Changing Treatment Paradigms in the Era of Resistance

Meeting the Challenges in HABP/VABP

Educational Needs

Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) continue to be associated with poor clinical outcomes despite continued advances in prevention and management. For critically ill patients, long-term outcomes are especially poor with high rates of in-hospital and 30-day mortality. Further complicating management decisions has been the emergence of the COVID-19 pandemic. Emerging data is demonstrating that up to a third of COVID-19 patients have a secondary infection, with bacterial superinfection or coinfection more likely in patients with severe illness. ICU COVID-19 patients with prolonged hospitalization and/or intubation are also at greater risk of infection with multidrug-resistant (MDR) Gram-negative bacteria, likely reflecting hospital-acquired infection. Patient outcomes are closely linked to timely and appropriate initial therapy. Evidence-based strategies have been identified to help improve long-term outcomes of HABP/VABP patients. These include the use of antibiograms, rapid diagnostics, and newer antimicrobials. Maximizing the potential of these tools requires ID clinicians to be fully competent on their use in clinical practice in order to tailor management approaches based on patient factors and needs. This program is designed to build competence, confidence, and skills in the management of HABP/VABP while increasing the understanding of how to utilize the latest tools as part of antimicrobial stewardship efforts.

Target Audience

This continuing medical education activity meets the needs of healthcare providers in a variety of practice settings, including large and small health systems, outpatient clinics, managed-care organizations, long-term care facilities, and academia. This activity would be especially beneficial for ID physicians and pharmacists who are on the frontline of managing patients with serious bacterial infections.

Learning Objectives

At the conclusion of the educational activity, the learner should be able to:

- Describe the evolving epidemiology and resistance mechanisms of Gram-negative pathogens that commonly cause hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP)
- Implement the latest evidence-based diagnostic and therapeutic approaches when managing patients with HABP/VABP caused by multidrug-resistant (MDR) Gram-negative bacteria
- Differentiate the pharmacology and antibacterial activity of newer antimicrobial agents targeting MDR Gram-negative bacteria
- Evaluate strategies to guide antimicrobial selection and pathogen-specific therapy to optimize clinical and economic outcomes of patients with HABP/VABP

Faculty

Keith A. Rodvold, PharmD, FCCP, FIDSA
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Educational Program

Episode 1	Current Landscape Overview *Keith Rodvold, PharmD*
Episode 2	Epidemiology and Clinical Impact of MDR Gram-Negative Bacterial Infections Including Institutional Experience *Edward Septimus, MD*
Episode 3	Changing Paradigms in the Treatment of MDR Gram-Negative Infections Including Clinical Patient Case *George Karam, MD*
Episode 4	A Review of the Clinical Evidence in HABP/VABP Including Clinical Patient Case *Marin Kollef, MD*
Episode 5	Utilizing Stewardship to Optimize Diagnosis and Management for HABP/VABP Including Institutional Experience *Melissa Johnson, PharmD*

FACULTY BIO

Keith A. Rodvold, PharmD, FCCP, FIDSA
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Dr. Keith A. Rodvold received his BS and PharmD degrees from the University of Minnesota. He completed his research fellowship in clinical pharmacokinetics and pharmacology at St. Paul-Ramsey Medical Center and the University of Minnesota and was a Clinical Pharmacy Specialist at St. Joseph's Hospital in Marshfield, Wisconsin. Dr. Rodvold was appointed as an Assistant Professor in the Department of Pharmacy Practice at the University of Illinois at Chicago in 1984, was promoted to the rank of Associate Professor with tenure in 1989, and to the rank of Professor in 1994. In addition, he is also a Professor of Pharmacy in Medicine in the College of Medicine at the University of Illinois at Chicago. Dr. Rodvold is currently conducting research in the area of clinical pharmacokinetics and pharmacodynamics of anti-infective agents.

Dr. Rodvold has authored more than 145 original research and review publications, 40 book chapters, and is co-editor of the textbook, Drug Interactions in Infectious Diseases. The American College of Clinical Pharmacy presented Dr. Rodvold with the 2003 Russell R. Miller Award in recognition of his sustained and outstanding contributions to the literature of clinical pharmacy. Dr. Rodvold is a former member of the Anti-Infective Drug Advisory Committee and Pediatric Drug Advisory Subcommittee for the Food and Drug Administration. He is an active member of numerous professional societies and has been elected Fellow of the Infectious Diseases Society of America, American College of Clinical Pharmacology, and American College of Clinical Pharmacy.

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Edward J. Septimus, MD, FACP, FIDSA, FSHEA, is Medical Director, Infection Prevention and Epidemiology at Hospital Corporation of America (HCA) and Professor of Internal Medicine at Texas A&M Health Science Center College of Medicine in Houston, TX. He is also Professor, Distinguished Senior Fellow, at the George Mason University School of Public Health. Dr. Septimus received his Bachelor of Science from The Ohio State University and his Doctor of Medicine degree from Baylor College of Medicine in Houston. He completed his postgraduate training in Internal Medicine and Infectious Diseases at Baylor College of Medicine in Houston and is board certified in both internal medicine and infectious diseases. He is fellow of the American College of Physicians, Infectious Diseases Society of America (IDSA), and Society for Healthcare Epidemiology of America (SHEA).

His practice interests include patient safety, infection prevention, antimicrobial stewardship and resistance, public health including vaccine preventable diseases, sepsis, medical informatics, clinical integration, and human factors engineering. Dr. Septimus has lectured nationally and internationally on surviving sepsis, reduction of healthcare-associated infections, antimicrobial stewardship, the economic case for quality, and employee health. He is Past President of the Texas Infectious Diseases Society and has served on the Board of Directors of the IDSA. He is on the IDSA Antimicrobial Resistance Committee, the SHEA Antimicrobial Stewardship Committee, and the IDSA Quality Measurement Committee. In 2011 he was appointed to the Healthcare-Associated Infections/Preventable Adverse Events Advisory Panel for the Texas Department of State Health Services. Dr. Septimus is also a member of the FDA Anti-Infective Drug Advisory Group and is co-chair of the National Quality Forum (NQF) Patient Safety Steering Committee. Dr. Septimus has published over 100 peer-reviewed articles and book chapters. He was the first recipient of the IDSA Annual Clinician Award, received the John S. Dunn Sr. Outstanding Teacher Award in 2010, 2011, 2013 and 2014, and received the Clinical Excellence Award from HealthTrust in 2013.

