2c: serine (penicillinases)	Penicillins and carbenicillin	Clavulanate, avibactam and other newer inhibitors	PSE (CARB)
	2f: serine (carbapenemases)	Penicillins, cephalosporins and carbapenems	Avibactam and other newer inhibitors	KPC, SME, NMC-A and GES-2
B: metallo (carbapenemase)	3: metallo (carbapenemases)	Most β-lactams, including carbapenems, but not monobactams	Chelating agents (EDTA) and ANT431	IMP, VIM and NDM
C: serine (cephalosporinases)	1: serine (cephalosporinases)	Penicillins and cephalosporins	Cloxacillin, avibactam and other newer inhibitors	Chromosomal AmpC, CMY, ACT-1 and DHA
D: serine (oxacillinases)	2d: serine (oxacillinases)	Penicillins and cloxacillin; some include cephalosporins and/or carbapenems	Sodium chloride; some by clavulanate, avibactam and other newer inhibitors	OXA-1/30, OXA-10, OXA-23 and OXA-48

Bush K & Bradford PA. *Nat Rev Microbiol.* 2019; 17: 295-306.

Distribution of Beta-Lactamase-Encoding Genes

***Escherichia coli* and *Klebsiella pneumoniae* Causing UTI or BSI**

- TEM- and SHV-type ESBLs described in 1980s and 1990s
  - 183 variants of TEM
  - 178 variants of SHV
- CTX-M-type ESBL is most common type of ESBL; spread worldwide since 2000
  - CTX-M-15 dominates
- OXA-type ESBL phenotype
- Other less common ESBLs
  - GES, PER, VEB, BES, BEL, SFO, and TLA beta-lactamases



E. coli (n=346)		*K. pneumoniae* (n=93)	
ESBL:	88.2%	ESBL:	75.3%
AmpC:	9.2%	AmpC:	4.4%
KPC:	0.6%	KPC:	12.9%
ST131 most common clonal complex		ST258 and ST307 most common clonal complex	

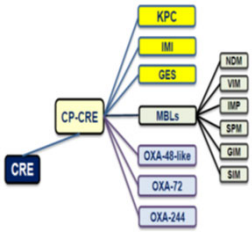
Bush K & Bradford PA. *Clin Microbiol Rev.* 2020; 33: e00047-19.
Mendes RE, et al. *Open Forum Infect Dis.* 2019; 6 (Suppl 1): S69-S78.

Carbapenem Resistance Terminology

Carbapenem-Specific Terms	Definitions
CRE	Carbapenem-Resistant Enterobacterales (*Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae*)
CRO	Carbapenem-Resistant Organisms (Enterobacteriaceae plus *Pseudomonas* and *Acinetobacter*)
CPE (CP-CRE)	Carbapenemase-Producing Enterobacterales
CPO (CP-CRO)	Carbapenemase-Producing Organisms

Livermore DM, et al. *Clin Infect Dis.* 2020; doi: 10.1093/cid/ciaa122. [Epub ahead of print]

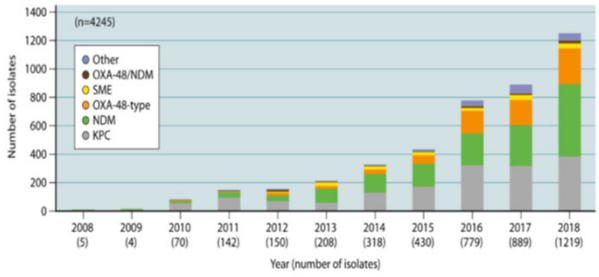
Carbapenemase-Producing-CRE



- Ambler Class A
  - KPC: *Klebsiella pneumonia* carbapenemase
  - IMI: Imipenem-hydrolyzing β-lactamase
  - GES: Guiana extended-spectrum β-lactamase
- Ambler Class B
  - MBLs: Metallo-β-lactamase
    - NDM: New Delhi MBL
    - VIM: Verona integrin-borne MBL
    - IMP: Imipenem-resistant *Pseudomonas* carbapenemase
    - SPM: Sao Paulo MBL
    - GIM: German imipenemase
    - SIM: Seoul imipenemase
- Ambler Class D
  - OXA: Oxacillinase

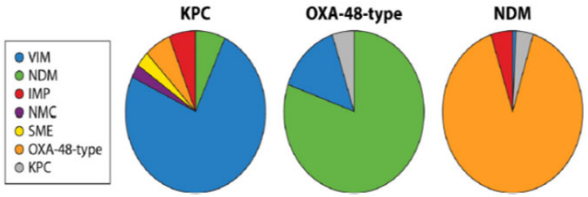
Suay-Garcia B and Perez-Gracia MT. *Antibiotics.* 2019; 8: 112.

Carbapenemase-Producing Enterbacterales in Canada



Bush K & Bradford PA. *Clin Microbiol Rev.* 2020; 33: e00047-19.

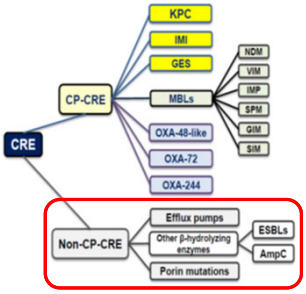
Co-Production of Carbapenemases in Same Gram-Negative Organism*



* Excluding *Acinetobacter* spp.

Bush K & Bradford PA. *Clin Microbiol Rev.* 2020; 33: e00047-19.

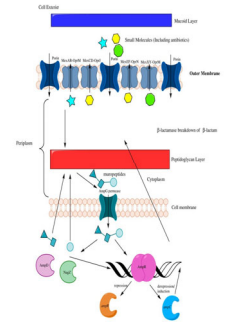
Non-Carbapenemase-Producing-CRE



- Efflux pumps
- Other beta-lactamases:
  - ESBLs: Extended-spectrum β-lactamases
  - AmpC: Ampicillinase
- Porin mutations

Suay-Garcia B and Perez-Gracia MT. *Antibiotics.* 2019; 8: 112.

