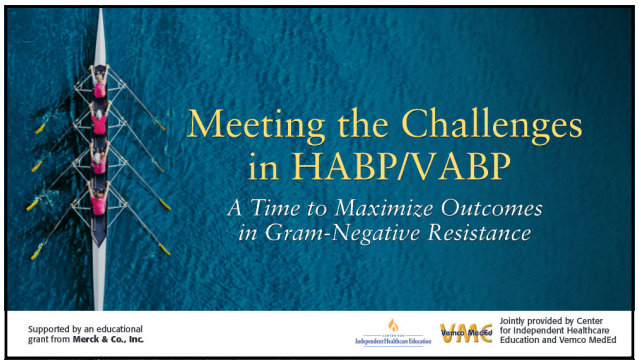
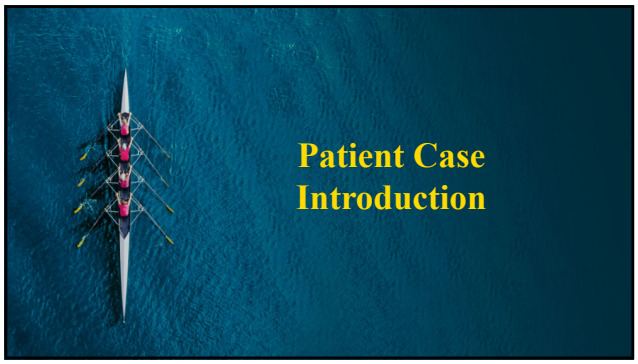


1



2

Patient Case: Jason

- 60-year-old male with history of COPD
- Admitted to hospital with URI symptoms and bilateral multifocal pneumonia
  - Initially treated with ceftriaxone IM 2 g and azithromycin IV 500 mg in the ER
- Found to have influenza A plus necrotizing pneumonia; MRSA suspected
  - Treatment is rapidly switched (Day 1) to vancomycin 1 g q12h and clindamycin 900 mg q8h plus oseltamivir

3

Patient Case (cont'd)

Hospital Day 3

- He developed ARDS requiring intubation and developed a bronchopleural fistula as well as pneumothorax
  - A chest tube is placed to manage pneumothorax
- Admission blood culture was positive for MRSA and he was transitioned to ceftaroline 600 mg q8h
- Hypoxia continued to worsen and his pneumothorax continued to expand despite chest tube suction and was transferred urgently to medical ICU

4

Patient Case (cont'd)

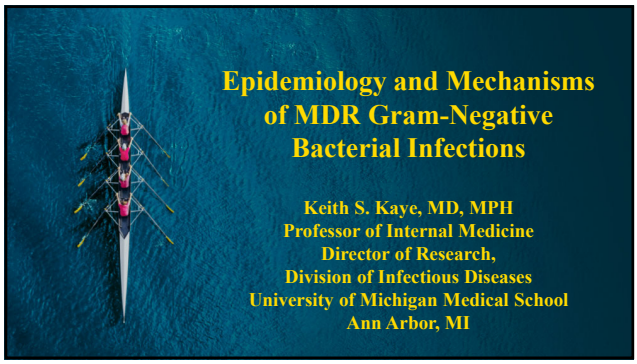
- Upon transfer to medical ICU, he is afebrile
- SpO_2 is 93% on 60% O_2 with a PEEP of 10 cm H_2O and a respiratory rate of 33/min
- Physical exam notable for a thin-appearing male who is intubated and sedated
- Heart sounds are obscured by a left bronchopleural fistula air leak
- Left lung sounds are described as a babbling brook air leak that is evident over the entire left chest
- He withdraws to pain in all 4 extremities

5

Suspected HAP/VAP: Management Decisions

- **What is the greatest limitation in making a rapid diagnosis?**
- **What can be used to help select appropriate initial empiric therapy while awaiting culture results?**
- **How do you manage inadequate response to treatment?**

6



7

Overview

- MDR Gram-negatives of importance
  - Enterobacteriaceae (extended-spectrum β-lactamase [ESBL]-producers, carbapenem-resistant [CRE])
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*
    - Prevalence in US and around the world
    - Mechanisms of carbapenem resistance
- Impact of resistance on outcomes
- Utilizing the antibiogram to improve outcomes

8

CDC: Drug-Resistant Gram-Negative Bacterial Infection Threats

Urgent and Serious

Urgent	Carbapenem-resistant Enterobacteriaceae (CRE)
Serious	ESBL-producing Enterobacteriaceae Multidrug-resistant *Acinetobacter* Multidrug-resistant *Pseudomonas aeruginosa*

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

9

WHO Priority Pathogens List For R&D of New Antibiotics

Priority 1: Critical

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

*Enterobacteriaceae include: *Klebsiella pneumonia*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., and *Morganella* spp.

WHO. Available at: http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/.

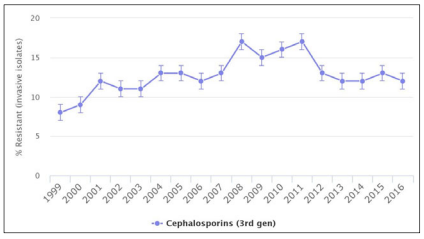
10

ESBL-producing Enterobacteriaceae

- Plasmid-mediated, most commonly produced by *Klebsiella pneumoniae*, *Escherichia coli*
- Overexpression of ampC β-lactamase (chromosomal and plasmid)
- Hydrolyze broad-spectrum β-lactams (not carbapenems)
- Often resistant to other antibiotic classes
- Carbapenems are first-line for invasive infection due to ESBL-producers
- Notable increases in ESBL-producers over past several years (CTX-M)
- More ESBLs = more carbapenem use

11

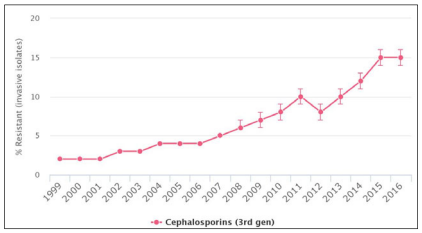
Prevalence of ESBL-producing *K. pneumoniae* in the US



Center for Disease Dynamics, Economics & Policy. Resistance Map. https://resistancemap.cddep.org/AntibioticResistance.php.

12

Prevalence of ESBL-producing *E. coli* in the US



Center for Disease Dynamics, Economics & Policy. Resistance Map. https://resistancemap.cddep.org/AntibioticResistance.php.

13

Unintended Consequences of Carbapenem Use

In an attempt to reduce ESBL rate, imipenem became preferred empiric antimicrobial instead of 3rd-generation cephalosporins

	1995	1996	Change (%)
Cephalosporin use*	5508 g	1106 g	-80
Imipenem use*	197 g	474 g	+140
Imipenem-resistant *P. aeruginosa* (number)	67	113	+68.7

*Unpaired median monthly gram use

Rahal JJ, et al. *JAMA*. 1998;280:1233-37.

14

Carbapenem Resistance Among Gram-Negative Bacilli

- Emerging problem in *Pseudomonas*, *Acinetobacter*, Enterobacteriaceae
- Risk factors include ICU stay, prolonged exposures to healthcare, indwelling devices, antibiotic exposures
  - Long-term acute care (LTAC) stay
- Often multidrug resistant (MDR) or extremely-drug resistant (XDR)
  - Severely limits treatment options
- All can cause pneumonia, bloodstream infection, wound infection
- Outbreaks reported in single and multiple institutions
- Horizontal spread important, but emergence of resistance (susceptible - - -> resistant) can also play a role

15

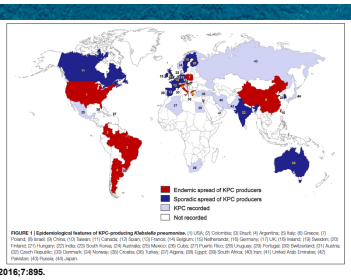
Klebsiella pneumoniae Carbapenemases (KPCs)

- Plasmid-mediated carbapenemase
- KPC-producing strains of *Klebsiella pneumoniae* and other Enterobacteriaceae
  - KPC-2, KPC-3
- Endemicity in many locales in the US
- Country-wide outbreak ongoing in several nations including Greece, Italy, Columbia and others
- Easily spread in the hospital – infection control nightmare
- Historically only susceptible to colistin, tigecycline and select aminoglycosides
  - Newer options available

Bratu S, et al. *Antimicrob Agents Chemother*. 2005;56:128-32.
Bradford PA, et al. *Clin Infect Dis*. 2004;39:55-60.
Leavitt A, et al. *Antimicrob Agents Chemother*. 2007;51:3026-9.
Carmeli Y, et al. *Clin Microbiol Infect*. 2010;16:102-11.

16

World-wide Spread of KPC-producing *K. pneumoniae*



Lee C-R, et al. *Front Microbiol*. 2016;7:895.

17

Other Carbapenemases

Class B carbapenemase (metallo-beta-lactamases)

- Most frequently identified carbapenemase worldwide:
  - New Delhi (NDM)
  - Verona integrin-encoded (VIM)
  - Imipenemase (IMP)
    - Efficiently hydrolyzes all β-lactams except aztreonam
    - Rare in US, but relatively common mechanism of CRE worldwide

Class D carbapenemase (mainly oxacillinases [e.g., OXA-48])

- Lineage back to narrow-spectrum oxacillinases
- Weakly hydrolyzes carbapenems
  - CDC 2015: 52 CRE isolates producing OXA-48-like carbapenemases from 43 patients in 19 states 6/10-8/15
    - 2/3 with travel in past year; ~50 hospitalized outside US; many with no travel history

Poirel L, et al. *J Antimicrob Chemother*. 2012;67:1597-1606.
Mathers AJ, et al. *J Clin Microbiol*. 2013;51(2):680-3.
Lyman M, et al. *MMWR*. 2015;64(47):1315-6. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6447a3.htm.

18

Prevalence of Carbapenem Resistance Mechanisms in Enterobacteriaceae in the US

CP-CRE by Mechanism, AR Lab Network, January 2017-December 2018

	CRE N=21,422 No. (%)*
Carbapenemase producing*	8145
KPC	7076 (87)
NDM	562 (7)
OXA-48-type	299 (4)
VIM	62 (1)
IMP	76 (1)

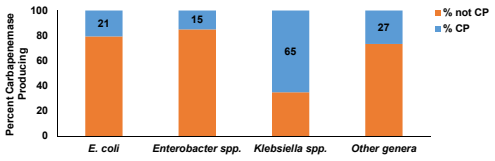
*Carbapenemase-producing defined as positive by phenotypic carbapenemase activity test or by molecular assay for one of 5 carbapenemases
†105 CP-CRE and 3 CP-CRPA had >1 carbapenemase identified

Preliminary data; subject to change

Thank you to Snigdha Vallabhaneni, MD, MPH for use of the slide.

