Conceptualization in Treating Infectious Diseases

A Framework to Achieve Optimal Outcomes

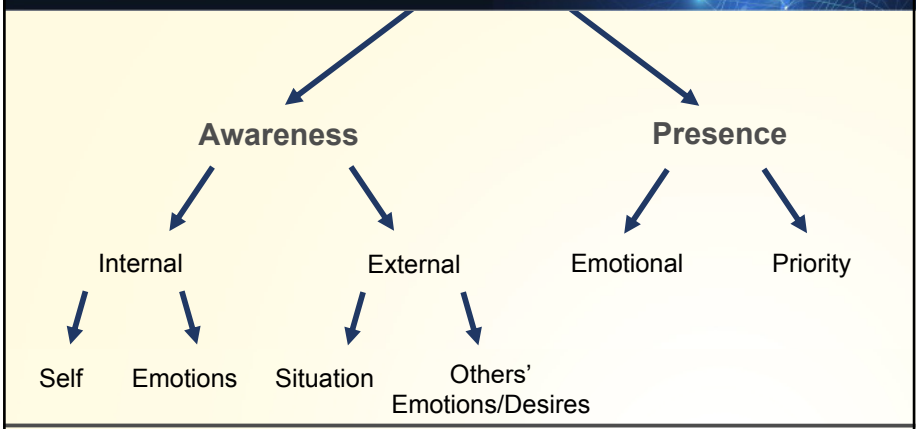
Activity Slides

The Learning Process

"The learning process can be divided into the accumulation of bits of information (memory) and the movement of these bits into patterns which are new to the individual (thinking). A little reflection will make it clear that the compulsive learner is incapable of thinking. There is always another bit of information to be memorized and, if they are all learned, there is little time to rearrange the bits in original patterns. It is also clear that without any bits there is no thinking. The hardest theoretical question in educational circles is the determination of the optimum number of bits for the most effective manipulation."

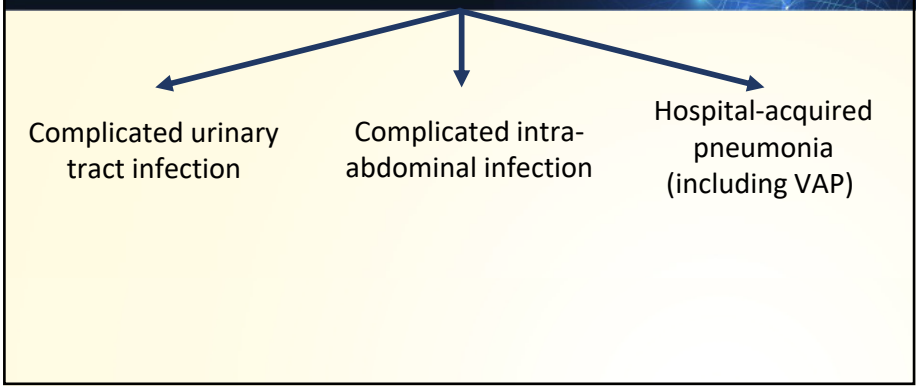
Stead EA, Jr. *A Way of Thinking: A Primer on the Art of Being a Doctor.* Carolina Academic Press, Durham, NC, 1995

Mindfulness



Jacob Peoples, August 2017

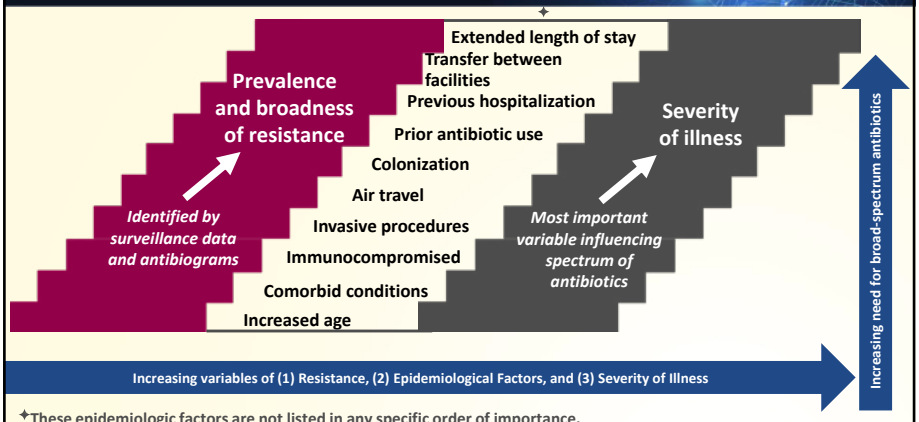
Standard Clinical Infections Studied in the Trials of New Antibiotics for Gram-Negative Infections



A Patient for Discussion

- A 52-year-old woman undergoes emergent 5-vessel coronary artery bypass graft surgery at a [redacted] hospital.
- Her post-operative course is complicated by intermittent bouts of flash pulmonary edema and associated hypotension.
- On post-op day 4, she develops fever, purulent sputum, and new pulmonary infiltrates on chest x-ray.
- Based on clinical findings and blood gases, the patient is managed [redacted].

Variables Influencing Patient Stratification for Empiric Antibiotic Therapy



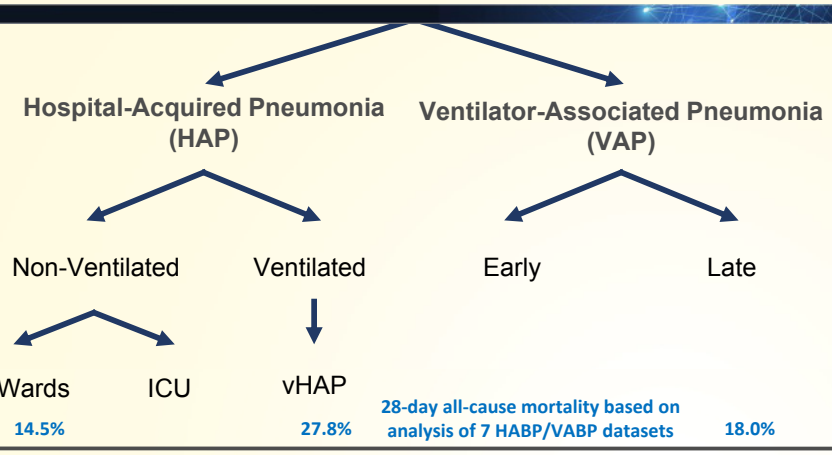
✦These epidemiologic factors are not listed in any specific order of importance.

Karam G, et al. *Crit Care.* 2016;20:136.

Nuances About Severity of Illness

- Hemodynamic stability
- Requirement for life-support measures
- Subjective impression about risk of mortality
- Characteristics of the infection itself

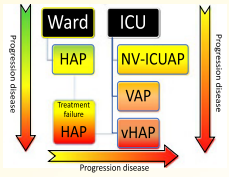
Nosocomial Pneumonia



Talbot GH, et al. *J Infect Dis.* 2019;219:1536–1544.