Resistance Mechanisms in Pseudomonas aeruginosa



- Mucoid layer
  - *P. aeruginosa* has a mucoid layer outside the outer membrane; increased thickness of this layer
- Outer membrane porins
  - Loss of porins inhibits antibiotic entry
- Efflux pumps
  - *P. aeruginosa* can carry efflux pumps in the outer membrane; when present, antibiotics can be pumped out the cell
- PBP alterations
  - In peptidoglycan layer; altered to prevent interaction of antibiotics with their targets
- Beta-lactamase upregulation
  - Regulation of the chromosomal AmpC, which involves a complex relationships between peptidoglycan breakdown, beta-lactam exposure, and gene regulation leading to overexpression of the AmpC enzyme
  - In periplasmic space of the bacteria; able to break down beta-lactam antibiotics and/or beta-lactamase inhibitors

Winkler ML, et al. *Antimicrob Agents Chemother.* 2015; 59: 1020-1029.

Understanding the Value of Antibiograms in Guiding Empiric Antimicrobial Selection

Antibiograms

- Microbiology laboratories are essential to stewardship programs by ensuring quality specimen collection, appropriate testing, implementation of rapid diagnostics, antimicrobial susceptibility testing, and data analysis
- Antibiograms summarize the proportion of organisms that are susceptible to specific antimicrobials during a specific period of time, usually annually
- Antibiograms are often used by stewardship programs to:
  - make formulary decisions
  - develop guidelines for empiric therapy
  - monitor local resistance rates over time

Avdic E, Carroll KC. *Infect Dis Clin N Am.* 2014; 28: 215-235.

Types of Antibiogram

- Antibiograms stratification by location (eg., ICU vs non-ICU)
- Antibiograms stratified by:
  - Population age group (eg., pediatrics)
  - Infection site (eg., blood or respiratory vs all sources)
  - Patient comorbidities (eg., cystic fibrosis)
  - Acquisition in the community versus healthcare setting
- Combination antibiograms
- Syndrome-specific antibiograms
- Use of antibiograms in constructing empiric regimen in patients with prolonged hospital stays

Avdic E, Carroll KC. *Infect Dis Clin N Am.* 2014; 28: 215-235.
Bariam TF, et al. *Clin Infect Dis.* 2016; 62: e51-e76.

CLSI Guidelines for Antibiograms

- Data should include:
  - only species with at least 30 isolates
  - diagnostic isolates only (not surveillance)
  - first isolate per patient in the period analyzed
  - results only for drugs that are routinely tested
- Data should be stratified by:
  - patient population (inpatients, outpatients)
  - location (ICU, wards)
  - specimens types (all, blood, urine)
- Antibiograms should be generated at least annually

Clinical and Laboratory Standards Institute (CLSI). 4th ed. CLSI Document M39-A4, 2014.
Avdic E, Carroll KC. *Infect Dis Clin N Am.* 2014; 28: 215-235.

Breakpoint Updates for Colistin and Polymyxin B

CLSI has revised colistin and polymyxin B breakpoints for several Gram-negative bacteria. What minimum inhibitory concentration (MIC) value will categorize *Pseudomonas aeruginosa* as "resistant"?

1. ≥ 1 mg/L
2. ≥ 2 mg/L
3. ≥ 4 mg/L
4. ≥ 16 mg/L

CLSI Revised Breakpoints for Polymyxins

Organism	Colistin and Polymyxin B MIC (mg/L)		
	Susceptible	Intermediate	Resistant
Revised CLSI – June 2019			
Acinetobacter spp.		≤ 2	≥ 4
Pseudomonas aeruginosa		≤ 2	≥ 4
Enterobacteriaceae		≤ 2	≥ 4

Suggested warnings/comments added to colistin / polymyxin B breakpoints:

1. Clinical and PK/PD data demonstrated this agent is of limited clinical efficacy;
2. If available, alternative [non-polymyxin] agents are strongly preferred; if these agents are not available, this breakpoint presumes use of colistin in combination with 1 or more additional, active antimicrobial;
3. Colistin should be given with a loading dose and maximum renally adjusted dose;
4. When given systemically, this drug is unlikely to be effective for pneumonia

CLSI, Clinical and Laboratory Standards Institute

Satlin MJ, et al. *Clin Infect Dis.* 2020; doi: 10.1093/cid/ciaa121. [Epub ahead of print]

USCAST Susceptibility Breakpoints for Polymyxins Against P. aeruginosa, A. baumannii, and Enterobacteriaceae

Polymyxin	MIC Breakpoint (mg/L)		Disk Content
	Susceptible	Resistant	
Colistin[1,2] *(no breakpoint for respiratory tract infections)*	≤ 2	≥ 4	10 µg
Polymyxin B[1,3] *(no breakpoint for respiratory tract or lower urinary tract infections)*	≤ 2	≥ 4	300 units

1. Use only broth microdilution methods (disk diffusion unreliable). Colistin susceptibility results can infer susceptibility to polymyxin B at ≤ 2 mg/L or vice versa for listed species, but not *S. maltophilia;*
2. Colistin dosing based on EMA package insert or dosing algorithm by Nation et al.;
3. Polymyxin B dosing 2.5 mg/kg/day, with renal adjustments;
4. Polymyxin therapies should be combined with a second active agent, whenever possible

USCAST, United States Committee on Antimicrobial Susceptibility Testing

Pogue JM, et al. *Antimicrob Agents Chemother.* 2020; 64: e01495-19.

Colistin and Polymyxin B

- Assumed an important role as "salvage therapy" for otherwise untreatable Gram-negative infections
- Emerging pharmacokinetic-pharmacodynamic data indicate the monotherapy is unlikely to generate plasma concentrations that are reliably efficacious
- Regrowth and the emergence of resistance with monotherapy are commonly reported even when concentrations exceed those achieved clinically
- Combination therapy has been suggested as a possible means of increasing antimicrobial activity and reducing the development of resistance

Bergen PJ, et al. *Pharmacother.* 2015; 35: 34-42.
Kassamali Z, Danziger L. *Pharmacother.* 2015; 35: 17-21.
Paul M, et al. *Lancet Infect Dis.* 2018; 18: 391-400.