19

Percent of CRE that are Carbapenemase-Producing (CP), by Genera (N=8,145), AR Lab Network 2017–2018

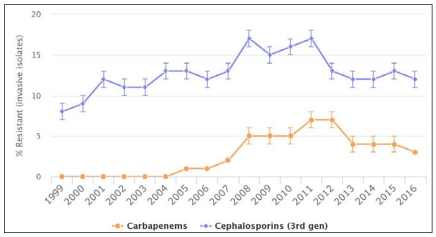


- Carbapenemase-producing CRE (CP-CRE) is defined as positive for mCIM or Carba-NP or PCR positive for one carbapenemase gene.
- For *Enterobacter*, CP-CRE is defined as positive for at least one carbapenemase gene.

Thank you to Snigdha Vallabhaneni, MD, MPH for use of the slide.

20

Antibiotic Resistance of *K. pneumoniae* in the US



Center for Disease Dynamics, Economics & Policy. Resistance Map. https://resistancemap.cddep.org/AntibioticResistance.php.

21

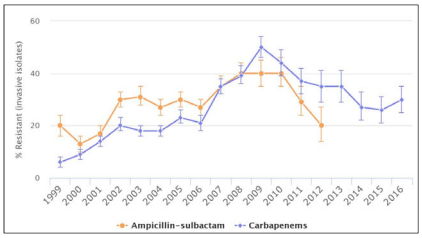
Acinetobacter baumannii

- Mechanisms of resistance multiple, diverse
  - Porin mutations
  - Altered PBPs
  - Metallo-beta-lactamases, serine carbapenemases (OXA)
    - OXA-23-like, OXA-24-like, OXA-51-like, OXA-58-like
- Carbapenem resistance seen in multiple geographic locales worldwide
- Problem pathogen in ICU patients (particularly in burn units), elderly and combat injuries from Middle East
- Can cause hospital outbreaks
- Treatment options: colistin, tigecycline, minocycline
  - Resistance to these agents reported

Landman D, et al. *J Antimicrob Chemother.* 2007;60:78-82.
Ahmed SS, et al. *J Pure Applied Microbiol.* 2016;10:1675-82.

22

Antibiotic Resistance of *Acinetobacter baumannii* in the US



Center for Disease Dynamics, Economics & Policy. Resistance Map.https://resistancemap.cddep.org/AntibioticResistance.php.

23

Pseudomonas aeruginosa

- Increasing resistance to quinolones, cephalosporins, carbapenems, particularly in the hospital and long-term care settings
- In the outpatient setting, patients with repeated quinolone exposures are at risk for developing resistance (i.e., recurrent UTI)
- "Grand old man" of resistant nosocomial pathogens
- Carbapenem resistance often multiple, diverse

24

Mechanisms of Acquired Resistance in *P. aeruginosa*

Antimicrobial class	Mechanism of resistance
β-lactams	β-lactamases (endogenous and acquired) Efflux pumps Changes in outer membrane permeability
Fluoroquinolones	Target site mutations Efflux pumps
Aminoglycosides	Aminoglycoside-modifying enzymes Efflux pumps 16s RNA Methylases
Polymyxins	Changes in lipopolysaccharide

Meletis G, Bagkeri M. *Pseudomonas aeruginosa: Multi-Drug-Resistance Development and Treatment Options*. 2013, http://www.intechopen.com/books/infection-control/pseudomonas-aeruginosa-multi-drug-resistance-development-and-treatment-options.
Lister PD, et al. *Clin Microbiol Rev*. 2009;22:582-610.

25

Prevalence of Carbapenem Resistance Mechanisms in *P. aeruginosa* in the US

CRPA by Mechanism, AR Lab Network, January 2017 – December 2018

	CRPA N=14,141 No. (%)
Carbapenemase producing*	458 (3)#
KPC	85 (19)
NDM	17 (4)
OXA-48-type	0
VIM	186 (41)
IMP	16 (3)

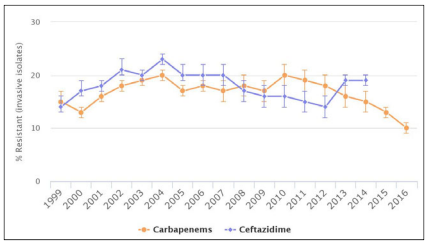
*Carbapenemase-producing defined as positive by phenotypic carbapenemase activity test or by molecular assay for one of 5 carbapenemases
3 CP-CRPA had >1 carbapenemase identified

Thank you to Snigdha Vallabhaneni, MD, MPH for use of the slide.

Preliminary data; subject to change

26

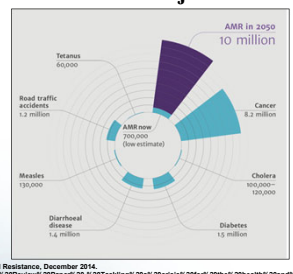
Carbapenem and Ceftazidime Resistance by *P. aeruginosa* in the US



Center for Disease Dynamics, Economics & Policy. Resistance Map. https://resistancemap.cddep.org/AntibioticResistance.php.

27

Projected Annual Deaths Attributable to AMR Compared to Other Major Causes of Death

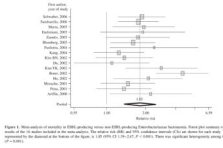


O'Neill J (Chair). The Review on Antimicrobial Resistance, December 2014.
https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.

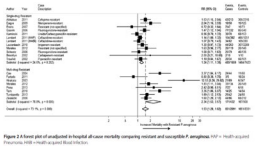
28

Does Resistance Impact Clinical Outcomes?

Impact of ESBL production on mortality In Enterobacteriaceae bacteremia[1]



Impact of carbapenem resistance on mortality in *Pseudomonas* Infection[2]



Poor outcomes driven by 1) patient population, 2) significant delays in time to appropriate therapy, 3) therapeutic options in patients with these infections

1. Schwaber MJ, Carmeli Y. *J Antimicrob Chemother*. 2007;60:913–920.
2. Nathwani D, et al. *Antimicrob Resist Infect Control*. 2014;3:32.

29

Epidemiology of Bloodstream Infections Caused by *Acinetobacter baumannii* and Impact of Drug Resistance to both Carbapenems and Ampicillin-Sulbactam on Clinical Outcomes

TABLE 3 Outcomes in patients with bloodstream infections caused by *A. baumannii*

	Data for subjects with BSI caused by:				
Outcome or length of stay	CASR *A. baumannii* (n = 68)	Non-CASR *A. baumannii* (n = 206)	OR	95% CI	P value
Outcome event, no. (%) of patients					
In-hospital mortality	29 (43)	42 (20)	2.90	1.61–5.23	<0.001
Emergency room visits within 60 days of discharge	10 (15)	35 (17)	0.84	0.39–1.80	0.65
Readmission within 60 days of discharge	15 (22)	49 (24)	0.91	0.47–1.75	0.87
Length of stay, days, median (interquartile range)					
Days from initial PBC[a] to initiation of appropriate therapy	2 (0–3)	2 (1–3)			0.63
Length of stay after PBC	9 (3–16.5)	9 (5–16)			0.33

Chopra T, et al. *Antimicrob Agents Chemother*. 2013;57:6270–75.

30

Carbapenem Resistance in Enterobacteriaceae Infection: Impact on Outcomes and Cost

Table 4. Multivariate-Adjusted Analyses of Infection-Related Outcomes: CRE vs CSE

Outcome[a]	CRE (N = 514)	CSE (N = 49 555)
Adjusted mean (95% CI)		
Duration of antibiotic therapy (d)[b]	8.5 (8.2 to 8.7)[c]	7.5 (7.5 to 7.5)
LOS (d)[b]	8.4 (8.2 to 8.7)[c]	7.6 (7.6 to 7.7)
In-hospital cost ($)[b]	19 816 (19 637 to 19 997)[c]	15 165 (15 031 to 15 300)
Adjusted OR (95% CI)[d]		
Discharged home	0.3 (0.3 to 0.3)[c]	
In-hospital death or discharged to hospice	2.2 (2.1 to 2.2)[c]	

Lodise TP, et al. *Open Forum Infect Dis.* 2019;6(6):ofz194.

31

Carbapenem Resistance in Enterobacteriaceae Infection: Importance of Timely Appropriate Therapy

Table 5. Multivariate-Adjusted Analyses of Infection-Related Outcomes: CRE (vs CSE) and Receipt of Delayed Appropriate Therapy (vs Receipt of Timely Appropriate Therapy)

	Timely Appropriate Therapy		Delayed Appropriate Therapy	
Outcome[a]	CSE (N = 33 426)	CRE (N = 229)	CSE (N = 16 129)	CRE (N = 285)
Adjusted mean (95% CI)				
Duration of antibiotic therapy (d)[b,c]	5.0 (5.0 to 5.1)	5.4 (5.2 to 5.5)	8.3 (8.2 to 8.4)	8.9 (8.6 to 9.1)
LOS (d)[b,c]	5.0 (4.9 to 5.0)	5.1 (5.0 to 5.3)	8.5 (8.4 to 8.7)	8.8 (8.6 to 9.1)
In-hospital cost ($)[b,c]	9875 (9749 to 10 002)	11 539 (11 372 to 11 709)	21 828 (21 479 to 22 182)	25 506 (25 124 to 25 893)
Adjusted OR (95% CI)[d]				
Discharged home	Reference	0.4 (0.4 to 0.4)	0.4 (0.4 to 0.4)	0.2 (0.1 to 0.2)
In-hospital death or discharged to hospice	Reference	1.9 (1.9 to 2.0)	1.9 (1.8 to 2.0)	3.7 (3.5 to 3.9)

Lodise TP, et al. *Open Forum Infect Dis.* 2019;6(6):ofz194.

32

Improving Patient Outcomes: Utilizing the Antibiogram

- **Annual summary of susceptibility rates for a healthcare institution**
- **Can help inform empiric antimicrobial choices**
  - Particularly important for resistant bacteria, such as *P. aeruginosa*
- **Unit-level antibiograms helpful**
  - Provide data even more locally than institution-wide antibiogram
  - Often differences in susceptibility between intensive care unit and ward unit
- **Combination antibiogram**
  - Provides susceptibility rates for a combination of antimicrobials (i.e., for a given pathogen, the rates of susceptibility to at least one agent in a given combination)
  - Particularly valuable for *P. aeruginosa* given the high rates of antimicrobial resistance

Hindler J, et al. *Clin Infect Dis.* 2007;44:867-73.
Thurman L, et al. *Am J Infect Dis.* 2014;10:88-94.
Smith Z, et al. *J Oncol Pharm Pract.* 2016;22:409-15.

33

Combination Antibiograms for *Pseudomonas aeruginosa*

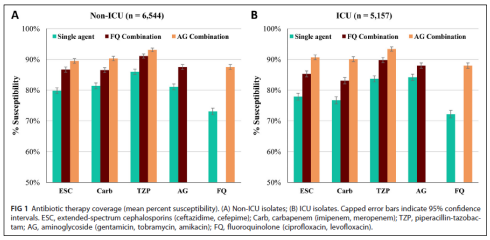


FIG 1 Antibiotic therapy coverage (mean percent susceptibility). (A) Non-ICU isolates; (B) ICU isolates. Capped error bars indicate 95% confidence intervals. ESC, extended-spectrum cephalosporins (ceftazidime, cefepime); Carb, carbapenem (imipenem, meropenem); TZP, piperacillin-tazobactam; AG, aminoglycoside (gentamicin, tobramycin, amikacin); FQ, fluoroquinolone (ciprofloxacin, levofloxacin).