Insights Into the Treatment of Nosocomial Pneumonia

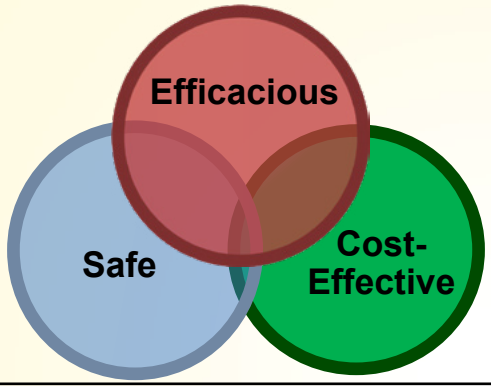
- Physiopathological approach to the progression of nosocomial pneumonia



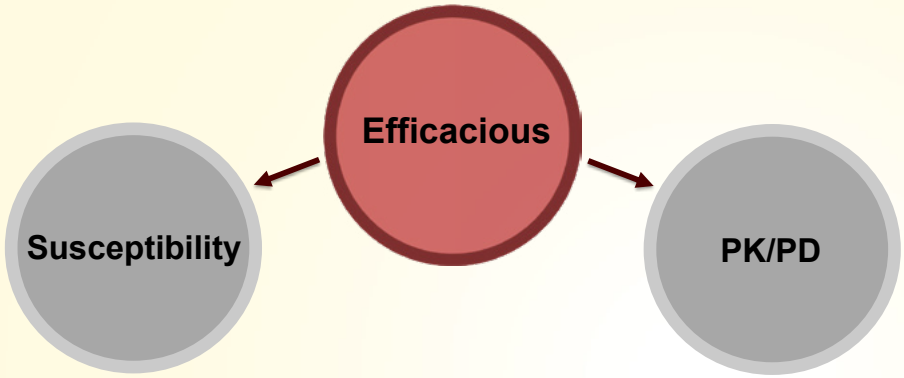
- Data from the National Surveillance Programme of Intensive Care Unit (ICU)-Acquired Infection in Europe Link for Infection Control through Surveillance (ENVIN-HELICS)
  - 30% likelihood of receiving inadequate empirical treatment for *Pseudomonas aeruginosa* infection, even with combination therapy
- Importance of antimicrobial optimization programs
  - Example: Antibiotic stewardship

Zaragoza R, et al. *Crit Care.* 2020;24:383.

Goals for Antimicrobial Therapy



Conceptual Components of Efficacy For Today's Discussion



The Normal Process for Determining Dose: Identifying PK/PD target

TABLE 3 Dose and T>MIC values for stasis and 1-log kill and the maximum extent of killing with 6-hourly dosing of ceftolozane against four wild-type *Enterobacteriaceae* strains and four *P. aeruginosa* strains[a]

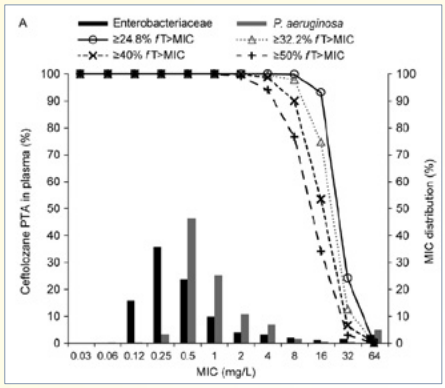
Organism	Static dose (mg/kg/6 h)	T>MIC (%)	1-Log kill dose (mg/kg/6 h)	T>MIC (%)	Maximal killing (log_{10} CFU/thigh)
Wild-type *Enterobacteriaceae* strains					
E. coli ATCC 25922	38.7	28.1	75.6	32.8	−2.95
E. coli NIH J	5.69	28.0	14.3	32.3	−2.49
K. pneumoniae ATCC 43816	61.2	25.2	127	32.0	−2.52
K. pneumoniae 216	36.0	24.0	76.6	29.2	−2.42
Mean		26.3 ± 2.1		31.6 ± 1.6	−2.60 ± 0.24
P. aeruginosa strains					
P. aeruginosa ATCC 27853	21.3	24.3	88.5	33.9	−1.92
P. aeruginosa 4034A	41.5	28.5	119	35.3	−2.61
P. aeruginosa PO2	12.2	21.7	50.5	30.1	−2.24
P. aeruginosa 313	21.4	21.4	51.9	26.7	−2.99
Mean		24.0 ± 3.3		31.5 ± 3.9	−2.44 ± 0.46
Mean for all strains		25.2 ± 2.8		31.5 ± 2.8	−2.52 ± 0.35

[a] Mean values are expressed as means ± the standard errors of the mean.

- Most commonly done via neutropenic thigh model (above), in vitro model, or hollow fiber infection model
- Identify serum target exposures

Craig WA, Andes DR. *Antimicrob Agents Chemother.* 2013;57:1577-1582.

Then Assess the Ability To Achieve That Target



Xiao AJ, et al. *J Clin Pharmacol.* 2016;56:56-66.

PD Targets May Differ for Pneumonia

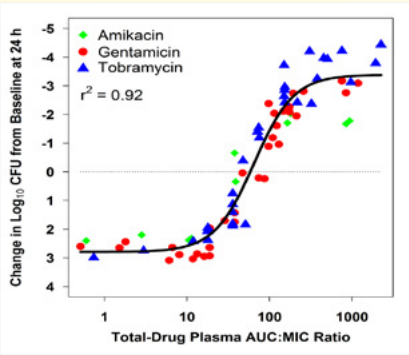
- Consideration needed for penetration of drug into lung
  - Penetration can vary, even within a class

Epithelial Lining Fluid Penetration of select β-lactams in healthy adults	
Drug	Penetration ratio (ELF to unbound plasma)
Ceftaroline	23%
Ceftazidime/Avibactam	31%/35% (total drug)
Ceftolozane/Tazobactam	59%
Piperacillin/Tazobactam	38%
Imipenem	55%

Rodvold K, et al. *Curr Opin Pharmacol.* 2017;36:114-123.

Different Strategies to Determine PD Targets for Pneumonia are Needed!

USCAST Rationale Document on Aminoglycosides



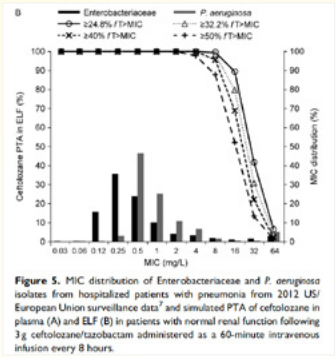
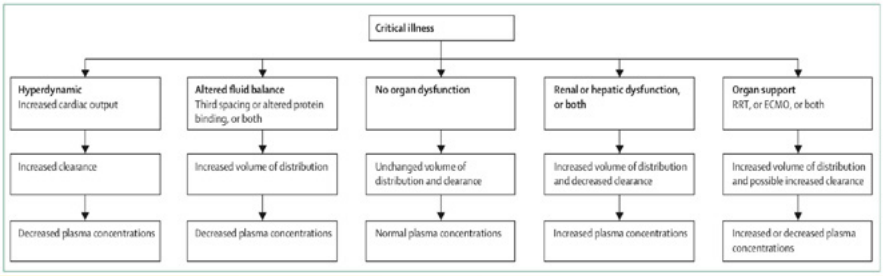


Figure 5. MIC distribution of Enterobacteriaceae and *P. aeruginosa* isolates from hospitalized patients with pneumonia from 2012 US/European Union surveillance data[7] and simulated PTA of ceftolozane in plasma (A) and ELF (B) in patients with normal renal function following 3 g ceftolozane/tazobactam administered as a 60-minute intravenous infusion every 8 hours.