Summary

- Infections caused by resistant pathogens are associated with serious health and economic adverse outcomes
- Trends in antimicrobial resistance prevalence are geographical distinct and pathogen specific
- Gram-negative bacterial species continue to develop diverse mechanisms of resistance that are diverse and with geographic preferences for specific variants
- Antibiograms remain a useful tool for antimicrobial stewardship strategies

New Tools to Advance Pathogen-specific Therapy

Robert A. Bonomo, MD, FIDSA

Case Study

- A 51-year-old man with T1DM underwent simultaneous pancreas and kidney transplantation after being maintained on peritoneal dialysis for 4 years
- Transplant procedure was uncomplicated; cefazolin was administered for prophylaxis
- Immediate evidence of acceptable renal allograft was observed and patient was transferred to surgical ICU
  - Induction immunosuppression included anti-thymocyte globulin, mycophenolate mofetil, tacrolimus, and methylprednisolone
- Patient was transferred to regular inpatient medical unit on postoperative day (POD) 2

Patel G, Perez F, Bonomo RA, et al. *Transplant Infect Dis.* 2015;17:289-296.

Case Study (cont'd)

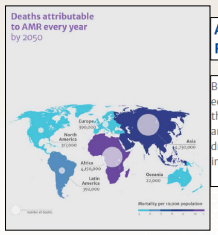
- On POD 4, patient experiences hypothermia (34.9°C), tachycardia (115 bpm), hypotension (90/60 mm Hg), and leukopenia (1700 WBC/mm^3)
  - During the day, patient complains of weakness and remains hypothermic, tachycardic, and hypotensive
- Patient is transferred to surgical ICU and examination reveals the abdomen is distended
- Blood and urine cultures are obtained and patient is started empirically on vancomycin and piperacillin/tazobactam

Patel G, Perez F, Bonomo RA, et al. *Transplant Infect Dis.* 2015;17:289-296.

Case Study – Points to Consider

- What are the patient's risk factors for a MDR infection?
- What additional diagnostic tests should be performed?
- What tools are available to help guide antimicrobial therapy?

By 2050, increases in antimicrobial resistance (AMR) will be responsible for 300 million deaths



ANTIMICROBIAL RESISTANCE: TACKLING A CRISIS FOR THE HEALTH AND WEALTH OF NATIONS

By setting out the full magnitude of the potential human and economic costs of rising drug resistance, this paper demonstrates that there is a clear global imperative to take this threat seriously and start finding solutions, not least as action taken now could dramatically reduce both the enormous financial and human impact of resistant infections in the future.

Total GDP Loss 100.2 Trillion USD

Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. Retrieved from https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.

Clinical Impact of Antimicrobial Resistance: ESBL Production and Mortality

Impact of ESBL production on mortality in Enterobacteriaceae bacteremia

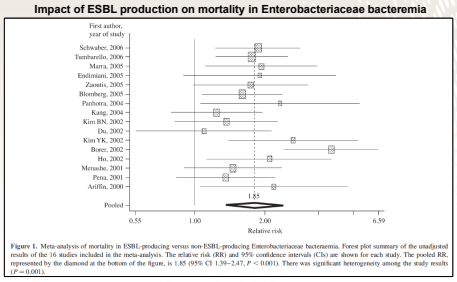
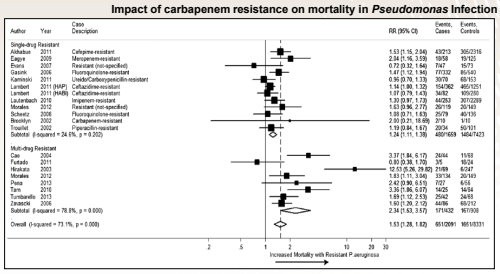


Figure 1. Meta-analysis of mortality in ESBL-producing versus non-ESBL-producing Enterobacteriaceae bacteremia. Forest plot summary of the unadjusted results of the 16 studies included in the meta-analysis. The relative risk (RR) and 95% confidence intervals (CIs) are shown for each study. The pooled RR, represented by the diamond at the bottom of the figure, is 1.85 (95% CI 1.39–2.47, $P < 0.001$). There was significant heterogeneity among the study results ($P = 0.001$).

Schwaber MJ, Carmeli Y. *J Antimicrob Chemother.* 2007;60:913–920.

Clinical Impact of Antimicrobial Resistance: Carbapenem Resistance by *Pseudomonas*

Impact of carbapenem resistance on mortality in *Pseudomonas* Infection

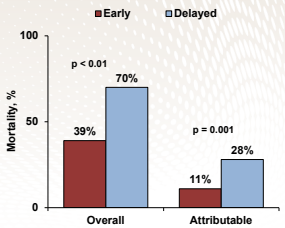


Clinical outcomes driven by:
1. **Patient factors**
2. **Timing of optimal appropriate therapy**

Nathwani D, et al. *Antimicrob Resist Infect Control.* 2014;3:32.

Early Appropriate Therapy is Essential in Reducing Mortality

- 107 patients with ventilator-associated pneumonia (VAP)
- Mean time from diagnosis of VAP to initiation of appropriate therapy was:
  - 28.6 hr in delayed group
  - 12.5 hr in early group



Iregui M, et al. *Chest.* 2002;122:262-268.