Puzniak L, et al. *Antimicrob Agents Chemother.* 2019;63:e02564-18.

34

Conclusions

- Gram-negative bacteria utilize a variety of resistance mechanisms
- Carbapenemases are becoming more widespread throughout the world
- Antimicrobial resistance adversely impacts clinical outcomes
- Antibiograms can provide an important tool in the clinical setting to combat resistance

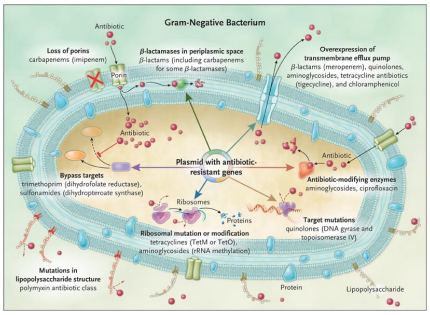
35

Available Tools to Address Challenges of MDR Gram-Negative Infections

George H. Karam, MD
Paula Garvey Manship Professor of Medicine
Department of Medicine
Louisiana State University School of Medicine in New Orleans
Baton Rouge Branch Campus
Baton Rouge, LA

36

Mechanisms of Resistance



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

37

An Approach To New Antibiotics for Gram-Negative Infections

Location of Antibiotic Mechanisms of Action

- Cell Wall Agents
  - Ceftolozane/ Tazobactam
  - Ceftazidime/ Avibactam
  - Meropenem/ Vaborbactam
  - Imipenem/ Relebactam
- Intracytoplasmic Agents
  - Delafloxacin
  - Plazomicin
  - Eravacycline
  - Omadacycline

38

The Evolution of Clinical Options for β-Lactam/β-Lactamase Inhibitor Therapy

- Piperacillin/ Tazobactam✦
- Ceftolozane/ Tazobactam
- Ceftazidime/ Avibactam
- Meropenem/ Vaborbactam
- Imipenem/ Relebactam

✦An old drug but new data about its efficacy in ESBL bloodstream infections

39


TRIALS

STUDY PROTOCOL Open Access

Meropenem versus piperacillin-tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible *Escherichia coli* and *Klebsiella* spp (the MERINO trial): study protocol for a randomised controlled trial

ClinicalTrials.gov Identifier: NCT02176122

Recruitment Status : Terminated (Secondary to third interim analysis by the study DSMB.)
First Posted : June 26, 2014
Last Update Posted : November 27, 2017

Pinned Tweet
MERINO Trial @MerinoTrial · Mar 17
We will be presenting the headline #MerinoTrial results in late breaker clinical trials session @ECCMID in Madrid - looking forward to sharing the results after years of hard work from many investigators in 9 countries #UQMedicine @UQ_News @ASIDANZ @davidantibiotic @padstamundo

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance
A Randomized Clinical Trial

40

Important Lessons Learned From the MERINO Trial

- Phenotypic ESBL production confirmed in 86.0% of isolates
  - 85.0% of *E. coli*
  - 92.5% of *K. pneumoniae*
- Genotypic expression
  - ESBL genes confirmed in 85.3% of isolates
  - ampC genes (predominantly blaCMY-2) confirmed in 10.2%
  - Both ESBL and ampC in 2%
- Predominant ESBL genes
  - blaCTX-M-type (83.5%)
    - blaCTX-M-15 (54.5%)
    - blaCTX-M-27 (13.0%)
    - blaCTX-M-14 (11.0%)
- Presence of narrow-spectrum oxacillinases (blaOXA-1 and variants) found in 67.6% of all strains
  - May compromise β-lactamase inhibition by tazobactam

Harris PNA, et al. *JAMA.* 2018;320:984-994.

41

ESBL Resistance in *E. coli* and *P. aeruginosa*

- ESBL-encoding genes commonly expressed in *P. aeruginosa* cloned and expressed in *E. coli* and *P. aeruginosa*
  - bla_{TEM}, bla_{SHV}, bla_{CTX-M}, bla_{VEB}, bla_{PER}, bla_{GES}, bla_{BEL}
- Variability in the activity of ceftazidime/avibactam (C/A) and ceftolozane/tazobactam (C/T)
  - ESBL PER-1 *P. aeruginosa* resistance to both C/A and C/T
  - ESBL GES-6 resistance to C/T but retained susceptibility to C/A
- Clinical deductions
  - Existent differences in the stability of β-lactamase inhibitor combinations in the presence of certain ESBLs
    - Avibactam more stable than tazobactam
    - Ceftolozane more stable than ceftazidime

Ortiz J-M, et al. *J Antimicrob Chemother.* 2019;74:1934-1939.

42

Conceptualization of *Pseudomonas aeruginosa*

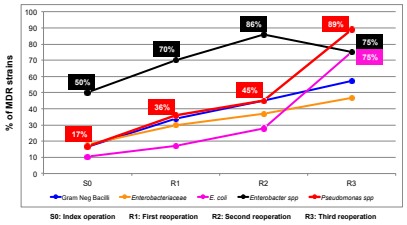
- A "ubiquitous" pathogen
- Recurrent themes in the epidemiologic settings in which the pathogen occurs
- Variability in the expression of β-lactamases
  - Chromosomally-mediated[1,2]
    - *amp*C β-lactamases
    - Porin channel closure
    - Efflux
  - Plasmid-mediated
    - ESBLs
- Adaptability to express resistance mutations to newer antimicrobial agents[3,4,5]

[1]Lister PD, Wolter DJ. *Clin Infect Dis.* 2005;40:S105-S114.
[2]Quale J, et al. *Antimicrob Agents Chemother* 2006;50:1633-1641.
[3]MacVane SH, et al. *Antimicrob Agents Chemother* 2017;61:e01183-17.
[4]Ahmed MS, et al. 28th ECCMID (April 21-24, 2018), Madrid, Spain. Abstract O0935.
[5]Zamudio R, et al. *Int J Antimicrob Agents* 2019;53:774–75.

43

Increased Risk of Resistant Gram-Negative Bacilli in Late Nosocomial Infections

- 98 ICU patients who underwent repeated surgery for persistent peritonitis
- Culture of peritoneal fluid at each reoperation
- Analysis of emergence of MDR organisms in surgical samples



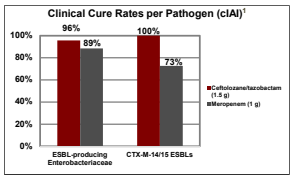
Montravers P, et al. *Crit Care.* 2015;19:70.

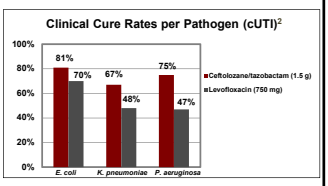
44

Ceftolozane-Tazobactam for Gram-negative Infections

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.

45

Expanded Indication for Ceftolozane-Tazobactam

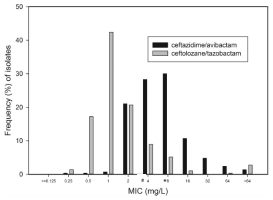
- June 2019, FDA-approved indication for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP)
- Pivotal trial: ASPECT-NP
  - Trial in 726 mechanically-ventilated patients
  - Compared ceftolozane/tazobactam vs. meropenem
- Emphasis in the trial on the pharmacologic parameter of dosing based on previously failed trials of new antibiotics for the treatment of pneumonia
  - Doripenem
  - Ceftobiprole
  - Tigecycline

Kollef MH, et al. *Lancet Infect Dis.* 2019;pii: S1473-3099(19)30403-7 [Epub ahead of print].

46

Treatment for Resistant *Pseudomonas aeruginosa*

- Comparison of *in vitro* inhibitory activity of ceftazidime-avibactam and ceftolozane-tazobactam against 290 meropenem-nonsusceptible *P. aeruginosa* non-duplicate clinical isolates from 34 U.S. hospitals
- Significantly higher inhibitory activity of ceftolozane-tazobactam versus ceftazidime-avibactam
- Exclusive presence of the VIM metallo-β-lactamase among only 4% of the subset of isolates nonsusceptible to ceftazidime-avibactam, ceftolozane-tazobactam, or both

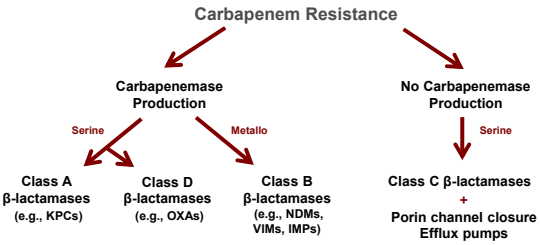


Susceptibility breakpoints are 4 mg/L for ceftazidime-avibactam (#) and 8 mg/L for ceftolozane-tazobactam (*)

Grupper M, et al. *Antimicrob Agents Chemother.* 2017;61:e00875-17.

47

Concept Map for Carbapenem Resistance



48

Ceftazidime-Avibactam: Summary of Clinical Trial Evidence

Study	Comparator	Key Efficacy vs Comparator
RECLAIM 1 and 2[1] • Plus metronidazole • cIAI • Randomized controlled trial (RCT); N = 1066	Meropenem	Noninferior for clinical cure rates at test of cure (TOC)
RECAPTURE 1 and 2[2] • cUTI/AP • RCT; N = 1033	Doripenem	Noninferior for symptomatic resolution at Day 5 (treatment period) and symptomatic resolution/ microbiological eradication at TOC
REPRISE[3] • cIAI or cUTI due to ceftazidime-resistant gram-negative pathogens • RCT; N = 333	Best Available Therapy (BAT)	Similar clinical cure rates at TOC
REPROVE[4] • Ceftazidime-resistant pathogens • Nosocomial pneumonia • RCT; N = 879	Meropenem	Noninferior for clinical cure rates at TOC
CRACKLE[5] • Infections caused by carbapenem-resistant Enterobacteriaceae • Bloodstream infection (46%); pneumonia (22%) • Prospective observational cohort study; N = 137	Colistin	• Decreased all-cause, 30-day mortality compared to colistin (9% vs 32%) • Using inverse probability of treatment weighting (IPTW), suggestion of superiority in treatment of carbapenem-resistant *K. pneumoniae*

[1]Mazuki JE, et al. *Clin Infect Dis.* 2016;62:1380-1389.
[2]Wagenlehner FM, et al. *Clin Infect Dis.* 2016;63:754-762.
[3]Carmeli Y, et al. *Lancet Infect Dis.* 2016;16:661-673.
[4]Torres A, et al. *Lancet Infect Dis.* 2018;18:285-295.
[5]van Duin D, et al. *Clin Infect Dis.* 2018:66:163-171.