Xiao AJ, et al. *J Clin Pharmacol.* 2016;56:56-66.

Pharmacokinetics Can Be (Somewhat Unpredictably) Altered in Sicker Patients



Roberts JA, et al. *Lancet ID.* 2014;14:498-509.

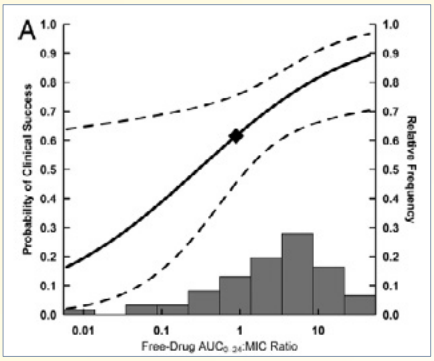
Impact of PK Changes in the Critically ill on ELF Concentrations

Epithelial Lining Fluid Penetration of select β-lactams in critically ill patients	
Drug	**Penetration ratio (ELF to unbound plasma)**
Piperacillin/Tazobactam	P: 39 – 85% T: 49 – 121%
Meropenem	25 – 81%
Ertapenem	20 – 32%
Cefepime	104%
Ceftazidime	21%

- In general, ELF penetration for β-lactams tends to be similar or higher in critically ill patients
- The variability (range) however is often much higher
- Remember, however, the penetration is a percentage of a serum concentration which will be lower due to increased volume
- Complex interplay with clearance can impact exposures in serum and at target site

Rodvold K, et al. *Curr Opin Pharmacol.* 2017;36:114-123.

Ignore PK/PD Considerations at Your Own Peril!



- $f_{AUC/MIC}$ ratio ≥0.9 was associated with success in HAP/VAP trial
- 78% vs. 36% clinical response rates based on this cutoff

Bhavnani S, et al. *Antimicrob Agents Chemother.* 2012;56:1965-1072.

Two Things Go Into This…..

PK:

- HAP patients fAUC exposures
  - 1.16 (0.54 – 3.5)
- VAP patients fAUC exposures
  - 0.97 (0.36 – 4.0)
- VAP patients ~20 % lower AUC
- VAP patients much wider range!

fAUC/MIC values
HAP: 5.61 (0.05 – 54.1)
VAP: 1.14 (<0.01 – 16.1)

PD:

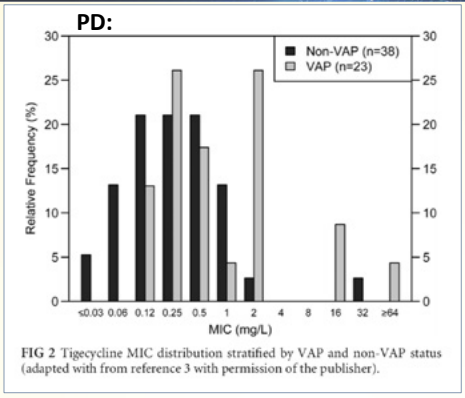


FIG 2 Tigecycline MIC distribution stratified by VAP and non-VAP status (adapted with from reference 3 with permission of the publisher).

Bhavnani S, et al. *Antimicrob Agents Chemother.* 2012; 56:1065-1072.

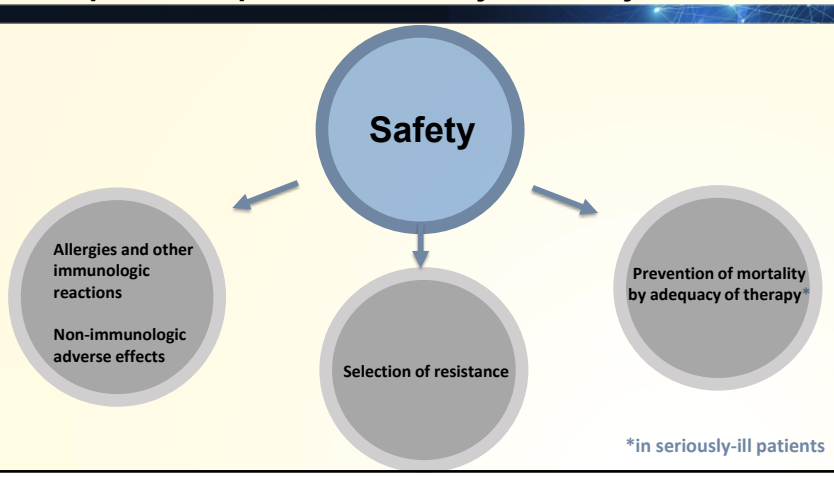
Comparison of Tigecycline with Imipenem/Cilastatin for the Treatment of Hospital-Acquired Pneumonia

Table 5
Clinical response VAP and non-VAP

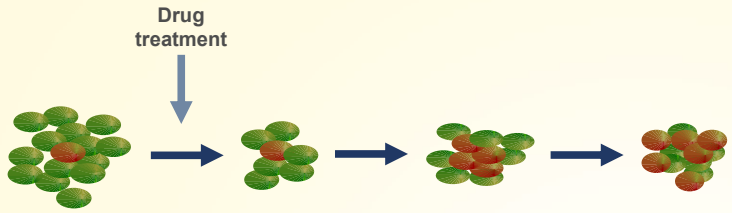
	n/N	Tigecycline (95% CI) (%)	*n/N*	Imipenem/cilastatin (95% CI) (%)	Difference (95% CI)
CE population					
VAP					
Cure	35/73	47.9 (36.1–60.0)	47/67	70.1 (57.7–80.7)	−22.2 (−37.8 to −4.9)
Failure	38/73	52.1	20/67	29.9	
Non-VAP					
Cure	147/195	75.4 (68.7–81.3)	143/176	81.3 (74.7–86.7)	−5.9 (−14.5 to 3.0)
Failure	48/195	24.6	33/176	18.8	

Freire AT, et al. *Diagn Microbiol Infect Dis.* 2010;68:140-151.

Conceptual Components of Safety for Today's Discussion



Resistance Due to Selection



Spontaneous mutation occurs in the absence of drug selection in a sensitive population

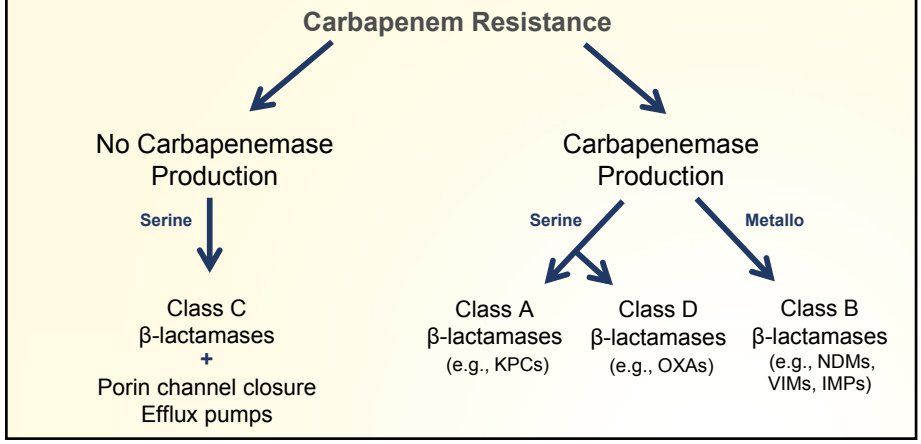
Mutant is selected for by drug treatment as sensitive strains die off

Resistant clone grows within what used to be a sensitive population

Resistance becomes clinically manifested during therapy

Sanders CC, Sanders WE. *J Infect Dis.* 1986;154:792-800.