Inappropriate Initial Antibiotic: A Key Predictor of Mortality

Analysis of 364 consecutive patients with respiratory failure and pneumonia from a single institution (January 2016 to December 2016)

Variables	aOR	95% CI	*P* Value
Age (1-point increments)	1.05	1.03 – 1.07	0.032
Male gender	3.67	2.02 – 6.67	0.030
APACHE II Score (1-point)	1.14	1.09 – 1.19	0.003
Shock	10.69	5.21 – 21.93	0.001
Inappropriate initial antibiotic	5.28	2.72 – 10.22	0.012

Fisher K, et al. *Surg Infect (Larchmt).* 2017;18:827-33.

Strategies to Improve Early, Appropriate Initial Therapy

- Use of antibiograms
- Identify risk factors for MDR infection
- Rapid molecular diagnostics
- Pathogen-specific therapy

Risk Factors for Antimicrobial-Resistant Infection

- Recent prior antimicrobial therapy (within previous 90 days)
- Current hospitalization for prolonged period
- Immunosuppressive therapy
- Residence in nursing home or LTCF
- Chronic dialysis within previous month
- Receipt of medical care in high-risk country
- Transfer from post-acute care facility
- Use of invasive devices

Cerceo E, et al. *Microb Drug Resist.* 2016;22:412-431.
Simner PJ, et al. *Open Forum Infect Dis.* 2018;5(5):ofy094.

Rapid Diagnostics: Genotype or Phenotype

- Prompt identification of antimicrobial-resistant pathogens is critical for initiating optimal antimicrobial therapy and infection control measures
- Rapid diagnostics can quickly determine antimicrobial susceptibility (AST) or identify specific resistance mechanisms (genotypic tests)
  - Advantages of genotypic testing: Results typically within 2 hr, conclusive identification of resistance genes, test directly from specimens without need to culture
  - Disadvantages of genotypic testing: Detection is limited to only those genes/enzymes queried by primers or probes (can miss unique/novel resistance mechanisms)

Novel Approaches to Hasten Detection of Pathogens and Antimicrobial Resistance in the Intensive Care Unit

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[2]Division of Infectious Diseases, Washington University School of Medicine, St. Louis, Missouri
[3]Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri

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Semin Respir Crit Care Med 2019;40:454-464.

Patient Goals

- Optimize survival
- Reduce hospital stay
- Prevent unnecessary drug toxicity
- Reduce medical costs
- Improve functional status and quality of life

Stewardship Goals

- Avoid resistance emergence
- Prevent colonization and infection with MDROs
- Prevent *C. difficile* infection
- Contain and/or prevent outbreaks of MDRO infections
- Reduce overall healthcare exposure and expenditures

Guillamet MCV, et al. *Semin Respir Crit Care Med.* 2019;40:454-464.

Rapid Diagnostics for Genotypic Testing

Technology	Examples	Pathogen/Resistance Detection	Turnaround Time	Clinical Considerations
Real time PCR	Xpert® MRSA/SA BC	MRSA, MSSA, mec A/C	≤ 2 hr	• Prompt differentiation between MRSA and MSSA
	BD Max™ MRSA Staph SR/XT	MRSA, MSSA, mec A/C	≤ 2 hr	
Multiplex PCR	Biofire Filmarray® BC	GBP, GNB, *Candida* spp., mecA, vanA/B, KPC	≤ 2 hr	• Comprehensive number of targets • Not Gram-stain dependent
	Verigene® BC-GP	GPB, mecA, vanA/B	2.5 hr	
	Verigene® BC-GN	GNB, CTX-M, IMP, KPC, NDM, OXA, VIM	2 hr	
	Curetis Unyuero™ BCU	GPB, GNB, fungal panel, mycobacteria, 16 resistance genes	4 hr	
	Icubate IC GPC	GPC, mec A, vanA, vanB	4-5hr	• Many false negatives for *S. pneumoniae*
MALDI-TOF MS	bioMérieux VITEK® MS	Database for bacteria, fungi, mycobacteria, molds	<2 hr	• Detect many potential pathogens • Able to detect limited resistance mechanisms
	Bruker Sepsityper®		<2 hr	
PNA-FISH	AdvanDx QuickFISH®	GPB, GNB, *Candida* spp.	<2 hr	• Limited target detection • Rapid phenotypic AST

Guillamet MCV, et al. *Semin Respir Crit Care Med.* 2019;40:454-464.

Framework for Managing Antimicrobial Treatment in Critically Ill Patients

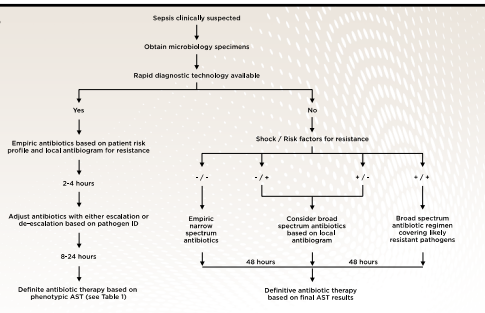
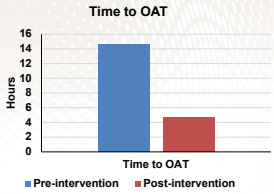


Fig. 2 A framework for managing antibiotic treatment in critically ill patients and including a pathway for the integration of rapid diagnostic technologies.

Guillamet MCV, et al. *Semin Respir Crit Care Med.* 2019;40:454-464.

Rapid Diagnostics Reduces the Time to Optimal Antimicrobial Treatment

- Compared timing of optimal antimicrobial treatment (OAT) for bloodstream infections pre- and post-intervention (use of Bio-Fire® FilmArray® blood culture identification) in ICU patients
  - Matched 110 patients
    - In post-intervention period, rapid diagnostic testing resulted in:
      - Treatment adjustment in 31.8% (35/110) of patients
        - Resulted in OAT (26 patients)
        - Resulted in tailoring following subsequent identification and AST results (9 patients)
    - Patient outcomes were not reported



Verroken A, et al. *PLoS ONE*. 2019;14(9):e0223122.