49

Ceftazidime-Avibactam
Emergence of Resistance Among Enterobacteriaceae

- First clinical case of a ceftazidime-avibactam-resistant *Klebsiella pneumoniae*, in a patient with no previous exposure[1]
  - Resistance due to porin mutations and the increased expression of KPC-3[2]
- 37 CRE-infected patients treated with ceftazidime-avibactam[3]
  - Clinical success was 59% (22/37) and 30-day survival was 76% (28/37)
  - CRE infections recurred within 90 days in 23% (5/22)
  - Resistance detected in 30% (3/10) of microbiologic failures
  - Development of resistance conferring bla_{KPC-3} mutations in *Klebsiella pneumoniae* within 10 to 19 days of ceftazidime-avibactam exposure, but may be ameliorated if carbapenem susceptibility is restored[4]
- Surveillance studies continue to document low frequency of ceftazidime-avibactam resistance among Enterobacteriaceae isolates carrying bla_{KPC}[5,6]

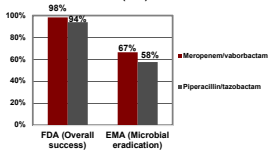
[1]Humphries RM, et al. *Antimicrob Agents Chemother.* 2015;59: 6505-6607.
[2]Nelson K, et al. *Antimicrob Agents Chemother.* 2017;61(10):e00989-17.
[3]Shields RK, et al. *Clin Infect Dis.* 2016; 63: 1615-1618.
[4]Shields RK, et al. *Antimicrob Agents Chemother.* 2017;61 (3): e02087-16.
[5]Castanheira M, et al. *Antimicrob Agents Chemother.* 2017;61(3): e02369-16.
[6]Spellberg B, Bonomo RA. *Clin Infect Dis.* 2016;63:1619-1621.

50

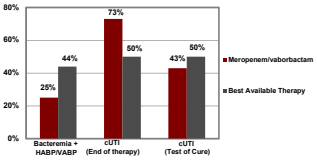
Meropenem-Vaborbactam Against Gram-negative Infections

Vaborbactam
- Unique boronic acid non-suicidal β-lactamase inhibitor
- Potent inhibitor of KPCs
- Minimal effect against meropenem-resistant *P. aeruginosa*

TANGO I (cIAI)[1]



TANGO II (Carbapenem-Resistant Enterobacteriaceae)[2]



[1]Kaye KS, et al. *JAMA.* 2018;319:788-799.
[2]Wunderink R, et al. *Infect Dis Ther.* 2018;7:439–455.

HABP, Hospital-acquired bacterial pneumonia
VABP, Ventilator-associated bacterial pneumonia

51

In Vitro Activity of Carbapenem/β-lactamase Inhibitor Combinations Against *P. aeruginosa*

4,500 isolates from 11 hospitals in Brooklyn and Queens, NY: Nov 2013 to Jan 2014[1]

Species (n)	Meropenem		Meropenem-Vaborbactam	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Klebsiella pneumoniae (KPC+) (121)	8	64	0.03 / 8	0.5 / 8
Pseudomonas aeruginosa (96)	8	32	8 / 8	32 / 8
Acinetobacter baumannii (98)	32	64	32 / 8	64 / 8

4,000 isolates from 11 hospitals in Brooklyn and Queens, NY: Nov 2013 to Jan 2014[2]

Species (n)	Imipenem		Imipenem-Relebactam	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
bla_{KPC}-possessing *K. pneumoniae* (111)	16	>16	0.25 / 4	1 / 4
Pseudomonas aeruginosa (490)	2	16	0.5 /4	2 /4
Imipenem-resistant *P. aeruginosa* (144)	8	>16	1 /4	2 /4

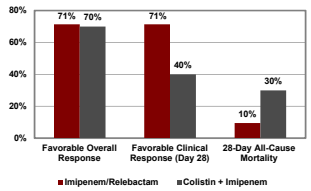
[1]Lapuebla A, et al. *Antimicrob Agents Chemother.* 2015;59:4856-4860.
[2]Lapuebla A, et al. *Antimicrob Agents Chemother.* 2015;59:5029-5031.

MIC values in μg/mL

52

Imipenem-Relebactam

RESTORE-IMI 1✦



[1]Lucasti C, et al. *Antimicrob Agents Chemother.* 2016;60:6234-6243.
[2]Sims M, et al. *J Antimicrob Chemother.* 2017;72:2616-2626.
✦Motsch J, et al. *Clin Infect Dis.* 2019; pii: ciz530 [Epub ahead of print].

- **Relebactam**
  - A novel diazabicyclooctane β-lactamase inhibitor
  - Potent inhibitor of KPCs
  - Restores activity of imipenem against *P. aeruginosa*
  - FDA approval in July 2019 based on clinical trials for cIAI[1] and cUTI[2]

53

Treatment for Resistant *Pseudomonas aeruginosa*

- Data on 5,447 isolates of *P. aeruginosa* submitted to the SMART✦ global surveillance program in 22 European countries in 2015–2017
  - Multidrug resistance in ⅓ of isolates
  - Multidrug resistance in 38% of lower respiratory tract isolates
- Activity of relebactam in restoring susceptibility to imipenem
  - In 75.2% (1254/1668) of imipenem-non-susceptible isolates of *P. aeruginosa*
  - In 69.6% (947/1361) of imipenem-non-susceptible isolates with an MDR phenotype
- Colistin the only other agent that retained activity against resistant *P. aeruginosa* strains

✦SMART, Study for Monitoring Antimicrobial Resistance Trends
Lob SH, et al. *J Antimicrob Chemother.* 2019;74:2284-2288.

54

Activity of New β-Lactam/β-Lactamase Inhibitor Combinations in the Presence of β-Lactamases

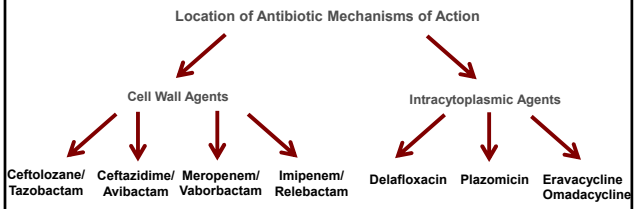
	AmpC (Ambler C)	Carbapenemases: KPCs (Ambler A)	Carbapenemases: Metallos (Ambler B)	Carbapenemases: OXAs (Ambler D)
Ceftolozane/Tazobactam	✦			
Ceftazidime/Avibactam				
Meropenem/Vaborbactam				
Imipenem/Relebactam				

Green = activity Yellow = variable activity Red = no activity

✦Activity based on the ceftolozane but not the tazobactam

55

An Approach To New Antibiotics for Gram-Negative Infections



56

Recently-Approved Intracytoplasmic Agents: Summary

Agent	Formulations	Activity	Comments
Delafloxacin (fluoroquinolone)	IV and oral	• Gram-positive and Gram-negative bacteria, including MRSA	• Approved in June 2017 for acute bacterial skin and skin structure infections • Boxed warning for increased risk of disabling and potentially irreversible serious AEs
Plazomicin (aminoglycoside)	IV only	• Gram-negative	• Approved in June 2018 for complicated UTI • Associated with nephrotoxicity
Omadacycline (novel aminomethylcycline)	IV, injection, oral	• Gram-positive (including MRSA and VRE) • Gram-negative • Atypicals (including *L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae*) • Anaerobes	• Approved in October 2018 for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections
Eravacycline (fluorocycline-type tetracycline)	Injection, IV	• Gram-positive • Gram-negative • Anaerobes	• Approved in August 2018 for complicated intraabdominal infections

57

The Concept of "Sparing" As It Relates To the Collateral Benefits of Newly-Approved Antibiotics

- **Carbapenem-sparing**
- **Pseudomonal-sparing**
- **Colistin-sparing**

58

The Clinical Response of "Colistin-Sparing"

(facilitated by data suggesting that newer agents might be better for CRE infections)

- Ceftazidime-avibactam
  - Higher rates of clinical success (*P*=0.006) and survival (*P*=0.01) and less nephrotoxicity than aminoglycoside- and colistin-containing regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia[1]
  - 23% reduced risk for death and 64% probability of better outcome compared to colistin for CRE[2]
- Meropenem-vaborbactam[3]
  - TANGO-2, comparing meropenem-vaborbactam monotherapy to best available therapy in serious infections due to CRE
    - Lower mortality and renal toxicity
- Plazomicin[4]
  - CARE Study, comparing plazomicin versus colistin combined with meropenem or tigecycline in patients with infections due to CRE
    - 70.5% relative reduction in all-cause mortality

[1]Shields RK, et al. *Antimicrob Agents Chemother.* 2017;61:e00883-17.
[2]van Duin D, et al. *Clin Infect Dis.* 2018;66:163-171.
[3]Wunderink R, et al. *Infect Dis Ther.* 2018;7:439–455.
[4]McKinnell JA, et al. *N Engl J Med.* 2019;380:791-793.

59

Stratification Based on Risk of Resistance

Risk factors for ESBL+ Enterobacteriaceae[1]	OR (95% CI)	*P* value
Recent hospitalization in past 12 months	5.69 (2.94–10.99)	0.001
Admission from another health care facility	5.61 (1.65–19.08)	0.006
Charlson comorbidity index >4	3.80 (1.90–7.59)	0.001
Previous therapy with β-lactams and/or quinolones	3.68 (1.96–6.91)	0.001
History of urinary catheterization in past 30 days	3.52 (1.96–6.91)	0.001
Age >70 years	3.20 (1.79–5.70)	0.001

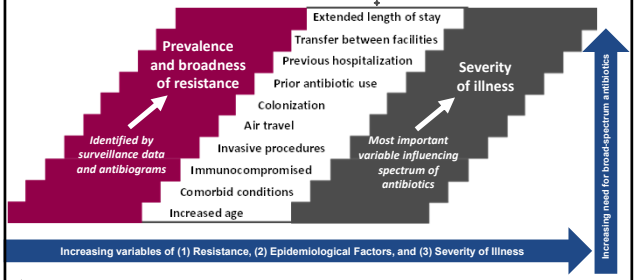
Patient Characteristics for Resistance in *P. aeruginosa* bacteremia (PAB)[2]	MDR PAB n = 127	Non-MDR PAB n = 582	*P* value
Nosocomial infection (%)	85	68	<0.0001
Longer hospital stay (mean days)	31.83	16.38	<0.0001
Prior antibiotic therapy (%)	85.8	53.4	<0.0001
Prior steroid therapy (%)	41.7	33.8	0.03
Bladder catheter (%)	53.5	37.5	<0.0001
Inappropriate empirical antibiotic (%)	62.2	27	<0.0001

Multivariate Analysis of Risk Factors for Isolation of Carbapenem-resistant Enterobacteriaceae (CRE)[3]	Adjusted odds ratio	95% Confidence Interval	*P* value
Weighted index comorbidity >3	4.85	1.63–14.41	0.004
Immune suppression	3.92	1.08–14.28	0.038
Indwelling devices	5.21	1.09–24.96	0.39
Any antibiotic exposure	3.89	0.71–21.46	0.119

[1]Tumbarello M, et al. *Antimicrob Agents Chemother.* 2011;55:3485–3490. [2]Morata L, et al. *Antimicrob Agents Chemother.* 2012;56:4833-4837.
[3]Bhargava A, et al. *Infect Control Hosp Epidemiol.* 2014;35:398-405.