Concept Map for Carbapenem Resistance



Clinical Approach to Resistance in Gram-Negative Bacteria

Non-carbapenemase

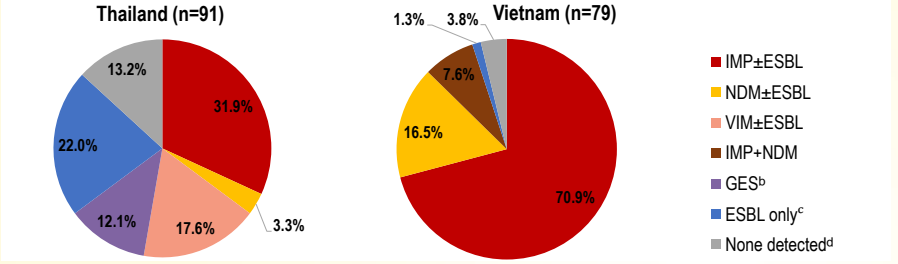
Carbapenemase, but not metallo

Carbapenemase, including metallo

Mechanisms of Resistance Against Clinical *P. aeruginosa* Isolates Collected in Asia/Pacific

SMART (Study for Monitoring Antimicrobial Resistance) Data: 2016-2018

Acquired β-lactamases detected among C/T-nonsusceptible *P. aeruginosa* isolates collected in Thailand and Vietnam[a]



[a] All isolates carry the chromosomally coded AmpC intrinsic to *P. aeruginosa*
[b] Includes 10 isolates carrying GES carbapenemases and 1 isolate carrying a GES ESBL
[c] Excludes 1 isolate carrying a GES ESBL
[d] None detected, no acquired β-lactamases included in the screening algorithm were detected by PCR

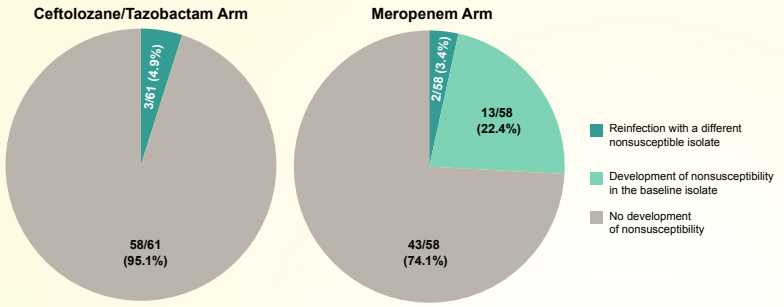
Lob S, et al. ICIC & ISAAR 2019; September 26-28, 2019; Gyeongju, Korea, Poster P2-CE13.

Clinical Approach to Treatment of Gram-Negative Infections in which *P. aeruginosa* May Be the Pathogen

Non-carbapenemase	Carbapenemase, but not metallo	Carbapenemase, including metallo
Ceftolozane/tazobactam	Ceftazidime/avibactam Meropenem/vaborbactam Imipenem/relebactam	Cefiderocol

Emergence of Nonsusceptibility Among Gram-Negative Respiratory Pathogens in the Phase 3 Nosocomial Pneumonia Trial ASPECT-NP

Emergence of Nonsusceptibility in Baseline *P aeruginosa* Lower Respiratory Tract Isolates



No baseline *P aeruginosa* isolates in the ceftolozane/tazobactam arm developed nonsusceptibility, compared with 22.4% in the meropenem arm

Motyl M, et al. 30th ECCMID; Paris, France; April 18–21, 2020. Poster 1215.

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;53:774–78.

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.

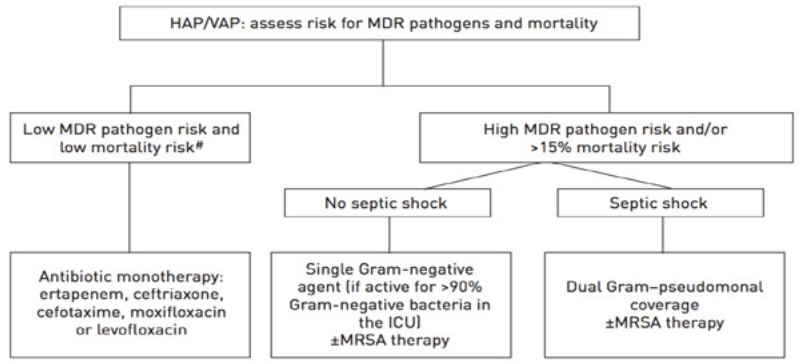
Recommendations for Initial Empiric Therapy for HAP (Non-Ventilator-Associated Pneumonia)

Not at High Risk for Mortality and No Risk Factors Increasing the Likelihood of MRSA✦	Not at High Risk of Mortality but With Factors Increasing the Likelihood of MRSA✦	High Risk of Mortality or Receipt of Intravenous Antibiotic in Prior 90 days✦
One of the following:	***One of the following:***	***Two of the following:***
• Piperacillin-tazobactam • Cefepime • Levofloxacin • Imipenem or meropenem	• Piperacillin-tazobactam • Cefepime or ceftazidime • Levofloxacin or ciprofloxacin • Imipenem or meropenem • Aztreonam ***Plus*** • Vancomycin ***or*** • Linezolid	• Piperacillin-tazobactam • Cefepime or ceftazidime • Levofloxacin or ciprofloxacin • Imipenem or meropenem • Amikacin, gentamicin, or tobramycin • Aztreonam ***Plus*** • Vancomycin or linezolid if coverage for MRSA ***or*** • Agents for MSSA✦

ATS/IDSA. *Clin Infect Dis.* 2016;63:e61-e111.

✦details in article

Approach To Potential Pathogens in HAP/VAP



Low mortality risk: ≤15% change of dying (a mortality rate that has been associated with better outcome using monotherapy than combination therapy when treating serious infection)

Torres A, et al. *Eur Respir J.* 2017;50:1700582 [https://doi.org/10.1183/13993003.00582-2017].

So How Do We Make This Our Own?