Use of a BAL Rapid Diagnostic Test for MRSA: Less Anti-MRSA Treatment and Lower Mortality

Comparison of outcomes with use of BAL rapid diagnostic test (Cepheid Xpert® platform) for MRSA vs. usual care in patients with suspected MRSA pneumonia

TABLE 5] Outcomes in RCT

Outcome	RPCR Group (n = 22)	Usual Care (n = 23)	P
Initial anti-MRSA treatment, h[a,b]	32 (22-48)	72 (50-113)	<.001
28-d total anti-MRSA treatment, h[a]	46 (24-73)	122 (66-219)	<.001
Duration of mechanical ventilation, h[c]	132 (54-209)	158 (44-464)	.44
ICU length of stay, d[a]	6 (5-14)	8 (6-26)	.19
Hospital length of stay, d[c]	15 (10-24)	29 (12-44)	.07
Any adverse event, No. (%)	13 (59.1)	17 (73.9)	.29
Acute renal failure	4 (18.2)	5 (21.7)	1.00
Thrombocytopenia	5 (22.7)	6 (26.1)	.79
Nosocomial infection	8 (36.4)	12 (52.2)	.29
In-hospital mortality	3 (13.6)	9 (39.1)	.05

RPCR, rapid automated PCR
Paonessa JR, et al. *Chest*. 2019;155:999-1007.

Newer Antimicrobials to Support Pathogen-Specific Therapy

Newer Antimicrobials Targeting MDR Gram-negative Pathogens

Beta-lactam/beta-lactamase inhibitors

- Ceftolozane-tazobactam
- Ceftazidime-avibactam
- Meropenem-vaborbactam
- Imipenem-relebactam

Others

- Eravacycline
- Plazomicin
- Cefiderocol

Ceftolozane-Tazobactam

- New cephalosporin plus an older beta-lactamase inhibitor
- Activity against ESBL-producing Enterobacteriaceae, MDR *P. aeruginosa*
- Indications:
  - Complicated UTIs plus pyelonephritis and complicated intra-abdominal infections (dosed 1.5 g q8h via IV infusion over 1 hour)
  - Hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) (dosed 3 g q8h via IV infusion over 1 hour)

Ceftolozane-Tazobactam Against Antimicrobial-Resistant *P. aeruginosa*

Ceftolozane-tazobactam susceptibility patterns of 3851 *Pseudomonas aeruginosa* isolates from United States hospitals (PACTS, 2012–2015):

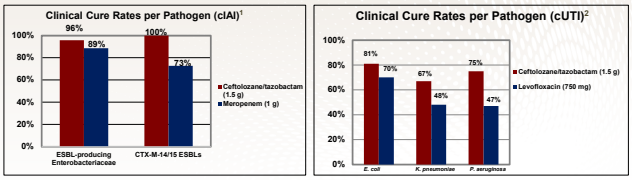
	% Susceptible	MIC_{50}	MIC_{90}
All isolates (n=3851)	97.0	0.5	2
Meropenem - Nonsusceptible (n=699)	87.6	1	8
Multidrug-resistant (MDR) (n=607)	84.0	2	8
Extensively drug-resistant (XDR) (n=363)	76.9	2	16
Nonsusceptible to cefepime, ceftazidime, meropenem, and piperacillin-tazobactam (n=241)	68.0	4	>32

Shortridge D, et al. *Antimicrob Agents Chemother* 2017; doi:10.1128/AAC.00465-17.

Ceftolozane-Tazobactam: Clinical Trial Results

Novel cephalosporin in combination with a β-lactamase inhibitor with broad-spectrum activity

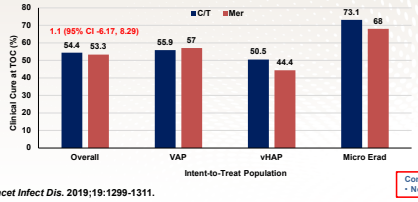
- **Ceftolozane stable in the presence of the 3 chromosomal mechanisms of resistance in *P. aeruginosa***



[1]Solomkin J, et al. *Clin Infect Dis.* 2015;60:1462-1471.
[2]Wagenlehner FM, et al. *Lancet.* 2015;385:1949-1956.

Ceftolozane-Tazobactam for Nosocomial Pneumonia (ASPECT-NP)

- Randomized controlled, double-blind phase III, non-inferiority trial comparing ceftolozane-tazobactam (3 g q8h) vs. meropenem (1 g q8h) for treatment of nosocomial pneumonia
  - All patients were ventilated



Kollef MH, et al. *Lancet Infect Dis.* 2019;19:1299-1311.

Conclusions:
- **Non-inferior in all patient populations**

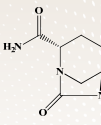
ASPECT-NP: Clinical Cure by Pathogen

Clinical Cure in Microbiologically Evaluable Population

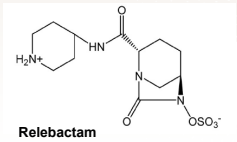
Pathogen	C/T n /N (%)	MER n/N (%)	% Treatment Difference (95% CI)
Overall	85/113 (75.2)	78/117 (66.7)	8.6 (-3.19, 19.94)
Enterobacteriaceae	62/83 (74.7)	58/90 (64.4)	10.3 (-3.50, 23.36)
ESBL+ Enterobacteriaceae	33/45 (73.3)	27/39 (69.2)	4.1 (-14.75, 23.06)
E. coli	17/23 (73.9)	16/23 (69.9)	4.3 (-20.86, 28.86)
ESBL+ *E. coli*	8/12 (66.7)	5/7 (71.4)	-4.8 (-39.06, 35.78)
K. pneumoniae	32/42 (76.2)	33/48 (68.8)	7.4 (-11.12, 24.91)
ESBL+ *K. pneumoniae*	22/30 (73.3)	19/27 (70.4)	3.0 (-19.53, 25.57)
P. aeruginosa	23/29 (79.3)	28/38 (73.7)	5.6 (-15.40, 24.70)
MDR *P. aeruginosa*	9/11 (81.8)	4/6 (66.7)	15.2 (-22.67, 54.07)
H. influenzae	11/12 (91.7)	4/8 (50.0)	41.7 (2.39, 70.96)

Martin-Loeches I, et al. Poster presented at ECCMID. Abstract #O0302.