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George H. Karam, MD is the holder of the Paula Garvey Manship Chair of Medicine in the Department of Internal Medicine at Louisiana State University (LSU) School of Medicine in New Orleans, LA. He attended medical school at LSU, and he completed his internal medicine internship, residency, and infectious diseases fellowship at the University of Alabama at Birmingham Medical Center in Birmingham, AL. He is a diplomate in internal medicine and infectious disease from the American Board of Internal Medicine (ABIM). He is a past Chairman of the ABIM Subspecialty Board on Infectious Diseases. He now serves as Program Director for the LSU Internal Medicine Residency Program in Baton Rouge and as Regional Director of Undergraduate Medical Education for the LSU School of Medicine in New Orleans.

Dr. Karam's scientific focus has been on the clinical aspects of bacterial resistance, with recent emphasis on antimicrobial stewardship. His work in medical education has been on the development of the personal elements of professionalism in residents and medical students.

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Dr. Marin Kollef is a Professor of Medicine at Washington University School of Medicine and Director of the Medical Intensive Care Unit and Respiratory Care Services at Barnes-Jewish Hospital in St. Louis, Missouri. He is a member of the Barnes-Jewish Hospital Critical Care Committee. Dr. Kollef was awarded Virginia E. and Sam J. Golman Chair in Respiratory Intensive Care Medicine in 2009. After completing his Bachelor of Science from the US Military Academy in West Point, NY, Dr. Kollef went on to receive his Doctor of Medicine degree from University of Rochester School of Medicine and Dentistry. Dr. Kollef then completed his residency in Internal Medicine and fellowship in Pulmonary Diseases and Critical Care at the Madigan Army Medical Center in Tacoma, Washington. He is a fellow of the American College of Physicians and the American College of Chest Physicians.

Dr. Kollef has lectured extensively on numerous critical care topics, including fungal infection, ventilator-associated pneumonia, antibiotic resistance, and optimization of antibiotic therapy. Dr. Kollef has authored peer-reviewed manuscripts, letters, case reports, editorials, and invited publications. He currently serves on the editorial boards of *Respiratory Care, Critical Care, Critical Care Medicine, Informed Decisions/Clinical Strategies*, and *Journal of Surgical Infections* and is a reviewer for many journals including *Chest, JAMA*, and the *New England Journal of Medicine*. Dr. Kollef is the recipient of numerous honors and awards including selection to "Best Doctors in America," Central Region and Barnes-Jewish Hospital Team Awards for Quality Improvement for programs directed to VAP prevention, bloodstream infection prevention, and the "Surviving Sepsis Initiative." He has received teaching awards and is a recognized expert in the performance of clinical outcomes research in the ICU setting. His clinical research focus has been the understanding and prevention of nosocomial infections and the improved care of mechanically ventilated patients. He is also a member of the American Thoracic Society, Society of Critical Care Medicine, American Association for Respiratory Care, and American Society of Clinical Investigation.

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Dr. Melissa D. Johnson, PharmD, MHS, AAHIVP is an Associate Professor of Medicine in the Division of Infectious Diseases & International Health at Duke University Medical Center in Durham, North Carolina. She also serves as a Liaison Clinical Pharmacist for Duke Antimicrobial Stewardship Outreach Network (DASON), which performs consulting services for 30 hospitals in 6 states. After obtaining a Bachelor of Science in Biochemistry from the University of Georgia, she completed her Doctor of Pharmacy at Campbell University and a Fellowship in Infectious Diseases Pharmacotherapy at DUMC. She also completed a Masters of Health Science in Clinical Research at Duke University School of Medicine, concentrating on biostatistics and epidemiology.

Her clinical research interests include invasive fungal infections in immunocompromised hosts with special focus on immunogenetics, pharmacogenetics, and pharmacodynamics. She has served as investigator for numerous clinical trials with antifungal, antiretroviral, and antibacterial agents. Dr. Johnson has been an active member of both the DUMC and Durham VAMC Antimicrobial Stewardship programs. She has published in numerous peer-reviewed journals, and is a reviewer for *Antimicrobial Agents and Chemotherapy, Clinical Infectious Diseases, Pharmacotherapy,* and *Journal of Antimicrobial Chemotherapy*. She has been an invited international and national speaker on topics such as antibiotic resistance, HIV, invasive fungal infections, and management of bacterial infections. She is an active member of the American College of Clinical Pharmacy (ACCP), American Society of Microbiology, and Society of Infectious Disease Pharmacists.

Current Landscape Overview

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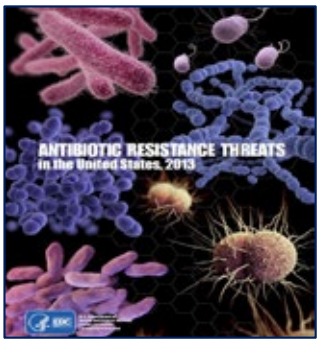
Antibiotic Resistance Threats Report



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

CDC Priority Lists – *2019*

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

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

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

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

New Anti-Infective Agents

FDA-Approval for HABP/VABP

Ceftazidime-Avibactam
February 1, 2018

Ceftolozane-Tazobactam
June 3, 2019

Imipenem-Relebactam
June 4, 2020

Cefiderocol
September 27, 2020

2018 **2019** **2020**

Treatment of patients 18 years of age and older with HABP and VABP, caused by susceptible Gram-negative microorganisms.

CME/CPE pre-symposium webinar, part of this educational initiative, provides detailed information on novel antimicrobials to treat HABP/VABP. Available at www.vemcomeded.com.

HABP = hospital-acquired bacterial pneumonia
VABP = ventilator-associated bacterial pneumonia
Imipenem-relebactam = Imipenem-cilastatin-relebactam

Talbot GH, et al. *Clin Infect Dis* 2019;69:1-11.
Prescribing Information: Avycaz® (3/2019), Zerbaxa® (4/2020), Recarbrio™ (6/2020), Fetroja® (9/2020)

New Anti-Infective Agents

FDA-Approval for HABP/VABP

Gram-Negative Microorganisms	Ceftazidime-Avibactam	Ceftolozane-Tazobactam	Imipenem-Relebactam	Cefiderocol
Acinetobacter calcoaceticus-baumannii complex			✱	✱
Enterobacter cloacea	✱	✱	✱	✱
Escherichia coli	✱	✱	✱	✱
Haemophilus influenzae	✱	✱	✱	
Klebsiella aerogenes			✱	
Klebsiella oxytoca		✱	✱	
Klebsiella pneumoniae	✱	✱	✱	✱
Proteus mirabilis	✱	✱		
Pseudomonas aeruginosa	✱	✱	✱	✱
Serratia marcescens	✱	✱	✱	✱