DRH	Monotherapy	Tobramycin	Ciprofloxacin	Amikacin
Cefepime	70	79	74	87
Pip/Tazo	68	82	77	88
Meropenem	75	83	78	87
Tobramycin	70			
Ciprofloxacin	61			
Amikacin	87			

- Create unit-specific antibiograms with all Gram-negative respiratory pathogens over a time frame
- Can determine what combination regimen is most likely to provide "appropriate" coverage
- These are general recommendations: DO NOT neglect patient specific factors
- Blind application of this to HAP can be problematic

Make Sure Antibiogram Assumptions Are Ones You Believe In

	Monotherapy	Cipro	Levo	Gent	Tobra	Amikacin
Pip-tazo	64	79	85	85	87	89
Cefepime	74	79	85	85	88	89
Ceftazidime	71	82	87	87	90	91
Meropenem	74	80	85	87	89	90
Ciprofloxacin	65					
Levofloxacin	72					
Gentamicin	79					
Tobramycin	83					
Amikacin	87					

Klatt M, et al. ECCMID 2021 (July 9-12); Vienna, Austria.

You Can't Really Target Amikacin MIC of 16 mg/L….

	Monotherapy	Cipro	Levo	Gent	Tobra	Amikacin
Pip-tazo	64	75	81	70	81	72
Cefepime	74	79	85	78	83	79
Ceftazidime	71	82	87	80	86	80
Meropenem	74	80	85	78	85	79
Ciprofloxacin	65					
Levofloxacin	72					
Gentamicin	79					
Tobramycin	83					
Amikacin	87					

Klatt M et al. ECCMID 2021 (July 9-12); Vienna, Austria.

What About Your Dosing Strategy?

	Monotherapy	Cipro	Levo	Gent	Tobra	Amikacin
Pip-tazo	64	75	81	70	81	72
Cefepime	74	79	85	78	83	79
Ceftazidime	71	82	87	80	86	80
Meropenem	74	80	85	78	85	79
Meropenem	83	85	90	85	87	86

Aminoglycoside breakpoints based on 90% PTA of achieving 1$\log_{10}$ reduction (tobra/gent ≤1, amikacin ≤2); Meropenem breakpoint based on 2 mg q8h dosing (3-hour infusion) – MIC breakpoint of 8

- Are you giving standard infusions of piperacillin-tazobactam?

Klatt M, et al. ECCMID 2021 (July 9-12); Vienna, Austria.

Uh oh…

	Monotherapy	Cipro	Levo	Gent	Tobra	Amikacin
Pip-tazo	54	75	81	70	81	72
Cefepime	74	79	85	78	83	79
Ceftazidime	71	82	87	80	86	80
Meropenem	74	80	85	78	85	79
Meropenem	83	85	90	85	87	86

- Are you giving standard infusions of piperacillin-tazobactam?

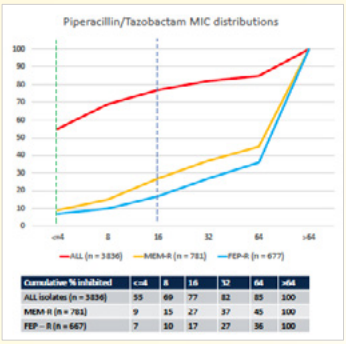
Klatt M, et al. ECCMID 2021 (July 9-12); Vienna, Austria.

Should We Be Considering New Drugs?

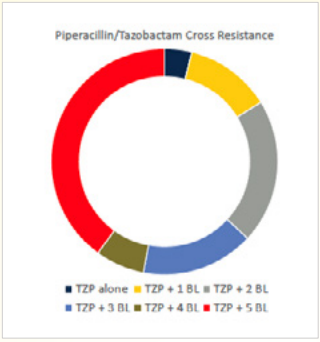
	Monotherapy	Cipro	Levo	Gent	Tobra	Amikacin
Pip-tazo	54	75	81	70	81	72
Cefepime	74	79	85	78	83	79
Ceftazidime	71	82	87	80	86	80
Meropenem	74	80	85	78	85	79
Meropenem	83	85	90	85	87	86
Ceftaz/avi	88	90	93	88	91	89
Mero/vabor	87	89	93	87	89	88

Klatt M, et al. ECCMID 2021 (July 9-12); Vienna, Austria.

If *P. aeruginosa* Is a Concern, Be Aware Cross-Resistance Within β-lactams Is Prevalent

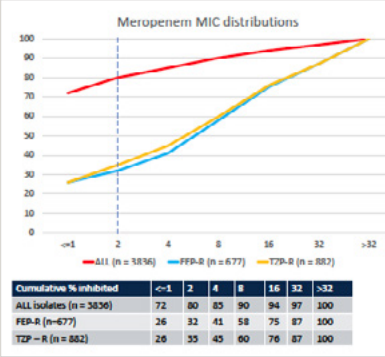


Cumulative % inhibited	<=4	8	16	32	64	>64
ALL isolates (n = 3836)	55	69	77	82	85	100
MEM-R (n = 781)	9	15	27	37	45	100
FEP – R (n = 667)	7	10	17	27	36	100

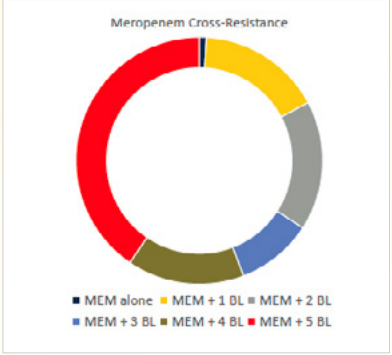


Patel TS, et al. IDWeek, October 2-6, 2019; Washington D.C., poster 1600.

Empiric Anti-Pseudomonal "Escalation" to Meropenem Is Not Really an Escalation

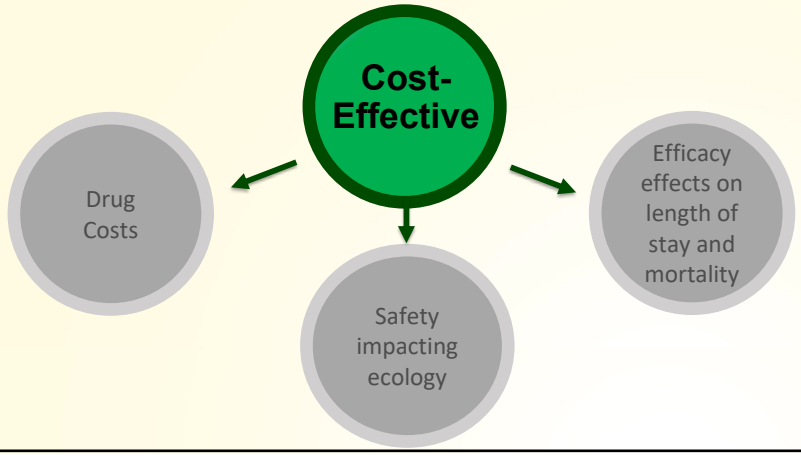


Cumulative % inhibited	<=1	2	4	8	16	32	>32
ALL isolates (n = 3836)	72	80	85	90	94	97	100
FEP-R (n=677)	26	32	41	58	75	87	100
TZP – R (n = 882)	26	35	45	60	76	87	100



Patel TS, et al. IDWeek, October 2-6, 2019, Washington D.C., poster 1600.