60

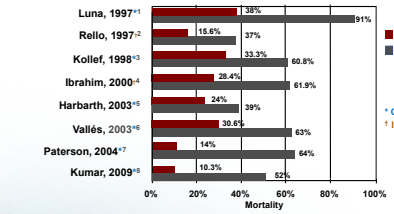
Variables Influencing Patient Stratification for Empiric Antibiotic Therapy



✦These epidemiologic factors are not listed in any specific order of importance.
Karam G, et al. *Crit Care.* 2016;20:136.

61

Mortality✦ Associated with Initial Inadequate Therapy In Critically-ill Patients with VAP, Sepsis, or Bacteremia



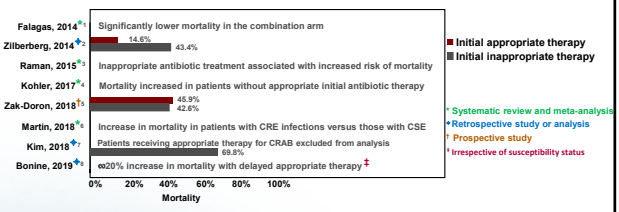
* Crude (overall) mortality
† Infection-related mortality

✦Because almost all of the evidence is from cohort studies, it is possible that the relationship between mortality and appropriate antibiotics is a surrogate for other components of care. (*Sem Respir Crit Care Med.* 2011;32:195-205.)

[1]Luna CM, et al. *Chest.* 1997;111:676.
[2]Rello J, et al. *Am J Respir Crit Care Med.* 1997;156:196.
[3]Kollef MH, et al. *Chest.* 1998;113:412.
[4]Ibrahim EH, et al. *Chest.* 2000;118:146.
[5]Harbarth S, et al. *Am J Med.* 2003;115:529.
[6]Vallés J, et al. *Chest.* 2003;123:1615.
[7]Paterson D, et al. *Ann Intern Med.* 2004;39:31.
[8]Kumar A, et al. *Chest.* 2009;136:1237.

62

Impact of Therapy on Mortality in Patients Infected with Carbapenem-Resistant Pathogens



* Systematic review and meta-analysis
✦Retrospective study or analysis
† Prospective study
‡ Irrespective of susceptibility status

CRE, Carbapenem-Resistant Enterobacteriaceae; CSE, C-Sensitive E; CRAB, Carbapenem-resistant *Acinetobacter baumannii*

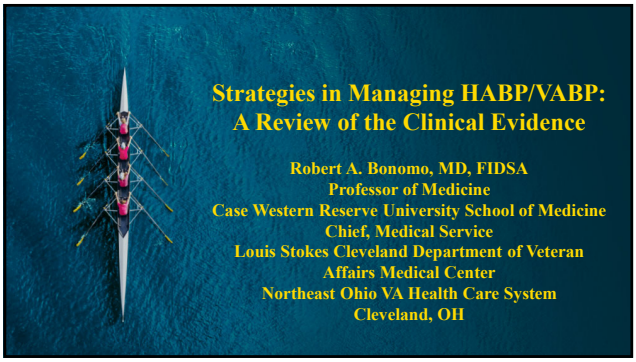
[1]Falagas ME, et al. *Antimicrob Agents Chemother.* 2014:58:654-663.
[2]Zilberberg MD, et al. *Crit Care.* 2014;18:596.
[3]Raman G, et al. *BMC Infect Dis.* 2015;15:395.
[4]Kohler PP, et al. *Infect Control Hosp Epidemiol.* 2017;38:1319-28.
[5]Zak-Doron, et al. *Clin Infect Dis.* 2018;67:1815-1823.
[6]Martin A, et al. *Open Forum Infect Dis.* 2018;5(7):ofy150.
[7]Kim T, et al. *Medicine.* 2018;97:43(e12984).
[8]Bonine NG, et al. *Am J Med Sci.* 2019;357:103-110.

63

Conclusions

- The availability of newer antimicrobials expands the opportunity for pathogen-specific therapy
  - ESBLs: carbapenems
  - KPCs: ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam
  - MDR *P. aeruginosa*: ceftolozane-tazobactam
  - Metallo-β-lactams, OXAs: ???
- Patient stratification can be an important tool in recognizing risk factors and selecting appropriate initial empiric therapy

64



Strategies in Managing HABP/VABP: A Review of the Clinical Evidence

Robert A. Bonomo, MD, FIDSA
Professor of Medicine
Case Western Reserve University School of Medicine
Chief, Medical Service
Louis Stokes Cleveland Department of Veteran Affairs Medical Center
Northeast Ohio VA Health Care System
Cleveland, OH

65

Suspected HAP/VAP: Management Decisions

- **If you suspect, how would you diagnose?**
- **What empirical regimen would you use while awaiting culture results?**
- **How do you handle a negative culture?**
- **How often will your treatment fail and how do you manage these patients?**

66

HAP and VAP: What's the Difference?

- Ventilator-associated pneumonia – occurs >48 hours after intubation
  - Early-onset vs. late-onset
  - ? Chronic home ventilation or other care facility

67

HAP and VAP: What's the Difference?

- Hospital-acquired pneumonia – occurs >48 hours after hospital admission
  - ? LTACs
  - ? Skilled nursing or inpatient rehab
  - Not associated with mechanical ventilation
  - Occurs more frequently than VAP

68

2016 IDSA/ATS HAP/VAP Guidelines

Goal: minimize antibiotic exposure

- **Avoid MRSA coverage if <20% of *S. aureus* are MRSA**
- **Avoid combination Gram-negative coverage if one agent covers >90% of isolates**

Table 2. Risk Factors for Multidrug-Resistant Pathogens

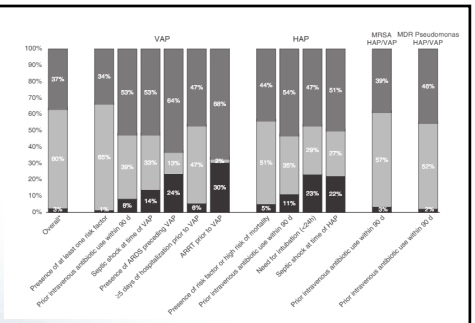
Risk factors for MDR VAP
Prior intravenous antibiotic use within 90 d
Septic shock at time of VAP
ARDS preceding VAP
Five or more days of hospitalization prior to the occurrence of VAP
Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP
Prior intravenous antibiotic use within 90 d
Risk factors for MRSA VAP/HAP
Prior intravenous antibiotic use within 90 d
Risk factors for MDR *Pseudomonas* VAP/HAP
Prior intravenous antibiotic use within 90 d

Kalil AC, et al. *Clin Infect Dis.* 2016;63(5):e61-111.

69

Adequacy of IDSA/ATS Guidelines

- Appropriate
- Overtreatment
- Undertreatment

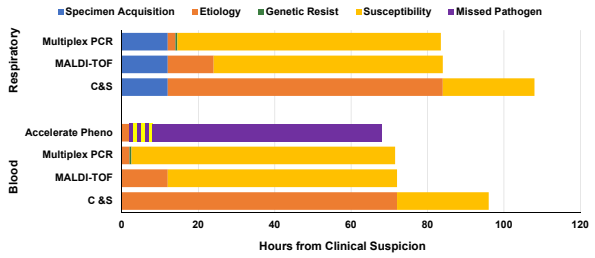


Ekren PK, et al. *Am J Respir Crit Care Med.* 2018;197:826-9.

70

71

The Beginning of the End of Empirical Treatment of HABP/VABP



72

[Original Research **Chest Infections**]

CHEST

Rapid Detection of Methicillin-Resistant *Staphylococcus aureus* in BAL

A Pilot Randomized Controlled Trial

Joseph R. Paonessa, MD; Raj D. Shah, MD; Chiagozie I. Pickens, MD; Bryan D. Lizza, PharmD; Helen K. Donnelly, RN, BSN; Michael Malczynski, BS; Chao Qi, PhD; and Richard G. Wunderink, MD

Paonessa JR, et al. *Chest.* 2019;155:999-1007.

73

Validation of BAL Rapid Diagnostic Test for MRSA

MRSA/SA SSTI Assay for Cepheid Xpert® platform

MRSA		Growth in Culture		
		Yes	No	Total
A-PCR Positive	Yes	22	4	26
	No	1	220	221
	Total	23	224	247

MSSA		Growth in Culture		
		Yes	No	Total
A-PCR Positive	Yes	24	20	44
	No	1	173	174
	Total	25	193	218

Growth 100 cfu/ml in culture, clinically thought negative and no treatment

MRSA Negative Predictive Value – 99.6%, Negative LR – 0.04

Paonessa JR, et al. *Chest.* 2019;155:999-1007.

LR, likelihood ratio; SSTI, skin and soft tissue infections

74

Culture only detects living bacteria.

PCR can't tell whether living or dead.

75

Randomized Controlled Trial of a BAL Rapid Diagnostic Test for MRSA

- Patients with suspected MRSA pneumonia with BAL
- Commitment to continue anti-MRSA treatment
- No other suspected infection source requiring MRSA coverage
- Primary team willingness to stop treatment based on result of rapid test

- Primary endpoint: decreased days of anti-MRSA treatment
- Secondary endpoint: safety
  - Subsequent anti-MRSA treatment over 28 days
  - Hospital-acquired infections
  - Organ dysfunction
  - Length of stay
  - Mortality

Paonessa JR, et al. *Chest.* 2019;155:999-1007.

76

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

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[a]	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[a]	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

Paonessa JR, et al. *Chest.* 2019;155:999-1007.

77

Randomized Controlled Trial of a BAL Rapid Diagnostic Test for MRSA

Study Conclusions:

- **Safe** and **beneficial** to discontinue or hold anti-MRSA treatment for suspected ventilated pneumonia
- Negative rapid test had carryover effect for other subsequent suspected infections
- ? PCR may detect MRSA subpopulation in MSSA culture
- PCR may be more sensitive than culture – may be true for other pathogens as well

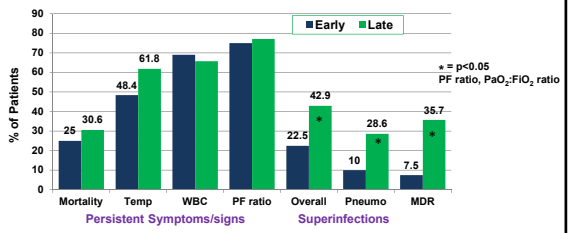
78

Suspected HAP/VAP: Management Decisions

- If you suspect, how would you diagnose?
- What empirical regimen would you use while awaiting culture results?
- How do you handle a negative culture?

79

Early Antibiotic Discontinuation in Culture-Negative Suspected VAP



Raman K, et al. *Crit Care Med.* 2013;41:1656-63.