HABP = hospital-acquired bacterial pneumonia
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Prescribing Information: Avycaz® (3/2019), Zerbaxa® (4/2020), Recarbrio™ (6/2020), Fetroja® (9/2020)

IDSA Guidance: ESBLs and DTR *P. aeruginosa*

(Non-Urinary Tract Infections)

Pathogen	Preferred Therapy
ESBL Enterobacterales[a]	Meropenem Imipenem-cilastatin Ertapenem
DTR *P. aeruginosa*[b]	Ceftolozane-tazobactam Ceftazidime-avibactam Imipenem-cilastatin-relebactam Alternative: cefiderocol

[a]For ESBL Enterobacterales infections, piperacillin-tazobactam and cefepime should be avoided, even if susceptibility to these agents has been demonstrated

[b]For DTR *P. aeruginosa* infections, combination therapy is not routinely recommended if in vitro susceptibility to a preferred agent is confirmed

DTR = difficult-to-treat
IDSA. IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-negative Infections, Sept. 8, 2020. Available at: https://www.idsociety.org/practice-guideline/amr-guidance/.

IDSA Guidance: Treatment for CRE Infections

(Non-Urinary Tract Infections)

CRE Phenotype/Genotype	Preferred Therapy
Ertapenem resistant, Meropenem susceptible*	Meropenem (extended infusion)
Ertapenem and meropenem resistant*	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam
KPC identified (or carbapenemase positive but identity unknown)	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam
Metallo-beta-lactamase carbapenemase identified	Ceftazidime-avibactam + Aztreonam Cefiderocol
OXA-48-like carbapenemase identified	Ceftazidime-avibactam

Note: For CRE infections, polymyxin B and colistin should be avoided; combination therapy (i.e., a beta-lactam plus an aminoglycoside, fluoroquinolone, or polymyxin) is not routinely recommended.

*Carbapenemase testing results are either not available or negative
IDSA. IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-negative Infections, Sept. 8, 2020.
Available at: https://www.idsociety.org/practice-guideline/amr-guidance/.

Summary

- 4 new beta-lactam agents are available for the treatment of adult patients with HABP/VABP caused by susceptible Gram-negative microorganisms
- Each agent has its own specific 'niche' against multidrug-resistant (MDR) Gram-negative microorganisms
- Treatment of HABP/VABP must be targeted to the individual patient based on the clinical situation, intrinsic host characteristic(s), susceptibility profile, and local epidemiology
- Real-life clinical experiences will further define patient- and pathogen-specific roles of these agents for optimal therapy of patients with HABP/VABP

Notes

Epidemiology and Clinical Impact of MDR Gram-Negative Bacterial Infections

Including Institutional Experience

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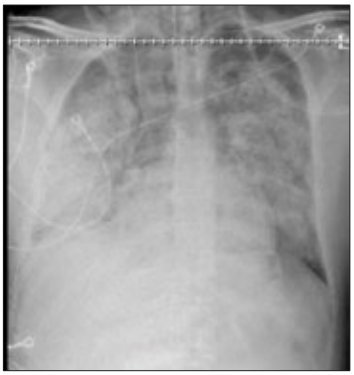
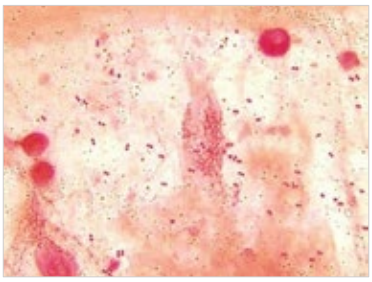
Patient Case: 53-year-old Male with Fever, Hemoptysis, and Shortness of Breath

- This is a 53 y/o Hispanic male admitted for shortness of breath, subjective fever, and hemoptysis for 2 weeks. No other close contacts are ill, no exposures, lives in the city.
  - Nonsmoker, social alcohol use
- Exam: T-101°F; P-120; RR- 32; BP- 110/60; O_2 Sat- 85%; Hb- 5.4; platelets- 648,000; Creatinine- 0.5; Na- 114; INR- 1.23; U/A- few RBCs; HIV negative; COVID-19- NP PCR negative; *Legionella* and SP U Ag- negative; Respiratory viral PCR- all negative
- Microbiology: BAL Gram stain: few WBC NOS; Culture- normal flora plus few *P. aeruginosa*; Blood- no growth; Acid fast bacilli and fungal stains- negative



Patient Case: Hospital Course

- Intubated Day 1, PICC line inserted
- Steroids started on Day 3
- Antibiotics:
  - Day 1–3: Azithromycin + ceftriaxone
  - Day 4–7: Meropenem
  - Day 8–12: Cefepime
- Extubated Day 7
- Day 12: Spike in fever to 103°F. Blood and sputum cultures were obtained. At 18 hours the lab calls you saying the blood culture is growing a GNB.



Clinical Consideration

What do you think is the most likely pathogen?

1. *Pseudomonas aeruginosa*
2. *Stenotrophomonas maltophilia*
3. *Acinetobacter baumannii*
4. None of the above

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- Intubated Day 1, PICC line inserted
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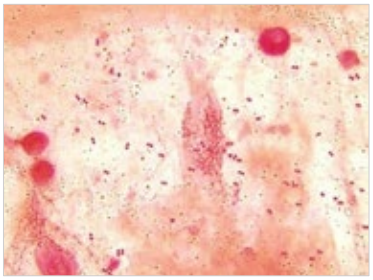

Clinical Consideration

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Knowing the Varied Definitions of Antimicrobial Resistance

- **Resistant:** Resistance to <3 groups of antibiotics
- **Multidrug-resistant (MDR):** Resistant to ≥3 groups of antibiotics
- **Extensively drug-resistant (XDR):** Resistant to ≥3 and sensitive to ≤2 groups of antibiotics
- **Pandrug-resistant (PDR):** Resistant to all groups of antibiotics

Rodrigo-Troyano A, Sibila O. *Respirology*. 2017;22:1288-1299.

Pneumonia Case Definitions

- **HABP:** Occurs ≥48 hours after admission, which was not incubating at time of admission and not on a ventilator
- **VABP:** Occurs >48-72 hours after intubation
- **HCAP:** Admitted with pneumonia who was hospitalized in acute care facility for ≥2 days within 90 days of admission or resides in LTC or received recent antimicrobial therapy or wound care in past 30 days, or attended a hemodialysis center.
- **CAP:** Pneumonia present on admission not captured by above categories

Corrado RE, et al. *Chest.* 2017:152:930-942.