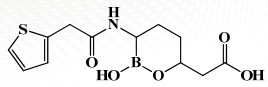
A Step Forward: Preserving the β-Lactam Promise – The "new generation of BLI"



Avibactam



Relebactam

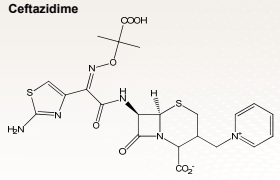


Vaborbactam

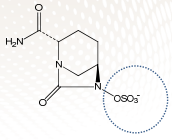
Ceftazidime/Avibactam

- **Older cephalosporin with new beta-lactamase inhibitor**
- **Avibactam resembles portions of the cephem bicyclic ring system**

Ceftazidime



Avibactam



- **Approved for complicated IAI, complicated UTI including pyelonephritis, and HABP/VABP**
- **Dosing: 2.5 g q8h IV infusion over 2 hours**

New β-Lactamase Inhibitors: a Therapeutic Renaissance in an MDR World

Against *Kp KPC*, AVI improves the activity of taz (~4x MIC reduction).

Sarah M. Drawz,[a] Krisztina M. Papp-Wallace,[b,c] Robert A. Bonomo[b,c,d,e]

Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, USA[a]; Research Service, Louis Stokes Cleveland Department of Veterans Affairs, Cleveland, Ohio, USA[b]; Departments of Medicine,[c] Pharmacology,[d] and Molecular Biology and Microbiology,[e] Case Western Reserve University, Cleveland, Ohio, USA

TABLE 1 MICs of β-lactam and β-lactam-avibactam combinations against select pathogens[a]

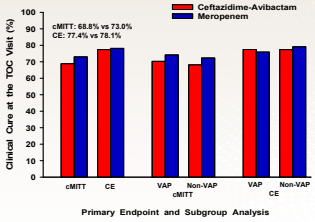
Pathogen	MIC (μg/ml)[b] CAZ	CAZ-AVI	CPT	CPT-AVI	ATM	ATM-AVI
K. pneumoniae with OXA-48	256/512	0.25/0.5				
K. pneumoniae with CTX-M-15	8/64	0.06/0.25				
K. pneumoniae with KPC-2	>512/>512	0.25/1			>512/>512	≤0.06/≤0.06
E. coli with ESBL	16/64	0.12/0.25				
E. coli with AmpC	16/64	0.12/0.5				
E. coli with OXA-48	4	<0.008				
E. coli with IMP-1	256	64				
Enterobacteriaceae with multiple β-lactamases, including KPC-2			>64/>64	0.5/2		
Enterobacteriaceae with multiple β-lactamases, including AmpC			256/>256	0.5/2		
Enterobacteriaceae with VIM	64–512	64–512			0.25–256	0.12–0.5
P. aeruginosa	8/64	4/8	>64/>64	16/>32	16/32	8/32
P. aeruginosa with ESBL PER-1	128/128	4/16				
A. baumannii			>64/>64	32/>32		
A. baumannii with PER-1, OXA-51, and OXA-58	128/≥512	32/256				
S. aureus			1/2	1/2		

[a] Data were adapted from references 15, 16, 19, 20, 21, and 24. Avibactam was added at 4 μg/ml. Abbreviations: CAZ, ceftazidime; AVI, avibactam; CPT, ceftaroline; ATM, aztreonam.

[b] Numbers separated by a forward slash indicate MIC—MIC$_{90}$ values. Empty cells indicate that values were not reported.

Ceftazidime-Avibactam for Nosocomial Pneumonia

Phase 3, Randomized, Multicenter Study (REPROVE Study)



Secondary Efficacy Endpoints

Per Pathogen Clinical Cure Rates and Favorable Microbiological Response at TOC	Ceftazidime-Avibactam	Meropenem
Clinical Cure (CE)		
K. pneumoniae	83.8% (31/37)	79.6% (39/49)
P. aeruginosa	64.3% (27/42)	77.1% (27/35)
Favorable Microbiological Response (eME)		
K. pneumoniae	78.4% (29/37)	79.6% (39/49)
P. aeruginosa	42.9% (18/42)	40.0% (14/35)

TOC, test-of-cure ; cMITT, clinically modified intent-to-treat; CE, clinically evaluable; mMITT, microbiological MITT; eME, extended microbiologically evaluable population

Torres A, et al. *Lancet Infect Dis.* 2018;18:285-295.

Ceftolozane-Tazobactam and Ceftazidime-Avibactam Against MDR *P. aeruginosa*

Number of isolates (cumulative %) inhibited at an MIC of:

	≤ 0.25	0.5	1	2	4	8	16	32	>32
Ceftazidime/ Avibactam		1 (0.3)	4 (1.5)	45 (15.2)	87 (45.1)	100 (71.8)	54 (87.9)	17 (93)	23 (100)
Ceftolozane/ Tazobactam			22 (12.6)	47 (39.4)	51 (68.6)	29 (85.1)	8 (89.7)	4 (92)	14 (100)

P. aeruginosa **resistant to ceftazidime, meropenem, & pip-tazobactam**

Red box = MIC_{50}
Sader HS, et al. *Antimicrob Agents Chemother.* 2015;59:3656-3659.
Farrell DJ, et al. *Antimicrob Agents Chemother.* 2013;57:6305-6310.

If AVI is biochemically better than other inhibitors, should there be a clinical correlate? "Real world" applications

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[4] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2]; for the Antibacterial Resistance Leadership Group

Van Duin D, et al. *Clin Infect Dis.* 2018;66:163-71.