Conceptual Components of Cost-Effectiveness for Today's Discussion



Ceftolozane/Tazobactam versus Polymyxin or Aminoglycoside-Based Regimens for the Treatment of Drug-Resistant *Pseudomonas aeruginosa*

- Retrospective, multicenter, comparative effectiveness study from 6 sites in Southeastern Michigan and Central Ohio
- Ceftolozane/tazobactam versus polymyxin/aminoglycoside-based therapy for MDR/XDR *P. aeruginosa*
- ~70% pneumonia (majority VAP), ~70% ICU, ~40% severe sepsis/septic shock

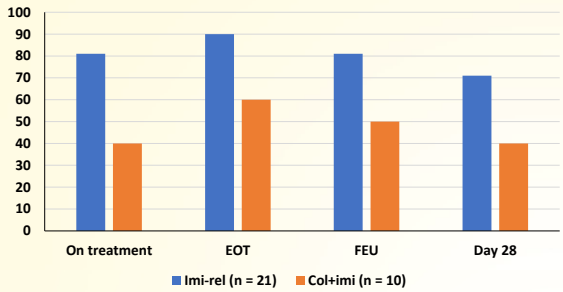
Table 3. Comparative clinical outcomes between Ceftolozane/Tazobactam and Polymyxin or Aminoglycoside treated patients

Outcome	Ceftolozane/ Tazobactam (N = 100)	Polymyxin/Aminoglycoside (N = 100)	*P* Value	Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Clinical cure	81	61	.002	2.72 (1.43–5.17)	2.63 (1.31–5.30)
In-hospital mortality	20	25	.40	0.75 (0.38–1.46)	0.62 (.30–1.28)
Acute kidney injury	6	34	<.001	0.12 (0.05–0.31)	0.08 (.03–.22)

Pogue JM, et al. *Clin Infect Dis.* 2020;71:304-310.

RESTORE-IMI 1:
Imipenem-Relebactam vs. Colistin + Imipenem

Favorable clinical response rates in mMITT population



Treatment emergent AKI occurred in 3/29 (10%) imipenem-relebactam patients versus 9/16 (56%) colistin + imipenem (*P*= 0.002)

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

Outcomes in Patients with Failure of Initial Antibiotic Therapy for HAP/VAP Prior to Enrollment in the Phase 3 ASPECT-NP Trial

	CT n/N (%)	MEM n/N (%)	% Treatment Difference (95% CI)
28-day all-cause mortality (ITT)	12/53 (22.6%)	18/40 (45.0%)	22.4 (3.11, 40.09)
Clinical cure at TOC (ITT)	26/53 (49.1%)	15/40 (37.5%)	11.6 (-8.61, 30.18)
28-day all-cause mortality (mITT)	7/39 (17.9%)	11/24 (45.8%)	27.9 (4.68, 49.98)
Clinical cure at TOC (CE)	21/33 (63.6%)	9/20 (45.0%)	18.6 (-8.23, 42.49)
Microbiologic response at TOC (mITT)	26/39 (66.7%)	16/24 (66.7%)	0.0 (-21.96, 23.66)
Microbiologic response at TOC (ME)	10/17 (58.8%)	4/7 (57.1%)	1.7 (-33.70,39.27)

Kollef M, et al. ISICEM 2020 Poster P423. *Crit Care.* 2020;24(Suppl 1):87(page 175).

The "Old Hats"

- Ceftolozane/tazobactam
  - Ceftolozane: broad-spectrum cephalosporin
  - Tazobactam: BLI, largely to improve Enterobacterales activity
  - Claim to fame: relatively stable to all MAJOR mechanisms of β-lactam resistance in *P. aeruginosa*
- Ceftazidime/avibactam
  - Avibactam: first-in-class non β-lactam β-lactamase inhibitor
  - Potent inhibitor of class A, C, and some class D enzymes
  - Notably KPC and OXA-48
  - Most relevant to *P. aeruginosa:* ampC type (class C)

Carbapenem-resistant *P. aeruginosa*:
Are ceftolozane/tazobactam and ceftazidime/avibactam the same?

	Ceftolozane/Tazobactam		Ceftazidime/Avibactam	
	% Susceptible	MIC50/90	% Susceptible	MIC50/90
Buehrle (n= 38)	92%	1/4	92%	4/8
Grupper (n= 290)	91%	1/4	81%	4/16
Humphries (n =220)	66%	NR	53%	NR

Buehrle DJ, et al. *Antimicrob Agents Chemother.* 2016;60:3227-3231.
Grupper M. *Antimicrob Agents Chemother.* 2017;61(10):e00875-17.
Humphries R, et al. *Antimicrob Agents Chemother.* 2017;61(12):e01858-17.

Antimicrobial Susceptibility and Carbapenem Co-Resistance Among Piperacillin/Tazobactam-Resistant (P/T-R) *Pseudomonas aeruginosa* Asia/Pacific SMART✦ Data: 2016-2018

Antimicrobial Agent	P/T-R (n=1262)	P/T-R + MEM-R (n=545)
Ceftolozane/tazobactam	64.6	34.3
Meropenem	40.3	0.0
Imipenem	46.7	5.3
Cefepime	28.6	9.5
Ceftazidime	22.9	12.5
Aztreonam	33.0	16.9
Ciprofloxacin	38.2	12.1
Amikacin	67.8	39.1
Colistin	97.7	95.6

✦SMART = Study for Monitoring Antimicrobial Resistance Trends MEM-R = Meropenem-resistant

Lob S, et al. 30th ECCMID. Paris, France; April 18–21, 2020. Abstract 2739.

Important To Know Your Own Data

Michigan Medicine 2018

P. aeruginosa	Ceftazidime/avibactam	Ceftolozane/tazobactam
All isolates n = 2,972	96%	94%
Pan β-lactam resistant N = 217	59%	42%

Patel TS, et al. IDWeek, October 2-6, 2019, Washington D.C., poster 522.

Does Meropenem-Vaborbactam Add Any Help?

- Vaborbactam
  - Unique boronic acid BLI
    - Designed to inhibit KPC, some inhibitory activity for ampC/ESBLs
  - Does minimal for meropenem in *P. aeruginosa*
    - Vaborbactam, much like meropenem, with porin/efflux issues

P. aeruginosa (n-98)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	% Susceptible
Piperacillin-tazobactam	16/4	>128/4	16/4 to > 128/4	52
Ceftazidime	8	>16	1 to > 16	37
Amikacin	4	16	≤0.5 to > 64	94
Ciprofloxacin	>4	>4	≤0.125 to > 4	35
Meropenem	8	32	4 to >64	0
Meropenem-RPX7009 (4µg/ml)	8/4	32/4	0.125/4 to >64/4	NA
Meropenem-RPX7009 (8µg/ml)	8/8	32/8	0.25/8 to 64/8	NA

Lapuebla A, et al. *Antimicrob Agents Chemother.* 2015;59:4856-4860.

Importantly, Things Are Not Absolute

Comparative in vitro activity of meropenem/vaborbactam and meropenem against a collection of real-world clinical isolates of *Pseudomonas aeruginosa*

Table 1. Susceptibility discordance of MEM and M/V by number of doubling dilutions for PSA isolates

MV MICs (mg/L) \ MEM MICs (mg/L)	N=2967	≤1	2	4	8	16	32	>32
≤1		2106	174	33	11	12	14	3
2		13	92	84	14	2	3	0
4		0	1	54	65	7	4	3
8		1	0	2	39	49	9	7
>8		1	0	0	2	42	71	51

Color Shading Key:

≥4 dilutions
3 dilutions
2 dilutions
1 dilutions
Same MICs
Unable to assess or MV > MEM

Patel TS, et al. IDWeek, October 2-6, 2019; Washington, DC, poster 521.