Comparing the Microbiology of Early vs Late HABP/VABP

- Early (<5 days) without risk factors
  - *Streptococcus pneumoniae*
  - *Hemophilus influenzae*
  - *Staphylococcus aureus*
- Late (after 5 days)
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*
  - MRSA
  - Other Gram-negative organisms based on local epidemiology

Torres A, et al. *ERJ Open Res.* 2018;4(2):00028-2018.

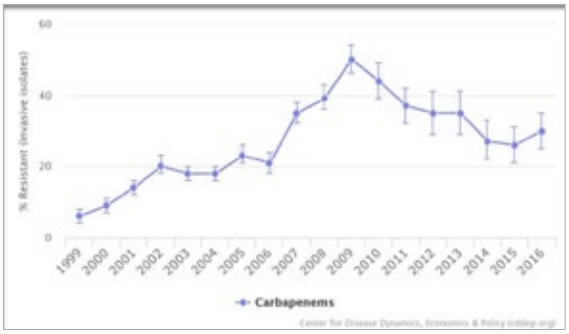
Etiology of HABP/VABP in ICU Patients: Data from the PROPHETIC Study

- Prospective cohort study of 4613 ICU patients from 28 US hospitals who were at high-risk of pneumonia in 2016
  - 537 met pre-defined criteria for nosocomial pneumonia

Pathogen	HABP (N=143)	VABP (N=394)
S. aureus	15.0%	23.5%
P. aeruginosa	9.2%	11.5%
Enterobacteriaceae	19.2%	26.1%
Klebsiella spp.	9.2%	10.6%
Enterobacter spp.	2.5%	7.0%
E. coli	5.8%	6.2%
Serratia spp.	1.7%	2.2%
H. influenzae	4.2%	3.6%
S. maltophilia	3.3%	3.9%
Acinetobacter spp.	0.8%	3.1%
S. pneumoniae	2.5%	1.4%
No pathogen identified	40.8%	34.2%

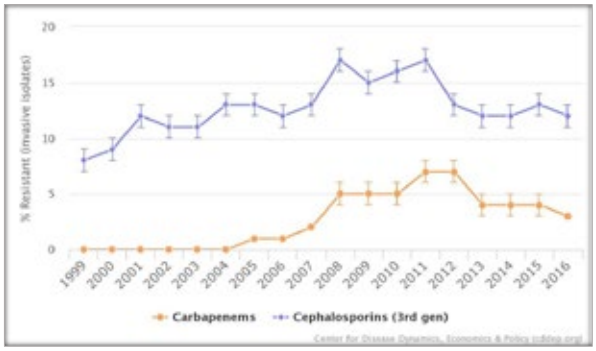
Bergin SP, et al. *Chest.* 2020;S0012-3692(20)31825-0 (Online ahead of print).

Prevalence of Carbapenem-Resistant *Acinetobacter baumannii* in the US



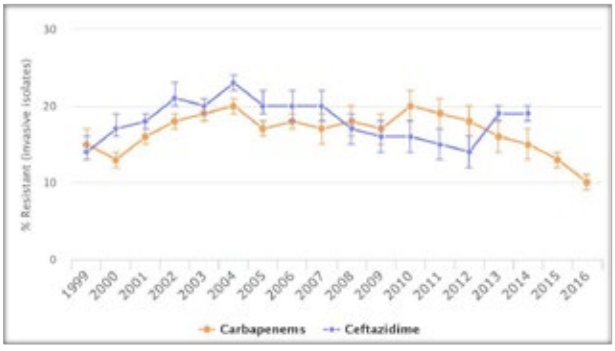
Center for Disease Dynamics, Economics & Policy. Resistance Map. https://resistancemap.cddep.org/AntibioticResistance.php.

Prevalence of *K. pneumoniae* Resistance in the US



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

Prevalence of *P. aeruginosa* Resistance in the US



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

P. aeruginosa in the US: Lower Susceptibility for Isolates Originating from ICU Patients

Isolates taken from ICU patients with pneumonia or bloodstream infections

	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

Susceptibility was higher for amikacin (98.1%), gentamicin (86.9%), and colistin (99.4%)

- **Would you consider these as preferred agents?**

N = 1543 isolates from 32 US hospitals from 2011 to 2017
Shortridge D, et al. *Open Forum Infect Dis.* 2019;6:ofz240.

Clinical Outcomes for Mechanically-Ventilated Patients with Pneumonia: Antibiotic Resistance Associated with Poorer Outcomes

	Antibiotic susceptible* (n=63)	Antibiotic resistant (n=104)	Pathogen negative (n=118)	Viral (n=79)
Deaths, n (%)	17 (27.0)	50 (48.1)	37 (31.4)	29 (36.7)
Length of stay (LOS), median [IQR]	15 [8, 25]	18.5 [11, 30.8]	11 [6.5, 20.5]	18 [9.5, 28.75]
ICU LOS, median [IQR]	8 [4, 16]	9 [6, 17]	6 [4, 12]	8 [4, 18.25]
Ventilator days, median [IQR]	4 [3, 11]	7.5 [4, 15]	4 [2, 8.5]	6 [2, 13]
Antibiotic days, median [IQR]	10 [7, 14]	11 [7, 14]	7 [5, 9.3]	7 [4, 11]

*Based on ceftriaxone susceptibility
Fisher K, et al. *Surg Infect.* 2017;18:827-833.

Resistance by *A. baumannii* Leads to Higher In-hospital Mortality Among Bloodstream Infections

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 PIC* to initiation of appropriate therapy	2 (0–3)	2 (1–3)			0.63
Length of stay after PIC	9 (3–16.5)	9 (5–16)			0.33

CASR = carbapenem and ampicillin-sulbactam resistance
Chopra T, et al. *Antimicrob Agents Chemother.* 2013;57:6270–75.

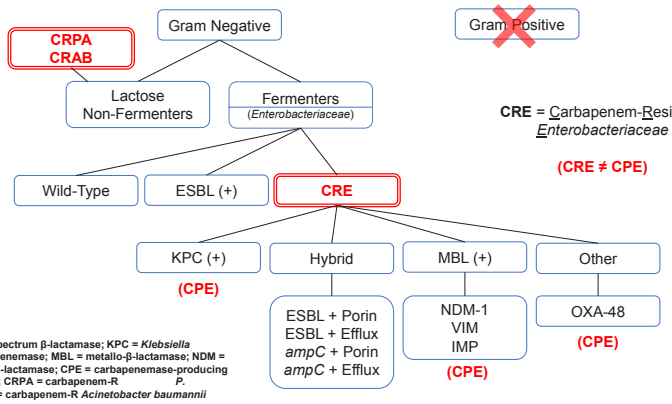
Carbapenem Resistance in Enterobacteriaceae Results in Higher Cost and In-hospital Death

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.