CRACKLE-I Study

- 137 patients met criteria; 38 patients were treated first with ceftazidime-avibactam and 99 with colistin.
- BSI (n=63, 46%) > PNA(n=30, 22%).
- No isolates had bla_{NDM}, bla_{VIM}, bla_{IMP} or bla_{OXA-48}.
- ST258A (18/54, 33%) and ST258B (23/54, 43%) were the most commonly encountered clades of CRKP

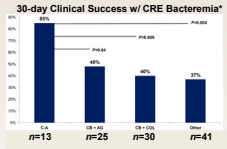
Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacteriaceae (CRACKLE), a prospective, multicenter, observational study.

Van Duin D, et al. *Clin Infect Dis.* 2018;66:163-71.

CRACKLE-I Study: Conclusions

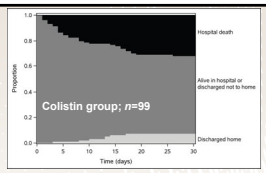
- In patients treated with TAZ AVI vs. colistin all-cause hospital mortality at 30-days after starting treatment was 9% vs 32%
- Thus…..In this prospective, observational, multi-center cohort, all-cause propensity adjusted mortality was decreased in patients with CRE infections started on ceftazidime/avibactam vs. colistin (absolute risk reduction 23% [95% CI 9%-35%], p=0.0012).

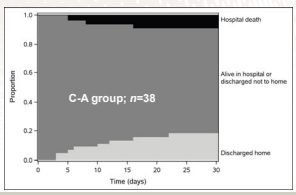
Van Duin D, et al. *Clin Infect Dis.* 2018;66:163-71.



"One good drug is better than two bad ones"

NEED VALIDATION

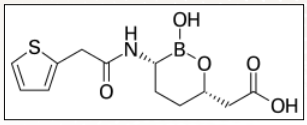




Van Duin D, et al. *Clin Infect Dis.* 2018;66:163-71.
*Shields, et al. *Antimicrob Agents Chemother.* 2017;61:e00883.

Meropenem/Vaborbactam

- Older carbapenem with new beta-lactamase inhibitor
- Indication: complicated UTI including pyelonephritis
- Dosing: 4 g q8h via IV infusion over 3 hours



TANGO I Study

JAMA | Original Investigation

Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection
The TANGO I Randomized Clinical Trial

Keith S. Kaye, MD, MPH; Tanaya Bhowmick, MD; Symeon Metallidis, MD; Susan C. Bleasdale, MD; Olexiy S. Sagan, MD; Viktor Stus, MD, PhD; Jose Vazquez, MD; Valerii Zaitsev, PhD; Mohamed Bidair, MD; Erik Chorvat, MD; Petru Octavian Dragoescu, MD; Elena Fedosiuk, MD; Juan P. Horcajada, MD, PhD; Claudia Murta, MD; Yaroslav Sarychev, MD; Ventislav Stoev, MD; Elizabeth Morgan, BS; Karen Fusaro, BS; David Griffith, BS; Olga Lomovskaya, PhD; Elizabeth L. Alexander, MD; Jeffery Loutit, MBChB; Michael N. Dudley, PharmD; Evangelos J. Giamarellos-Bourboulis, MD, PhD

- **Phase 3, MC, MN, RCT (TANGO I) conducted 11/ 2014 to 4/ 2016**
- **Patients (≥18 years) with c UTI, stratified by infection type and geographic region**

TANGO I Results

For the FDA primary end point, overall success occurred in 189 of 192 (98.4%) with meropenem-vaborbactam vs 171 of 182 (94.0%) with piperacillin-tazobactam (difference, 4.5% [95% CI, 0.7% to 9.1%]; *P* < .001 for noninferiority).

How do you translate these studies to CREs? MDROs?

Infect Dis Ther (2018) 7:439–455
https://doi.org/10.1007/s40121-018-0214-1

ORIGINAL RESEARCH

Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial

Richard G. Wunderink · Evangelos J. Giamarellos-Bourboulis · Galia Rahav · Amy J. Mathers · Matteo Bassetti · Jose Vazquez · Oliver A. Cornely · Joseph Solomkin · Tanaya Bhowmick · Jihad Bishara · George L. Daikos · Tim Felton · Maria Jose Lopez Furst · Eun Jeong Kwak · Francesco Menichetti · Ilana Oren · Elizabeth L. Alexander · David Griffith · Olga Lomovskaya · Jeffery Loutit · Shu Zhang · Michael N. Dudley · Keith S. Kaye

Received: August 13, 2018 / Published online: October 1, 2018

Monotherapy with M/V for CRE infection was associated with increased clinical cure, decreased mortality, and reduced nephrotoxicity compared with BAT.

Clinical Infectious Diseases
INVITED ARTICLE
REVIEWS OF ANTI-INFECTIVE AGENTS: Louis D. Saravolatz, Section Editor

Ceftazidime/Avibactam, Meropenem/Vaborbactam, or Both? Clinical and Formulary Considerations

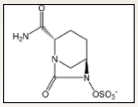
Jason M. Pogue,[1,2] Robert A. Bonomo,[3,4,5] and Keith S. Kaye[6]

Table 1. In Vitro Activity of Ceftazidime/Avibactam and Meropenem/Vaborbactam Against Problematic Gram-negative Pathogens

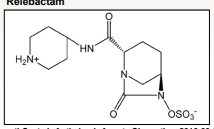
Organism	Resistance Present	Ceftazidime/ Avibactam	Meropenem/ Vaborbactam
Enterobacteriaceae			
	ESBL	+++	+++
	AmpC	+++	+++
	KPC	+++	+++
	MBL	–	*
	OXA-48–like	+++	*
Acinetobacter baumannii			
	Carbapenem- resistant	–	–
Pseudomonas aeruginosa			
	Carbapenem-resistant	++	–
	Pan-β-lactam resistant	+	–
Stenotrophomonas maltophilia			
	Ceftazidime-resistant	–	–