80

Preliminary BAL/NBBAL Biofire® Pneumonia Panel Results Northwestern Memorial Hospital 2019

Operating characteristics of the platform for each individual organism detected.

Bacteria	Sensitivity	Specificity	PPV	NPV
Pseudomonas	16/16 = 100%	116/120 = 96.7%	16/20 = 80%	116/116 = 100%
S. aureus	13/13 = 100%	116/123 = 94.3%	13/20 = 65%	116/116 = 100%
E. cloacae	4/4 = 100%	130/132 = 98.4%	4/6 = 66.7%	130/130 = 100%
E. coli	3/3 = 100%	128/133 = 96.2%	3/8 = 37.5%	128/128 = 100%
K. oxytoca	2/2 = 100%	131/134 = 97.8%	2/5 = 40%	131/131 = 100%
K. pneumoniae	6/6 = 100%	129/130 = 99.2%	6/7 = 85.7%	129/129 = 100%
H. influenzae	4/5 = 80%	126/131 = 96.2%	4/9 = 44.4%	126/127 = 99.2%
E. aerogenes	5/5 = 100%	131/131 = 100%	5/5 = 100%	131/131 = 100%
S. marcescens	3/3 = 100%	133/133 = 100%	3/3 = 100%	133/133 = 100%
Proteus spp.	4/4 = 100%	131/132 = 99.2%	4/5 = 80%	131/131 = 100%

BAL, bronchoalveolar lavage; NBBAL, non-bronchoscopic BAL

81

Suspected HAP/VAP: Management Decisions

- If you suspect, how would you diagnose?
- What empirical regimen would you use while awaiting culture results?
- How do you handle a negative culture?
- How often will your treatment fail and how do you manage these patients?

82

Kollef *et al. Critical Care* 2012, **16**:R218
http://ccforum.com/content/16/6/R218

CRITICAL CARE

RESEARCH Open Access

A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia

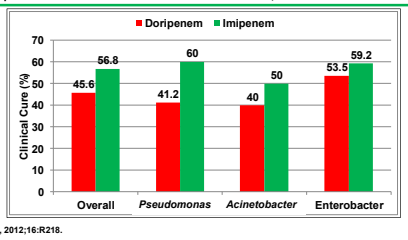
Marin H Kollef[1*], Jean Chastre[2], Marc Clavel[3], Marcos I Restrepo[4], Bart Michiels[5], Koné Kaniga[6], Iolanda Cirillo[6], Holly Kimko[6] and Rebecca Redman[6]

- Carbapenem class associated with lowest mortality in HAP/VAP Guideline analysis
- Doripenem given as prolonged 3-hour infusion
- Routinely, doripenem 2 tube dilutions more active (lower MIC) than imipenem

83

Clinical Response in Carbapenem VAP Trial

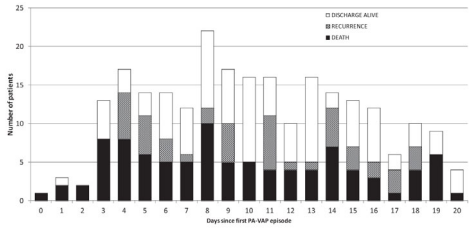
Doripenem overall clinical cure rate difference was -11.2%, 95% CI of difference -26.3 to 3.8%



Kollef MH, et al, *Crit Care*, 2012;16:R218.

84

Response in *P. aeruginosa* VAP: Can We Do Better and Is There Room for Improvement?



Planquette B, et al. *Am J Respir Crit Care Med*. 2013;188:69-76.

85

New Treatments Needed for *Pseudomonas* and other XDR/PDR Pathogens

- Enhanced anti-Pseudomonal activity
  - Ceftolozane/(tazobactam)
  - (Ceftazidime)/avibactam
- Specific anti-Pseudomonal antibiotics
  - Murepavidin
  - Small molecule inhibitors of Type 3 Secretion
- Anti-Pseudomonal antibodies

86

ASPECT-NP: a randomised, controlled, double-blind, phase 3, non-inferiority trial of ceftolozane/tazobactam versus meropenem for treatment of nosocomial pneumonia

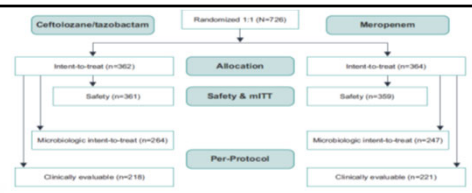
Marin H. Kollef, MD,[1] Martin Nováček, MD,[2] Ülo Kivistik, MD,[3] Álvaro Réa-Neto, MD,[4] Nobuaki Shime, MD, PhD,[5] Ignacio Martin-Loeches, MD,[6,7] Jean-François Timsit, MD,[8] Richard G. Wunderink, MD,[9] Christopher J. Bruno, MD,[10] Jennifer A. Huntington, PharmD,[10] Gina Lin, MS,[10] Brian Yu, PharmD,[10] Joan R. Butterton, MD,[10] Elizabeth G. Rhee, MD[10*]

Key Points: 1) All patients were ventilated
2) Used a 3 g dose of ceftolozane/tazobactam

***Manuscript submitted and under review 2019**
Abstracts presented ECCMID 2019

* Please note that since this live meeting, the study has been published online at *Lancet Infect Dis* 2019.

87



Baseline LRT pathogen (mITT population)	N=264	N=247
Gram-negative pathogens, n (%)	259 (98.1%)	240 (97.2%)
Pseudomonas aeruginosa, n (%)	63 (23.9%)	65 (26.3%)
MDR, n (%)	24 (9.1%)	11 (4.5%)
XDR, n (%)	10 (3.8%)	5 (2.0%)
Enterobacteriaceae, n (%)	195 (73.9%)	185 (74.9%)

Kollef MH, et al. *Lancet Infect Dis*. 2019;pii: S1473-3099(19)30403-7 [Epub ahead of print].

88

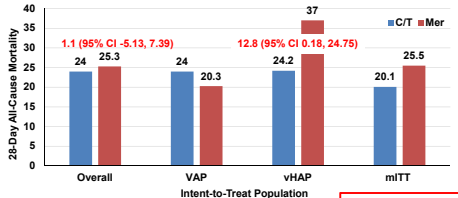
ASPECT-NP: Baseline Characteristics

Characteristic	Ceftolozane/tazobactam (n=362) n (%)	Meropenem (n=364) n (%)
Primary diagnosis		
VAP	263 (72.7)	256 (70.3)
Ventilated HAP	99 (27.3)	108 (29.7)
Prior abx use	318 (87.8)	323 (88.7)
APACHE II score		
≤14	89 (24.6)	93 (25.5)
≥20	124 (34.3)	115 (31.6)
In ICU	334 (92.3)	334 (91.8)
Duration of prior hospitalization		
≥5 days	278 (76.8)	279 (76.6)
Duration of prior MV		
≥5 days	182 (50.3)	176 (48.4)
Failed prior abx therapy for NP	53 (14.6)	40 (11.0)

Kollef MH, et al. *Lancet Infect Dis*. 2019;pii: S1473-3099(19)30403-7 [Epub ahead of print].

89

ASPECT-NP Results: 28-Day All-Cause Mortality

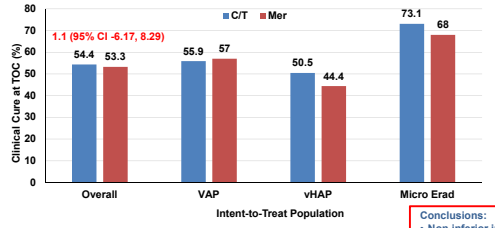


Kollef MH, et al. *Lancet Infect Dis*. 2019;pii: S1473-3099(19)30403-7 [Epub ahead of print].
Kollef M, et al. Poster presented at ECCMID (April 13-16, 2019), Amsterdam, poster Abstract #P1917.

Conclusions:
- Non-inferior in overall patient population
- Advantage with ceftolozane-tazobactam among ventilated HAP

90

ASPECT-NP Results: Clinical Cure at Test-of-Cure (TOC)



Conclusions:
- Non-inferior in all patient populations

Kollef MH, et al. *Lancet Infect Dis*. 2019;pii: S1473-3099(19)30403-7 [Epub ahead of print].
Kollef M, et al. Poster presented at ECCMID (April 13-16, 2019), Amsterdam, poster Abstract #P1917.

91

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 (April 13-16, 2019), Amsterdam, poster Abstract #O0302.

92

ASPECT-NP: Microbiological Eradication by Pathogen

Microbiological Eradication in Microbiologically Evaluable Population

Pathogen	C/T n /N (%)	MER n/N (%)	% Treatment Difference (95% CI)
Overall	79/113 (69.9)	73/117 (62.4)	7.5 (-4.69, 19.38)
Enterobacteriaceae	57/83 (68.7)	59/90 (65.6)	3.1 (-10.80, 16.75)
ESBL+ Enterobacteriaceae	30/45 (66.7)	27/39 (69.2)	-2.6 (-21.59, 17.14)
E. coli	18/23 (78.3)	17/23 (73.9)	4.3 (-19.94, 28.04)
ESBL+ *E. coli*	10/12 (83.3)	6/7 (85.7)	-2.4 (-32.86, 36.53)
K. pneumoniae	30/42 (71.4)	32/48 (66.7)	4.8 (-14.23, 22.92)
ESBL+ *K. pneumoniae*	20/30 (66.7)	18/27 (66.7)	0.0 (-23.15, 23.54)
P. aeruginosa	23/29 (79.3)	21/38 (55.3)	24.0 (1.11, 43.01)
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 (April 13-16, 2019), Amsterdam, poster Abstract #O0302.