Recognizing the Varied Mechanisms of Enterobacteriaceae Resistance

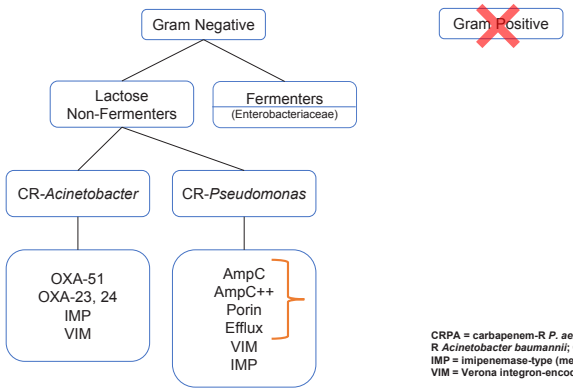


CRE = Carbapenem-Resistant *Enterobacteriaceae*

(CRE ≠ CPE)

ESBL = extended-spectrum β-lactamase; KPC = *Klebsiella pneumoniae* carbapenemase; MBL = metallo-β-lactamase; NDM = New Delhi metallo-β-lactamase; CPE = carbapenemase-producing Enterobacteriaceae; CRPA = carbapenem-R *P. aeruginosa*; CRAB = carbapenem-R *Acinetobacter baumannii*

Mechanisms of Resistance by Non-Fermenters (*Pseudomonas* and *Acinetobacter*)



CRPA = carbapenem-R *P. aeruginosa*; CRAB = carbapenem-R *Acinetobacter baumannii*; OXA = oxacillinase-type; IMP = imipenemase-type (metallo-β-lactamase); VIM = Verona integron-encoded metallo-β-lactamase

Back to Patient Case: Initial Rapid Diagnostics Results

- By Verigene, blood isolate was identified as an *Acinetobacter* sp.
- No resistance genes were identified

Tools for Rapid Identification of Positive Blood Cultures

Panel	Targets	Accuracy Rate, %
FilmArray BCID Panel, Biofire Diagnostics, Salt Lake City, Utah	▪ Detects 19 bacterial targets, 3 resistance genes, and 5 yeast targets	91–92
Verigene BC-GP and BC-GN-RUO, Nanosphere, Inc., Northbrook, IL	▪ BC-GP test has 12 bacterial targets and 3 resistance markers ▪ BC-GN-RUO test has 9 bacterial targets and 6 resistance markers	90–96 94–98

Bhatti MM, et al. *J Clin Microbiol*. 2014;52:3433–3436.

Blood Culture Identification Film Array (BCID) Panel: Detecting a Wide Variety of Pathogens

Gram+ Bacteria
Enterococcus
Listeria monocytogenes
Staphylococcus
  S. aureus
Streptococcus
  S. agalactiae
  S. pyogenes
  S. pneumoniae

Antibiotic Resistance
mecA – methicillin resistant
van A/B – vancomycin resistant
KPC – carbapenem resistant

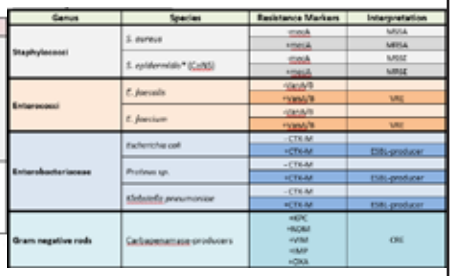
Gram- Bacteria
Acinetobacter baumannii
Haemophilus influenzae
Neisseria meningitidis
Pseudomonas aeruginosa
Enterobacteriaceae
  Enterobacter cloacae complex
  Escherichia coli
  Klebsiella oxytoca
  Klebsiella pneumoniae
  Proteus
  Serratia marcescens

Yeast
Candida albicans
Candida glabrata
Candida krusei
Candida parapsilosis
Candida tropicalis

Verigene Blood Culture Panel: Which Organisms are Detected?

Gram Positives	Gram Negatives
Staphylococcus species, specifically: • *S. aureus* • *S. epidermidis** (CoNS) • *S. lugdinensis*	**Enterobacteriaceae:** • *Citrobacter sp.* • *Enterobacter sp.* • *Escherichia coli* • *Klebsiella oxytoca* • *Klebsiella pneumoniae* • *Proteus sp.*
Streptococcus species, specifically: • *S. anginosus* • *S. agalactiae* • *S. pneumoniae* • *S. pyogenes*	**Others:** • *Acinetobacter sp.* • *Pseudomonas aeruginosa* • *Serratia marcescens*
Enterococcus species: • *E. faecalis* • *E. faecium*	

*reported as Staphylococcus Species, Not *S. aureus* (CoNS)



Clinical Consideration

Which antibiotic would you prescribe for empiric therapy?

1. Ampicillin/sulbactam
2. Amikacin
3. Meropenem
4. Colistin
5. None of the above

Patient Case: Susceptibility Profile of *Acinetobacter* Isolate

	Acinetobacter baumannii							
Drug	INTERP.	MIC.	INTERP.	MIC.	INTERP.	MIC.	INTERP.	MIC.
Amikacin	S	<=8						
Ampicillin	R	>16						
Ampicillin/Sulbactam	I	16/8						
Cefepime	R	>16						
Ceftazidime/Avibactam							I	12
Ciprofloxacin	R	>2						
Colistin			S	.5				
Gentamicin								
Gentamycin Synergy Screen								
Levofloxacin	R	>4						
Meropenem	R	>8						
Minocycline					R	16		
Piperacillin/Tazobactam								
Streptomycin Synergy Screen								
Tetracycline	R	>8						
Tobramycin	S	<=2						
Vancomycin								
Eravacycline		0.7						

Know Your Local Data: Mechanisms for Resistant GNB in Texas

Texas Region	IMP	KPC	NDM	VIM	OXA-48	mcr	*C. auris*	Total
1	1	11	3	35	0	0	0	50
2/3	1	24	31	3	2	0	0	61
4/5N	0	5	0	0	0	0	0	5
6/5S	**2**	**109**	**12**	**5**	**2**	**0**	**5**	**135**
7	4	82	5	7	2	0	0	100
8	0	31	2	2	0	0	0	35
9/10	0	2	0	0	0	0	0	2
11	0	66	0	1	0	0	0	67