Imipenem/Relebactam

- Addition of "avibactam-like" β-lactamase inhibitor to imipenem-cilastatin
- As with avibactam, will handle the β-lactamase part of imipenem resistance
  - Will not be overly helpful against carbapenemases in *P. aeruginosa* (largely MBL)
  - Imipenem hydrolysis by ampC insufficient for resistance, but when combined with porin deficiency it can cause resistance

	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	% Susceptible
Imipenem-resistant *P. aeruginosa* (n=144)				
Imipenem	8	>16	4 to >16	0
Imipenem + relebactam	1/4	2/4	0.25/4 to >64/4	92

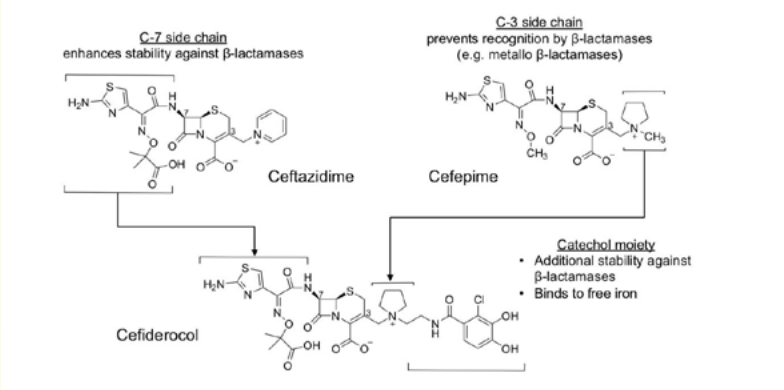
Lapuebla A, et al. *Antimicrob Agents Chemother.* 2015;59:5029-5031.

Activity of Imipenem/Relebactam Against MDR *Pseudomonas aeruginosa* in Europe: SMART 2015-2017

MDR Phenotype	Imipenem/ relebactam	Imipenem	Cefepime	Aztreonam	Pip/Tazo
R to 3 agents N = 547	99%	61%	58%	2%	39%
R to 4 agents N = 342	97%	42%	32%	1%	12%
R to 5 agents N = 490	83%	14%	5%	0%	5%
R to 6 agents N = 509	40%	0%	0.4%	0%	0%
R to 7 agents N = 14	64%	0%	0%	0%	0%

Lob SH, et al. *J Antimicrob Chemother.* 2019;74:2284-2288.

Cefiderocol



Zhanel GG, et al. *Drugs.* 2019;79:271-289.

Cefiderocol Activity Against CR-PA

P. aeruginosa (n=82)						
cefiderocol	≤0.03–1	0.12	0.5	NA	NA	NA
meropenem	4–>64	32	>64	0	14.6	85.4
ceftazidime	4–>64	32	>64	13.4	26.8	59.8
cefepime	1–>16	16	>16	25.6	43.9	30.5
ceftazidime/avibactam	1–>64	16	>64	NA	NA	NA
ceftolozane/tazobactam	0.5–>64	>64	>64	NA	NA	NA
aztreonam	≤0.5–>32	16	>32	48.8	19.5	31.7
amikacin	≤4–>64	64	>64	40.2	8.5	51.2
ciprofloxacin	≤0.25–>4	>4	>4	19.5	1.2	79.3
colistin	≤0.5–>8	≤0.5	1	97.6	1.2	1.2
tigecycline	≤0.25–>4	>4	>4	NA	NA	NA

Pseudomonas aeruginosa (all)	0.06	0.5	≤ 0.002 to 8	2	8	0.5	8
Multidrug-resistant	0.25	1	≤ 0.002 to 32	32	> 64	32	> 64
Ceftazidime-avibactam non-susceptible[e]	0.12	1	≤ 0.002 to 4	16	64	16	64
Ceftolozane-tazobactam non-susceptible[f]	0.25	4	0.004 to 8	8	64	16	32
Meropenem non-susceptible[a]	0.25	1	0.008 to 4	8	64	8	16

Falagas ME, et al. *J Antimicrob Chemother.* 2017;72:1704-1708.
Zhanel GG, et al. *Drugs.* 2019;79:271-289.

Cefiderocol versus Best Available Therapy for the Treatment of Serious Infections Caused by Carbapenem-Resistant Gram-Negative Bacteria: CREDIBLE-CR

Results from the randomized, open-label, multicenter, pathogen-focused, descriptive phase 3 trials

	Nosocomial pneumonia		Bloodstream infections or sepsis		Complicated urinary tract infections		Overall	
	Cefiderocol (n=45)	Best available therapy (n=22)	Cefiderocol (n=30)	Best available therapy (n=17)	Cefiderocol (n=26)	Best available therapy (n=10)	Cefiderocol (n=101)	Best available therapy (n=49)
Day 14	11 (24%; 12·9–39·5)	3 (14%; 2·9–34·9)	5 (17%; 5·6–34·7)	1 (6%; 0·1–28·7)	3 (12%; 2·4–30·2)	2 (20%; 2·5–55·6)	19 (19%; 11·7–27·8)	6 (12%; 4·6–24·8)
Day 28	14 (31%; 18·2–46·6)	4 (18%; 5·2–40·3)	7 (23%; 9·9–42·3)	3 (18%; 3·8–43·4)	4 (15%; 4·4–34·9)	2 (20%; 2·5–55·6)	25 (25%; 16·7–34·3)	9 (18%; 8·8–32·0)
End of study	19 (42%; 27·7–57·8)	4 (18%; 5·2–40·3)	11 (37%; 19·9–56·1)	3 (18%; 3·8–43·4)	4 (15%; 4·4–34·9)	2 (20%; 2·5–55·6)	34 (34%; 24·6–43·8)	9 (18%; 8·8–32·0)

Data are n (%; 95% CI) by clinical diagnosis and overall. Percentages were calculated using n as the denominator, where n was the number of patients in the safety population who had the specified clinical diagnosis and known vital status at each timepoint.

Table 5: **All-cause mortality in the safety population**

Bassetti M, et al. *Lancet Infect Dis.* 2021;21:226-240.

Did I Mention the Need to Make it Your Own?