93

ASPECT-NP: Ceftolozane/tazobactam (C/T) vs. Meropenem (MER) for HABP/VABP

- No significant differences in safety profile in critically ill patients
- Benefit in subgroup of patients who had failed prior therapy
  - Clinical cure at TOC: C/T: 49.1%
    MER: 37.5%
- NOTE: all ventilated patients
  dose was 3 grams q8 hours (not lower dose approved for cUTI/cIAI)

Pivotal trial for FDA approval of ceftolozane/tazobactam for HABP/VABP in June 2019

94

Ceftazidime-Avibactam for Nosocomial Pneumonia: REPROVE Trial

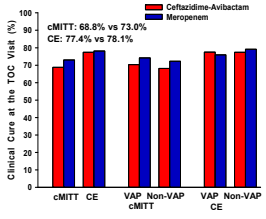
- Compared ceftazidime-avibactam (2000-500 mg q8h) vs meropenem (1000 mg q8h) in adults with nosocomial pneumonia
  - About 1/3 VAP
  - APACHE II score 20–30: ~13.5%
- Predominant pathogens:
  - *K. pneumoniae* (n=130, 36.6%)
  - *P. aeruginosa* (n=105, 29.6%)
  - *S. aureus* (n=58, 16.3%)
  - Polymicrobial: ~20%

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

95

Ceftazidime-avibactam for Nosocomial Pneumonia

Phase 3, Randomized, Multicenter Study (REPROVE Study)



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

Secondary Efficacy Endpoints

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

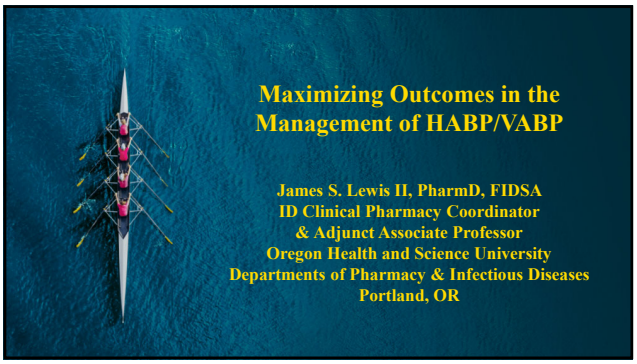
TOC, test-of-cure ; cMITT, clinically modified intent-to-treat; CE, clinically evaluable; mMITT, microbiological MITT; eME, extended microbiologically evaluable population

96

Summary

- Optimal management of HABP/VABP involves providing timely appropriate initial therapy while minimizing antimicrobial exposure
- The use of rapid diagnostics can effectively reduce antimicrobial exposure without compromising outcomes
  - Requires a willingness to discontinue antimicrobial based on rapid test result
- Newer β-lactam/β-lactamase inhibitor combinations offer additional options for the treatment of HABP/VABP caused by difficult pathogens

97



98

Objectives

- HAP/VAP guidelines
- Antimicrobial stewardship
  - Interprofessional collaboration
  - Maximizing PK/PD, duration of therapy, de-escalation
  - Pathogen-specific antimicrobial selection

99

What do the Guidelines Say? – Microbiology & Stewardship

1. We recommend that all hospitals regularly generate and disseminate a local antibiogram, ideally one that is specific to their intensive care population(s) if possible.

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

100

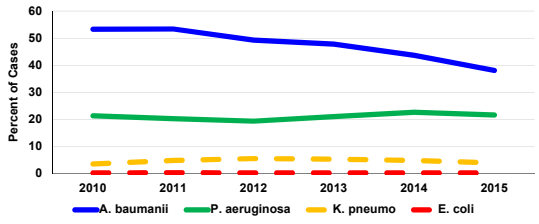
Ceftolozane-Tazobactam for Ventilated Nosocomial Pneumonia

- In patients with positive baseline LRT cultures
  - (70%) causative Gram-negative pathogens
  - Enterobacteriaceae (74%)
  - *P. aeruginosa* (25%)
- Importance of knowing your local antibiogram for these organisms
- Importance of knowing the risk factors for MDR pathogens

Kollef MH, et al. *Lancet Infect Dis*. 2019;pii: S1473-3099(19)30403-7 [Epub ahead of print].

101

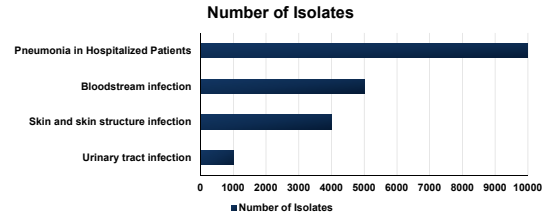
Percentage of Total Carbapenem-Resistant Cases Contributed By Pathogen



Cai B, et al. *Open Forum Infect Dis*. 2017;4: DOI: 10.1093/ofid/ofx176.

102

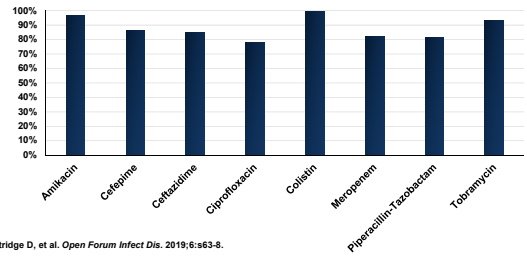
Distribution of *P. aeruginosa* Isolates by Infection Type – North America (SENTRY 1997–2016)



Shortridge D, et al. *Open Forum Infect Dis.* 2019;6:s63-8.

103

North America *P. aeruginosa* Susceptibility: SENTRY Antimicrobial Surveillance Program 2013–2016



Shortridge D, et al. *Open Forum Infect Dis.* 2019;6:s63-8.

104

Susceptibility of *P. aeruginosa* From U.S. ICU Patients With Bloodstream Infections or Pneumonia

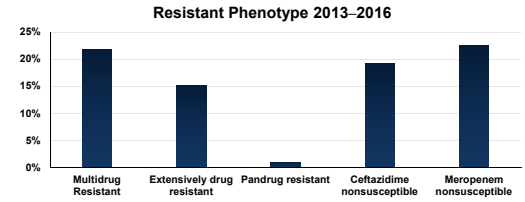
	MIC_{90}, mg/L	% Susceptible
Aztreonam	>16	66.5
Cefepime	16	83.8
Ceftazidime	32	82.0
Ciprofloxacin	>4	73.9
Meropenem	8	76.3
Piperacillin-tazobactam	>64	77.1

Amikacin, gentamicin, and colistin look better – 98%, 87%, 99.4% - excited to use them?

Shortridge D, et al. *Open Forum Infect Dis.* 2019;6:ofz240.

105

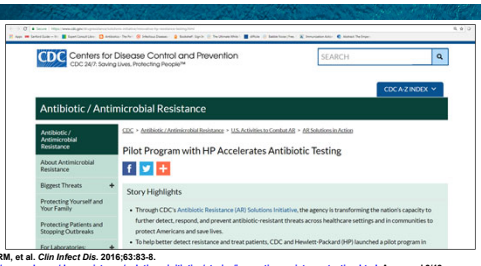
Geographic Temporal Patterns of Antimicrobial Resistance in *P. aeruginosa* From the SENTRY Antimicrobial Surveillance Program



Shortridge D, et al. *Open Forum Infect Dis.* 2019;6:s63-8.

106

Issues With New Agents: Susceptibility Testing



Humphries RM, et al. *Clin Infect Dis.* 2016;63:83-8.
CDC. https://www.cdc.gov/drugresistance/solutions-initiative/stories/innovative-resistance-testing.html. Accessed 9/19.

107

Availability of Susceptibility Testing

Antimicrobial	Disk Diffusion	Gradient Diffusion		Other	
		Liofilchem	E-Test	Sensititre Tray	Automated Systems
Ceftazidime-avibactam	Yes	Yes	Yes	Yes	Microscan Vitek-2 (Q4 2020?)
Ceftolozane-tazobactam	Yes	Yes	Yes	Yes	Microscan Vitek-2
Dalbavancin	No	Yes	No	Yes	No
Delafloxacin	Yes	Yes	Soon (Q1 2020?)	Yes	No
Eravacycline	Yes	Yes	No	No	No
Meropenem-vaborbactam	Yes	Yes	Yes	Yes	BD Phoenix
Omadacycline	Yes	Yes	No	No	No
Plazomicin	Yes	Yes	Soon (Q3 2020?)	No	No

Slide Courtesy of Kristi Traugott, PharmD.

108

What do the Guidelines Say?

Values and preferences: These recommendations place a high value on targeting the specific pathogens associated with VAP as narrowly as possible to assure adequate treatment while minimizing overtreatment and its undesirable consequences.

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

109

What do the Guidelines Say? Stewardship & Empiric Antibiotic Selection

Table 2. Risk Factors for Multidrug-Resistant Pathogens
Risk factors for MDR VAP
Prior intravenous antibiotic use within 90d
Septic shock at time of VAP
ARDS preceding VAP
Five or more days of hospitalization prior to the occurrence of VAP
Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP
Prior intravenous antibiotic use within 90d
Risk factors for MRSA HAP/VAP
Prior intravenous antibiotic use within 90d
Risk factors for MDR *Pseudomonas* VAP/HAP
Prior intravenous antibiotic use within 90d

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

110

Empiric Treatment Options for Clinically Suspected VAP Where Empiric MRSA Coverage & Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

Gram-positive MRSA Antibiotic	Gram-negative Antibiotic With Antipseudomonal Activity: β-Lactam-Based Agents	Gram-negative Antibiotic With Antipseudomonal Activity: Non-β-Lactam-Based Agents
Vancomycin 15mg/kg IV q8-12h	Piperacillin-tazobactam 4.5g IV Q6h	Ciprofloxacin 400mg IV Q8h
		Levofloxacin 750mg IV Q24h
OR	OR	OR
Linezolid 600mg IV Q12h	Cefepime 2g IV Q8h	Amikacin 15-20mg/kg IV q24h
	Ceftazidime 2g IV Q8h	Gentamicin 5-7mg/kg IV Q24h
		Tobramycin 5-7mg/kg IV Q24h
	OR	OR
	Imipenem 500mg IV q6h	Colistin 2.5mg IV Q12h (after load)
	Meropenem 1g IV q8h	Polymyxin B 1.25-1.5mg/kg IVQ12h

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

111

What's Missing, What's New, & What's an Option?

- Ceftolozane-Tazobactam: FDA-approved pneumonia indication
- Ceftazidime-Avibactam: FDA-approved pneumonia indication
- Meropenem-Vaborbactam: Not active for Mero-R *P. aeruginosa*
- Imipenem-Relebactam – No pneumonia data currently*
- Cefiderocol – Not yet FDA-approved, intriguing activity+

*Results from RESTORE-IMI2 were released on September 30, 2019 that showed non-inferiority with imipenem-relebactam compared with pip/tazo for HABP/VABP

+ Cefidercol was approved by the FDA on November 14, 2019 for treatment of Complicated Urinary Tract Infections (cUTI) in Adult Patients with Limited or No Alternative Treatment Options

Castanheira M, et al. *Antimicrob Agents Chemother.* 2018;62:e00313-18.

112

What's Missing, What's New, & What's an Option?

- Plazomicin:
  - Variable *P. aeruginosa* activity
  - <<potent than tobramycin
  - Issues with aminoglycosides in pneumonia
- Eravacycline:
  - No *P. aeruginosa* activity, no pneumonia data
  - MDR *Acinetobacter* spp.?
  - Metallo-beta-lactamase stability
- Delafloxacin:
  - No advantage over levofloxacin or ciprofloxacin for *P. aeruginosa*
  - Comparable to levofloxacin and ciprofloxacin for other GNRs

113

New Consensus Guidelines for the Optimal Use of Polymyxins


PHARMACOTHERAPY accp

Special Article | Free Access

International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

Brian T. Tsuji, Jason M. Pogue, Alexandre P. Zavascki, Mical Paul ... See all authors

Tsuji, BT, et al. *Pharmacotherapy.* 2019;39:10-39.

114

Interesting Quotes

- "…in the lung infection model ... for *A. baumannii*, it was **not even possible to achieve bacteriostasis** for two of the three tested strains with the highest tolerable systemic dosage regimen of colistin."
- "…based on the thigh infection model, this exposure would be expected to achieve bactericidal activity against an isolate with an MIC of 2 mg/L … unless the MIC of the infecting strain is well below the breakpoint, this target is **very likely to be suboptimal for the systemic treatment of a lung infection**."