Know Your Local Data: *Acinetobacter* Resistance in Texas

Texas Region	OXA-23	OXA-24/40	OXA-48	Total
1	8	5	0	13
2/3	23	42	0	65
4/5N	3	0	0	3
6/5S	**32**	**16**	**0**	**48**
7	50	17	0	67
8	28	0	0	28
9/10	0	1	0	1
11	65	6	0	71

Selecting an Appropriate Agent: Activity of Newer Agents

Drug Name	ESBL activity	KPC activity	NDM activity	OXA activity	*Pseudomonas*	*Acinetobacter*	*Stenotrophomonas*
Ceftazidime-avibactam	Yes	Yes	No	Yes	Yes	No	No
Ceftolozane-tazobactam	Yes	No	No	No	Yes	No	No
Imipenem-relebactam	Yes	Yes	No	No	Yes	No	No
Eravacycline	Yes	Yes	Yes	Yes	No	Yes	Yes
Plazomicin	Yes	Yes	Yes	Yes	Variable	No	No
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Livermore DM, et al. *Antimicrob Agents Chemother.* 2016;60:3840.
Stewart A, et al. *Antimicrob Agents Chemother.* 2018;62:e01195.
Otsuka Y. *Chem Pharm Bull.* 2020;68:182-190.

Changing Paradigms in the Treatment of MDR Gram-negative Infections

Including Clinical Patient Case

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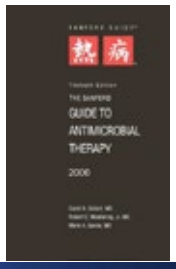
Baton Rouge Branch Campus
Baton Rouge, LA

Cambridge Dictionary

paradigm: a model of something,
or a very clear and typical example of something



Clinical Case

- A 37-year-old man with a 20-year history of fistulizing Crohn's disease was on business 6 weeks ago in Germany and developed fever and abdominal pain.
- Work-up was unrevealing for an etiology, but he responded to 5 days of therapy with meropenem.
- He returned to the United States one week later and did well until 2 weeks before the present admission, when he presented to the Emergency Department with an acute abdomen.
- At surgery, he was found to have a bowel wall abscess extending 16 cm and underwent a partial colectomy.
- His post-operative course was complicated by persistent fever and increasing shortness of breath, and he was empirically treated with piperacillin/tazobactam and linezolid.
- On post-op day 6, the patient acutely decompensated. Chest x-ray showed multilobar pneumonia.
- Over the next 12 hours, his respiratory status deteriorated, and he was moved to the ICU.

Pathogen Distribution in HAP and VAP

CDC NNIS and NHSN Data

	HAP						VAP
	1984[1]	1986 - 1989[2]	1990 - 1992[3]	1990 - 1996[4]	1990 - 1999[5]	1995 - 2001[6]	2006 - 2007[7]
S. aureus	13%	16%	20%	19%	18%	21.4%	24.4%
P. aeruginosa	17%	17%	16%	17%	17%	16.3%	16.3%
Enterobacter	9%	11%	11%	11%	11%	10.3%	8.4%
Klebsiella	12%	7%	7%	8%	7%	6.7%	7.5%
E. coli	6%	6%	5%	4%	4%	4.0%	4.6%
H. influenzae				5%	4%	3.7%	NR
Acinetobacter				4%	NR	5.0%	8.4%

[1]CDC. *MMWR.* 1986;35:17S.
[2]Schaberg DR, et al. *Am J Med.* 1991;91:72S-75S.
[3]Emori TG, Gaynes RP. *Clin Microbiol Rev.* 1993;6:428-42.
[4]NNIS. *Am J Infect Control.* 1996;24:380-388.
[5]NNIS. *Am J Infect Control.* 1999;27:520-32 (ICUs).
[6]CDC NNIS System, 2001 (unpublished data).
[7]Hidron AI, et al. *Infect Control Hosp Epidemiol.* 2008;29:996-1-11.

NNIS = National Nosocomial Infections Surveillance
NHSN = National Healthcare Safety Network

Roadmap for the Pathogens to be Considered in the Changing Paradigm

Infectious Diseases Society of America Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Released on September 8, 2020

- Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E)
- Carbapenem-Resistant Enterobacterales (CRE)
- Difficult-to-Treat Resistance in *Pseudomonas aeruginosa* (DTR-*P. aeruginosa*)

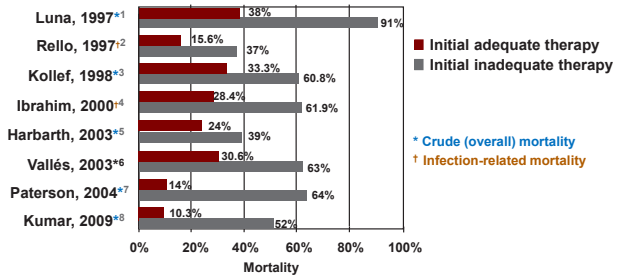
IDSA. Available at: https://www.idsociety.org/practice-guideline/amr-guidance/.

Potential Consequences of Inadequate Therapy and Treatment Failure

Objective #1

- Mortality
- Economy
- Ecology

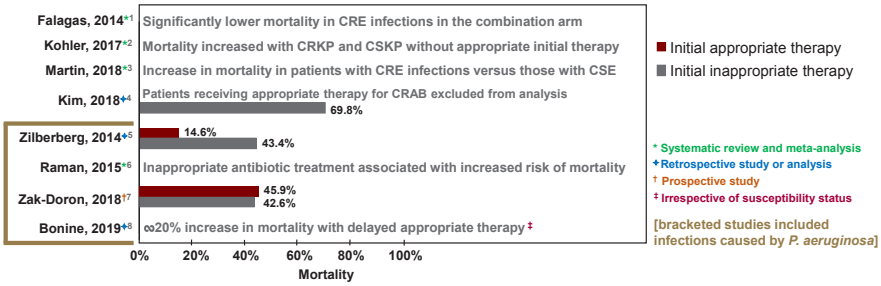
Mortality✦ Associated with Initial Inadequate Therapy In Critically-ill Patients with VAP, Sepsis, or Bacteremia



✦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. (Levinson AT, et al. *Semin 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.