		Single-Agent Resistance			Double-Agent Resistance			Triple-Agent Resistance	Novel Agent Resistance			
	Overall (N=694)	P/T (MIC > 16) (N=171)	Mero (MIC > 2) (N=140)	Cefepime (MIC > 8) (N=101)	Mero + P/T (N=97)	Cefepime + P/T (N=87)	Cefepime + Mero (N=65)	Cefepime + P/T + Mero (N=58)	M/V (MIC > 8) (N=37)	I/R (MIC > 2) (N=21)	C/A (MIC > 8) (N=40)	C/T (MIC > 4) (N=44)
P/T	75%		31%	14%			11%		8%	38%	23%	32%
Mero	80%	43%		36%		33%			0%	5%	13%	20%
Cefepime	85%	49%	54%		40%				27%	33%	13%	27%
M/V	95%	80%	74%	73%	65%	71%	58%	57%		48%	48%	57%
I/R	97%	91%	83%	84%	85%	85%	75%	78%	65%		68%	73%
C/A	94%	82%	75%	65%	70%	66%	51%	50%	43%	48%		34%
C/T	94%	82%	75%	68%	71%	70%	54%	55%	49%	52%	28%	
Cefiderocol	98%	96%	94%	90%	94%	92%	88%	90%	89%	95%	80%	80%

A Patient for Discussion

- A 52-year-old woman undergoes emergent 5-vessel coronary artery bypass graft surgery at a [redacted] hospital.
- Her post-operative course is complicated by intermittent bouts of flash pulmonary edema and associated hypotension.
- On post-op day 4, she develops fever, purulent sputum, and new pulmonary infiltrates on chest x-ray.
- Based on clinical findings and blood gases, the patient is managed [redacted].

A Patient for Discussion

- A 52-year-old woman undergoes emergent 5-vessel coronary artery bypass graft surgery at a community hospital with no significant patterns of resistance.
- Her post-operative course is complicated by intermittent bouts of flash pulmonary edema and associated hypotension.
- On post-op day 4, she develops fever, purulent sputum, and new pulmonary infiltrates on chest x-ray.
- Based she is hemodynamically stable with good oxygenation on 4 liters of nasal oxygen, she is managed on the ward.

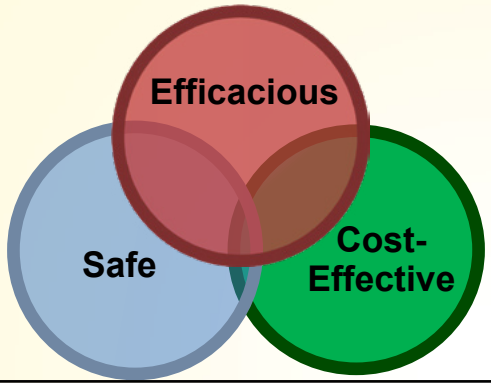
A Patient for Discussion

- A 52-year-old woman undergoes emergent 5-vessel coronary artery bypass graft surgery at an academic medical center with a 5% rate of serine carbapenemases.
- Her post-operative course is complicated by intermittent bouts of flash pulmonary edema and associated hypotension.
- On post-op day 4, she develops fever, purulent sputum, and new pulmonary infiltrates on chest x-ray.
- Because of profound hypoxemia and hemodynamic instability, she is moved to the ICU and intubated.

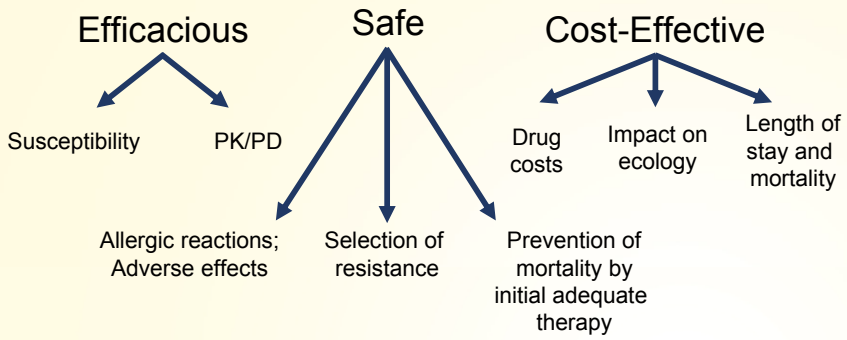
A Patient for Discussion

- A 52-year-old woman undergoes emergent 5-vessel coronary artery bypass graft surgery at an urban inner city hospital medical center that has experienced a recent outbreak of infection due to metallo carbapenemases.
- Her post-operative course is complicated by intermittent bouts of flash pulmonary edema and associated hypotension.
- On post-op day 4, she develops fever, purulent sputum, and new pulmonary infiltrates on chest x-ray.
- Because of profound hypoxemia and hemodynamic instability, she is moved to the ICU and intubated.

A Conceptual Approach to Antibiotic Therapy



A Conceptual Framework for Antibiotic Therapy

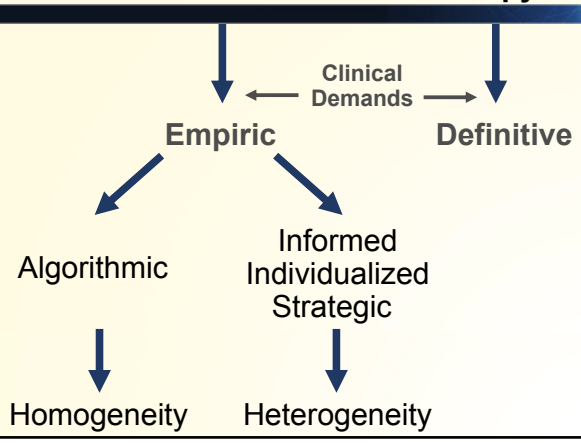


Quality of Antibiotic Use

Homogeneous	Heterogeneous
Drug formulary	Open access
Restrictive policies	Choice
Forced consultation	Initiated consultation
Controlled information	Open information
Static guidelines	Dynamic guidelines
Monosynaptic decisions	Polysynaptic decisions
Epidemic resistance	Stable resistance
Controls resistance	*Manages* resistance
Regulatory policies	Quality improvement
Component management	Clinical integration
Enforced Decisions	Informed Decisions

Burke JP, Pestotnik SL. in: *Antibiotic Therapy and Control of Antimicrobial Resistance in Hospitals*. Paris: Elsevier; 1999:89-95.

A Concept Map for Fundamental Forms of Antimicrobial Therapy



Continuing Professional Development

Reflect | Plan | Do | Evaluate

Center for Independent Healthcare Education is committed to supporting pharmacists in their Continuing Professional Development (CPD) and lifelong learning. Please use this form to incorporate the learning from this educational activity into your everyday practice.

Continuing Professional Development: a self-directed, ongoing, systematic and outcomes-focused approach to learning and professional development that assists individuals in developing and maintaining continuing competence, enhancing their professional practice, and supporting achievement of their career goals.

CPD Value Statement:

"Pharmacists who adopt a CPD approach accept the responsibility to fully engage in and document their learning through reflecting on their practice, assessing and identifying professional learning needs and opportunities, developing and implementing a personal learning plan, and evaluating their learning outcomes with the goal of enhancing the knowledge, skills, attitudes and values required for their pharmacy practice."

REFLECT

Consider my current knowledge and skills, and self-assess my professional development needs and goals in the area of multi-drug resistant Gram-negative infections.

PLAN

Develop a "Personal Learning Plan" to achieve intended outcomes, based on what and how I want or need to learn.

Develop objectives that are specific for you, measurable, achievable, relevant to the learning/ practice topic, and define the time frame to achieve them.

DO

Implement my learning plan utilizing an appropriate range of learning activities and methods.

List learning activities that you will engage in to meet your goals.

List resources (e.g. materials, other people) that you might use to help achieve your goal.

EVALUATE

Consider the outcomes and effectiveness of each learning activity and my overall plan, and what (if anything) I want or need to do next.

Monitor progress regularly toward achievement of your goal.