Tsuji, BT, et al. *Pharmacotherapy.* 2019;39:10-39.

115

J Antimicrob Chemother
doi:10.1093/jac/dkx522
Journal of Antimicrobial Chemotherapy

Exploring colistin pharmacodynamics against *Klebsiella pneumoniae*: a need to revise current susceptibility breakpoints

Marilena Tsala[1], Sophia Vourli[1], Panagiota-Christina Georgiou[1], Spyros Pournaras[1,2], Athanasios Tsakris[2], George L. Daikos[3], Johan W. Mouton[4] and Joseph Meletiadis[1,4]*

- PK/PD target fAUC/MIC = 25
- PTAs built for most often used clinical regimens including loading
- fAUC/MIC target attainment of:
  - 100% at MIC of ≤0.5 mg/L
  - 5–70% at MIC of 1 mg/L
  - 0% at MIC of 2 mg/L

PTA, probability of target attainment
Tsala M, et al. *J Antimicrob Chemother.* 2018;73:953-61.

116

Comment

Evidence to improve the treatment of infections caused by carbapenem-resistant Gram-negative bacteria

- "The high patient mortality rate (44% at 28 days)… is sobering – considering that infection with bacteria susceptible to colistin was a criterion for inclusion and that colistin dosing was carefully controlled – but is not surprising."
- "…low Charlson and SOFA scores…"
- "…colistin, either as monotherapy or combined with a carbapenem, is not that effective."

Perez F, Bonomo RA. *Lancet Infect Dis.* 2018;18:358-60.

117

Clinical Infectious Diseases
MAJOR ARTICLE

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

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[3] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5] Robert A. Salata,[6] 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,[15,16,17] and Scott Evans[18]; for the Antibacterial Resistance Leadership Group

- 38 patients treated with ceftazidime-avibactam vs. 99 patients treated with colistin
- Often used in combination
- All-cause hospital mortality 30 days after start of treatment:
  - Ceftazidime-avibactam: 9%
  - Colistin: 32%
  - 95% CI: 9–35%, p=.001

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

118

New CLSI Colistin/Polymyxin B Comments

- Clinical and PK/PD data suggest that this agent is of limited clinical efficacy, even if a susceptible result is obtained.
- If available, alternative non-polymyxin agents are strongly preferred. If these agents are not available, this breakpoint presumes use of colistin in combination with one or more additional, active antimicrobials.
- Colistin (methanesulfonate) should be given with a loading dose and maximum renally-adjusted doses.
- Polymyxin B should be given with a loading dose and maximum recommended doses.
- When given intravenously, this drug is unlikely to be effective for pneumonia.

CLSI June 2019 Agenda Book Materials – Presentation of the Colistin/Polymyxin B Ad-Hoc Working Group.

119

120

What Do We Know About the Newer Agents in Pneumonia?

- Ceftazidime-avibactam: FDA-approved indication
- Ceftolozane-tazobactam: FDA-approved indication – NEW DOSE
- Currently none of the other agents with indications
- History of struggles in HAP/VAP with new agents
- In vitro activity vs. clinical data

121

Activity of New 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.

122

P. aeruginosa Resistant to: Ceftazidime, Meropenem, & Pip-Tazobactam

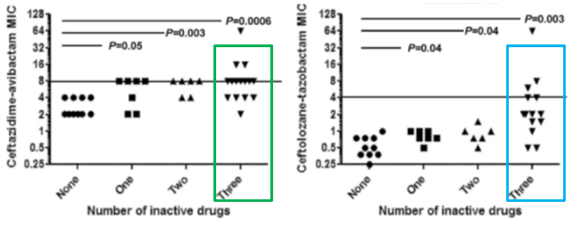
Number of isolates (cumulative %) inhibited at an MIC of:

	≤ 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)

Sader HS, et al. *Antimicrob Agents Chemother.* 2015;59:3656-3659.
Farrell DJ, et al. *Antimicrob Agents Chemother.* 2013;57:6305-6310.

123

Ceftazidime-Avibactam & Ceftolozane-Tazobactam vs. Resistant *P. aeruginosa*



Buehrle DJ, et al. *Antimicrob Agents Chemother.* 2016;60:3227-31.

124

Ceftolozane-Tazobactam & Imipenem-Relebactam for MDR *P. aeruginosa*

Cross-susceptibility of ceftolozane-tazobactam and imipenem-relebactam vs MDR *P. aeruginosa* from ICU & non-ICU wards (n=442)

		Imipenem-Relebactam		
		Susceptible	Intermediate	Resistant
Ceftolozane-Tazobactam	Susceptible	297 (67.2%)	37 (8.4%)	24 (5.4%)
	Intermediate	31 (7.0%)	6 (1.4%)	7 (1.6%)
	Resistant	21 (4.8%)	7 (1.6%)	12 (2.7%)

21/40 (52.5%) of ceftolozane-tazobactam R isolates were imipenem-relebactam susceptible

Depestel D, et al. *Crit Care Med.* 2019;47(suppl 1): Abstract 658.

125

Ceftazidime-Avibactam Phase 3 Trials

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

- HABP/VABP
- cUTI
- cIAI

Torres A, et al. *Lancet Infect Dis.* 2018;18:285-295.
Avycaz® (ceftazidime-avibactam) Prescribing Information. Allergan USA Inc., Madison, NJ. Updated March 2019.

126

Ceftazidime-Avibactam HAP/VAP Trial – An Interesting Finding

- Increasing MICs (≥4× baseline) at EOT or TOC and same genotype as the baseline isolate were observed in:
  - 1 patient in ceftazidime/avibactam group – *K. pneumoniae*
  - 11 patients in meropenem group – 10 with *P. aeruginosa*
- Consistent theme with *P. aeruginosa* & carbapenems?

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

127

Further Evidence

Ceftazidime vs. Carbapenems vs. Piperacillin-Tazobactam as Single Definitive Therapy for *Pseudomonas aeruginosa* Bloodstream Infection – A Multi-Site Retrospective Study

- No difference in mortality
- No difference in clinical or microbiologic failure
- Adverse events similar
- Higher rates of antipseudomonal drug-resistant *P. aeruginosa* with carbapenem use (p=0.007)

Babich T, et al. *Clin Infect Dis.* 2019; doi: 10.1093/cid/ciz668.

128

Conclusions

- Knowing the susceptibility of the organisms you're likely to encounter in HABP/VABP is critical
- Resistance is more common in ICU settings/patients
- Susceptibility testing of newer agents can be challenging
- Colistin/Polymyxin B need to largely disappear from clinical use
- There are very important differences between new agents both in available clinical data and in vitro activity

129

130

Patient Case (Review)

Transferred to medical ICU (Hospital Day 3)

- Given ceftaroline 600 mg q8h for suspected MRSA infection
- SpO_2 is 93% on 60% O_2 with a PEEP of 10 cm H_2O and a respiratory rate of 33/min
- Physical exam notable for a thin-appearing male who is intubated and sedated
- Heart sounds are obscured by a left bronchopleural fistula air leak
- Left lung sounds are described as a babbling brook air leak that is evident over the entire left chest
- He withdraws to pain in all 4 extremities

131

Patient Case (cont'd)

- CXR reveals left pneumothorax, bilateral airspace disease involving the lower lung zones, worsening on the right
- A second chest tube is placed the day after ICU transfer
- Patient is changed back to vancomycin + clindamycin and oseltamivir is restarted
- WBC is 15,700/mm^3 with a lactate of 2.2 mmol/L
- Cefepime 2 g q8h is added to the regimen for suspected superinfection

132

Patient Case (cont'd)

Day 3 in the Medical ICU (Day 6 total)

- Blood culture is negative
- WBC=21,500/mm^3
- Temp to 38.6°C overnight
- Increasing purulence is noted from one of the left chest tubes
- Severe bilateral necrotizing pneumonia is noted on CXR with slightly increased opacification of the left lower lobe
- Additional cultures are sent from multiple sites

133

Patient Case (cont'd)

- Patient expires overnight
- Endotracheal tube aspirate and 3 blood cultures reveal *P. aeruginosa*
  - Resistant to meropenem, ciprofloxacin, cefepime, and pip-tazo
  - Susceptible to gentamicin and tobramycin

134

Discussion Topics: What Could Have Been Done Differently?

- **What role does the antibiogram play in this scenario?**
- **Should rapid diagnostics have been considered?**
- **What factors should guide antimicrobial treatment selection?**

135

Discussion Topics: What Could Have Been Done Differently?

- **What role does the antibiogram play in this scenario?**
- **Should rapid diagnostics have been considered?**
- **What factors should guide antimicrobial treatment selection?**

136

Audience Question

The ICU antibiogram shows that 30% of *P. aeruginosa* isolates are resistant to cefepime. How would this impact your decision for initial empiric treatment of HAP/VAP?

1. Still consider cefepime unless a Gram stain identifies a Gram-negative pathogen from sputum sample
2. Still consider cefepime until culture and susceptibility results are available
3. Give preference to other antimicrobials with higher susceptibility rates initially
4. Avoid cefepime entirely

137

Discussion Topics: What Could Have Been Done Differently?

- **What role does the antibiogram play in this scenario?**
- **Should rapid diagnostics have been considered?**
- **What factors should guide antimicrobial treatment selection?**

138

Audience Question

If available at your institution, when would you consider the use of rapid diagnostics?

1. At the first sign of infection for every patient
2. At the first sign of infection among patients at risk of MDR infection
3. At the first sign of infection in seriously ill patients (e.g., ICU)
4. When the patient fails to improve with initial antimicrobial therapy

139

Discussion Topics:
What Could Have Been Done Differently?

- **What role does the antibiogram play in this scenario?**
- **Should rapid diagnostics have been considered?**
- **What factors should guide antimicrobial treatment selection?**

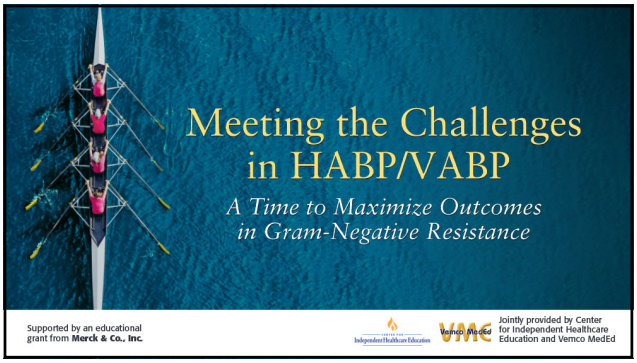
140

Audience Question

- **Endotracheal tube aspirate and 3 blood cultures reveal *P. aeruginosa***
  - **Resistant to meropenem, ciprofloxacin, cefepime, and pip-tazo**
  - **Susceptible to gentamicin and tobramycin**
- **What would you have selected for this patient?**

1. Gentamicin
2. Tobramycin
3. Ceftolozane-tazobactam
4. Colistin
5. Combination of 2 of the above

141



142