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



CRE = Carbapenem-resistant Enterobacteriaceae; CSE = C-Sensitive E; CRAB = Carbapenem-resistant *Acinetobacter baumannii;* CRKP = Carbapenem-resistant *Klebsiella pneumoniae;* CSKP = Carbapenem-sensitive *Klebsiella pneumoniae*

[1]Falagas ME, et al. *Antimicrob Agents Chemother.* 2014:58:654-663.
[2]Kohler PP. *Infect Control Hosp Epidemiol.* 2017;38:1319-1328.
[3]Martin A, et al. *Open Forum Infect Dis.* 2018;5(7):ofy150.
[4]Kim T, et al. *Medicine.* 2018;97:43(e12984).
[5]Zilberberg MD, et al. *Crit Care.* 2014;18:596.
[6]Raman G, et al. *BMC Infect Dis.* 2015;15:395.
[7]Zak-Doron, et al. *Clin Infect Dis.* 2018;67:1815-1823.
[8]Bonine NG, et al. *Am J Med Sci.* 2019;357:103-110.

Economic Impact of Delays in Inappropriate Empiric Therapy (IET)

- Retrospective cohort study in the Premier Research database from 175 US hospitals between 2009 and 2013
- Among 40,137 patients with Enterobacteriaceae infections, 4984 (13.2%) received inappropriate empiric therapy
  - Of the Enterobacteriaceae, only 1.3% had carbapenem resistance
- Each additional day of IET resulted in additional cost of $766 relative to adequate treatment

Zilberberg MD, et al. *Antimicrob Resist Infect Control.* 2017;6:124.

Potential Economic Burden of Infections Caused by Carbapenem-Resistant Enterobacteriaceae in the US

- Constructed a CRE clinical and economics outcomes model to determine the cost of CRE in the US
- Analysis based on the then-current rate of 2.93 CRE cases per 100,000 population
- Costs rise proportionally with the incidence of CRE, increasing by 2.0 times, 3.4 times, and 5.1 times for incidence rates of 6, 10, and 15 per 100,000 persons

Bartsch SM, et al. *Clin Microbiol Infect.* 2017;23:48.e9e48.e16.

Economic Burden of Antibiotic Resistance in ESKAPE Organisms: A Systematic Review

- 103 studies in English and Chinese with economic focus used
  - Variability in the element evaluated (with 71 on total hospital cost or charge)
- Meta-analyses not performed because of the variability in reports between mean or median costs or charges as primary outcome
- Despite limitations, usual trend of higher economic burden imposed by resistant pathogens
  - Representative example: carbapenem-resistant (CR) *P. aeruginosa*
    - 1.5 times higher mean hospital cost
    - Up to 3.09 times median total (direct and indirect) cost

Zhen X, et al. *Antimicrob Resist Infect Control.* 2019;8:137.

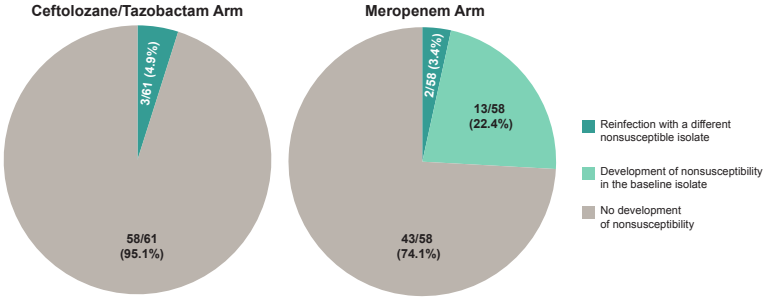
"Collateral" Effects of Antibiotic Use

- Collateral damage[1]
  - Described as the unanticipated consequences that may occur with antibiotics
- Collateral benefits[2]
  - Used to explain advantages that might be gained from antibiotics above that of antimicrobial killing

[1]Paterson DL. *Clin Infect Dis.* 2004;38(Suppl 4):S341-345.
[2]Goldstein EJC. *Current Opin Infect Dis.* 2011;24:S21-S31.

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.

De-Escalation of Therapy*

Stage 1 ⟶ **Efficacy**
Administering broad-spectrum antibiotic therapy to improve outcomes (decrease mortality, prevent organ dysfunction, and decrease length of stay)

Stage 2 ⟶ **Ecology**
Focusing on de-escalating as a means to minimize resistance and improve cost-effectiveness‡

*With invasive candidiasis, sometimes referred to as transition or stepdown therapy

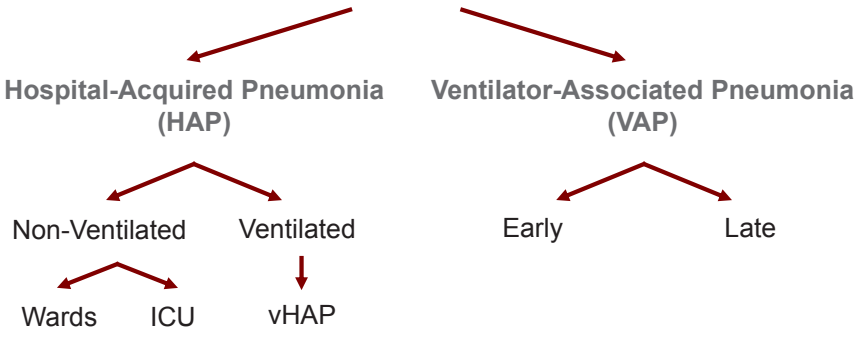
‡In some patients, redirection of therapy needed to cover resistant pathogens not covered with the initial regimen, to provide source control, or to treat fungal pathogens

Nosocomial Pneumonia As a Clinical Example of an Infectious Process Undergoing a Paradigm Shift

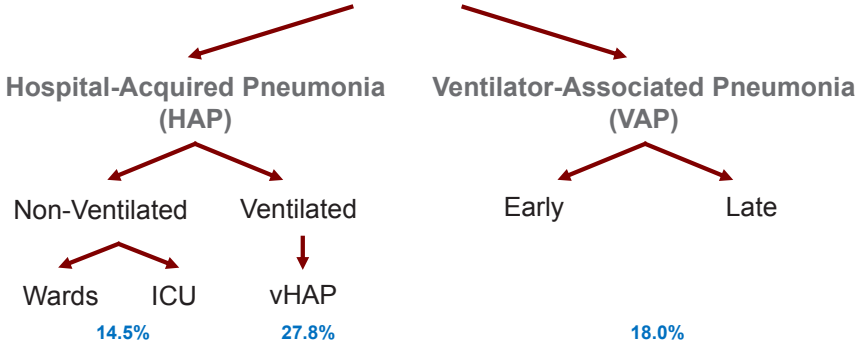
Objective #2

- Variability in the entities within the domain of "nosocomial pneumonia"
- A pathogen-specific approach to HABP/VABP