Imipenem-Cilastatin-Relebactam

Avibactam



Relebactam



Relebactam
- A novel diazabicyclooctane β-lactamase inhibitor
- Potent inhibitor of KPCs
- Restores activity of imipenem against *P. aeruginosa*

Imipenem-Cilastatin-Relebactam
- FDA approved in July 2019 based on clinical trials for cIAI[1] and cUTI[2]
- Dosing: 1.25 g q6h via IV infusion over 30 minutes

[1]**Lucasti C, et al. *Antimicrob Agents Chemother.* 2016;60:6234-6243.**
[2]**Sims M, et al. *J Antimicrob Chemother.* 2017;72:2616-2626.**

Clinical Infectious Diseases

MAJOR ARTICLE

RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections

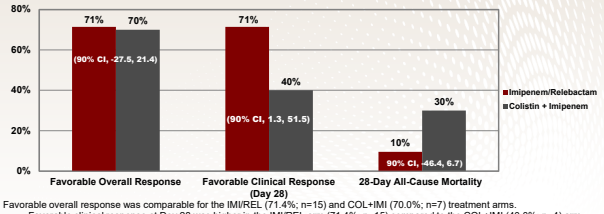
Johann Motsch,[1] Cláudia Murta De Oliveira,[2] Viktor Stus,[3] Ithar Köksal,[4] Olexiy Lyulko,[5] Helen W. Boucher,[6] Keith S. Kaye,[7] Thomas M. File Jr,[8] Michelle L. Brown,[9] Ireen Khan,[9] Jiejun Du,[9] Hee-Koung Joeng,[9] Robert W. Tipping,[9] Angela Aggrey,[9] Katherine Young,[9] Nicholas A. Kartsonis,[9] Joan R. Butterton,[9] and Amanda Paschke[9]

[1]Universitätsklinikum Heidelberg, Germany; [2]Santa Casa de Misericórdia, Belo Horizonte, Brazil; [3]Dnipropetrovsk Medical Academy, Dnipro, Ukraine; [4]Karadeniz Technical University School of Medicine, Trabzon, Turkey; [5]Department of Urology, Zaporozhye State Medical University, Zaporozhye, Ukraine; [6]Tufts Medical Center, Boston, Massachusetts; [7]University of Michigan, Ann Arbor Michigan; [8]Summa Health, Akron, Ohio; and [9]Merck & Co., Inc., Kenilworth, New Jersey

- Multicenter, randomized, DB, comparator-controlled trial: IMI/REL vs COL+IMI in pts with imi-non- susceptible bacterial infections.
- Patients with HABP/VABP, cIAI, or cUTI caused by one or more imi-non-susceptible (but Colistin- and IMI/REL susceptible) pathogens, were randomized 2:1 to receive IMI/REL or COL+IMI in a double-blind fashion.
- Study duration was 5-21 days for cUTI and cIAI; 7-21 days for HABP/VABP.

Motsch J, et al. *Clin Infect Dis.* 2020;70:1799-1808.

RESTORE-IMI 1: Clinical Outcomes



- Favorable overall response was comparable for the IMI/REL (71.4%; n=15) and COL+IMI (70.0%; n=7) treatment arms.
  - Favorable clinical response at Day 28 was higher in the IMI/REL arm (71.4%; n=15) compared to the COL+IMI (40.0%; n=4) arm, and 28-day all-cause mortality was lower in the IMI/REL arm (9.5%; n=2) vs. COL + IMI (30.0%; n=3), respectively.
- Adverse events occurred in 16.1% of patients (n=31) in the IMI/REL arm vs. 31.3% of patients (n=16) in the COL+IMI arm.
  - Treatment-emergent nephrotoxicity was lower with IMI-REL (10%; 3/29)

Motsch J, et al. *Clin Infect Dis.* 2020;70:1799-1808.

Other Newer Antimicrobials

Agent	Class	Indications	In Vitro Activity
Plazomicin	Semi-synthetic amino-glycoside	cUTI including pyelonephritis	Aminoglycoside-resistant, MDR, PDR, XDR Enterobacteriaceae (but not NDM)
Eravacycline	Novel fluorocycline	cIAI	Broad-spectrum including MDR Gram-positive and Gram-negative, anaerobes, CRE, *A. baumannii*, some colistin-resistant bacteria (reduced activity against *P. aeruginosa*)
Cefiderocol	Siderophore cephalosporin	cUTI including pyelonephritis	ESBL, KPC, and MBL Enterobacteriaceae, MDR *P. aeruginosa*, *A. baumannii*

Activity of Newer Agents vs. Problematic Organisms/Resistance Mechanisms

	CR-Pa	CR-Acineto	ESBL-Eb	KPC-Eb	Metallo-BL	OXA-48-Eb
Ceftolozane-Tazobactam	+	-	+/-	-	-	?
Ceftazidime-Avibactam	+	-	+	+	-	+
Meropenem-Vaborbactam	-	-	+	+	-	-
Imipenem-Relebactam	+	-	+	+	-	-
Cefiderocol	+	+	+	+	+	+
Plazomicin	-	-	+	+	-*	-*
Eravacycline	-	+/-	+	+/-	+/-	+/-

*Resistance due to presence of 16rRNA methyltransferases in many of these organisms

1) Jacobs MR, et al. *IDWeek* 2108 Poster 1348.
2) Livermore DM, et al. *Antimicrob Agents Chemother.* 2016;60:3840.
3) Stewart A, et al. *Antimicrob Agents Chemother.* 2018;62:e01195.

What Do I Do in Clinical Practice?

- ESBL-producers
- CRE
- MDR *P. aeruginosa*

Conclusions

- Though MDR Gram-negative bacteria present challenges, there are tools available to help select appropriate initial therapy
  - Rapid diagnostics
  - Newer antimicrobials that can potentially overcome resistance mechanisms
- With the expansion of the antimicrobial armamentarium, clinicians have a greater ability to utilize a pathogen-specific approach in antimicrobial selection