Nosocomial Pneumonia



Nosocomial Pneumonia



28-day all-cause mortality (ACM) based on analysis of 7 HABP/VABP datasets

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

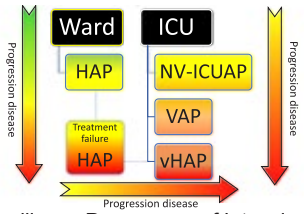
Comparison of Mortality Risk of Ventilator-Acquired Bacterial Pneumonia and Non-Ventilator ICU-Acquired Bacterial Pneumonia

- Longitudinal prospective study of 14,212 patients in French ICUs and who stayed for more than 48 hours
  - 7,735 at risk of ventilator-associated pneumonia
    - VAP in 1,161 patients (8%)
  - 9,747 at risk of non-ventilator ICU–hospital-acquired pneumonia
    - nvICU-HAP in 176 patients (1%)
- Increased 30-day mortality (when adjusted on prognostic variables)
  - In VAP – 38% increase (hazard ratio, 1.38 [1.24–1.52]; $p<0.0001$)
  - In nvICU-HAP – 82% increase (hazard ratio, 1.82 [1.35–2.45]; $p<0.0001$)
    - 23% crude mortality

Ibn Saied W, et al. *Crit Care Med.* 2019;47:345–352.

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.

Potential Pathogens in HAP, VAP, HCAP

Potential Pathogens with No Risk Factors for MDR Pathogens Early Onset (<5 days) Any Disease Severity	Potential Pathogens with Late Onset (≥5 days) or Risk Factors for MDR Pathogens
Streptococcus pneumoniae *Haemophilus influenzae* Methicillin-sensitive *S. aureus* Antibiotic-sensitive enteric Gram-negative bacilli ▪ *E. coli* ▪ *Klebsiella pneumoniae* ▪ *Enterobacter* species ▪ *Proteus* species ▪ *Serratia marcescens*	Pathogens with early-onset disease plus MDR pathogens ▪ *Pseudomonas aeruginosa* ▪ *Klebsiella pneumoniae* (ESBL) ▪ *Acinetobacter* species MRSA *Legionella pneumophila*

ATS/IDSA. *Am J Respir Crit Care Med.* 2005;171:388-416.

Approach To Potential Pathogens in HAP/VAP (ATS/IDSA)

Risk of Multidrug Resistance

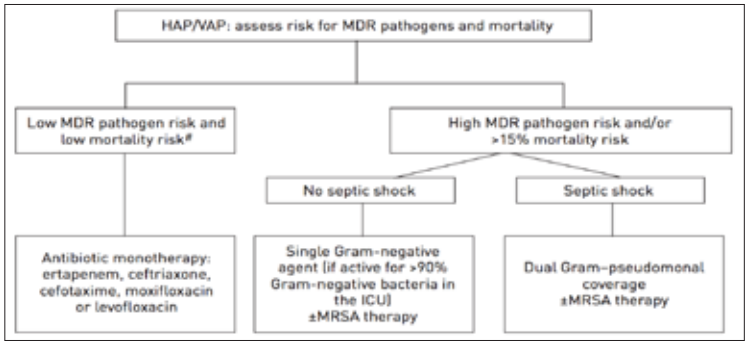
- Empiric therapy of VAP
  - *Staphylococcus aureus*
  - *Pseudomonas aeruginosa* and other Gram-negative bacilli
    - Stratified by recommendations for 2 drugs versus 1 drug
- Recommended initial empiric antibiotic therapy for HAP (non-ventilator-associated pneumonia)

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: ▪ Piperacillin-tazobactam ▪ Cefepime ▪ Levofloxacin ▪ Imipenem or meropenem	***One of the following:*** ▪ Piperacillin-tazobactam ▪ Cefepime or ceftazidime ▪ Levofloxacin or ciprofloxacin ▪ Imipenem or meropenem ▪ Aztreonam ***Plus*** ▪ Vancomycin ***or*** ▪ Linezolid	***Two of the following:*** ▪ 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✦

✦details in article

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

Approach To Potential Pathogens in HAP/VAP (ERS/ESICM/ESCMID/ALAT)

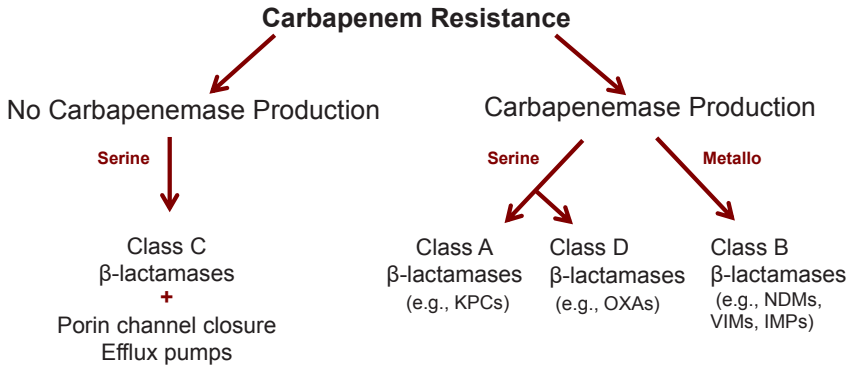


Low mortality risk: ≤15% change of dying (a mortality rate that has been associated with better outcome using monotherapy than combination therapy when treating serious infection)

ERS = European Respiratory Society; ESCMID = European Society of Microbiology and Infectious Diseases
ESICM = European Society of Intensive Care Medicine; ALAT = Associacion Latinoamericana del Torax

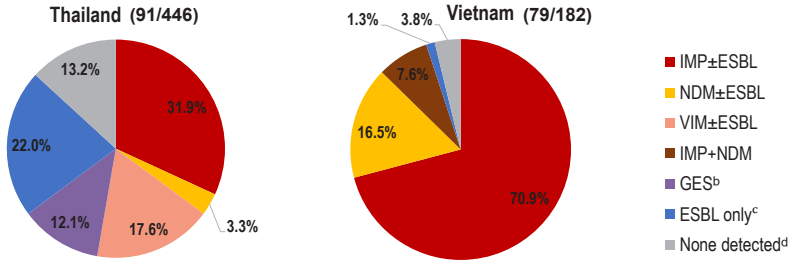
Torres A, et al. *Eur Respir J.* 2017;50:1700582 [https://doi.org/10.1183/13993003.00582-2017].

Concept Map for Carbapenem Resistance



Evolving Patterns of Resistance in 3,973 *P. aeruginosa* Isolates Collected in Asia/Pacific SMART✦ Data: 2016-2018

Carbapenemases in *P. aeruginosa* in Asia/Pacific Countries*



*Overall rate of 4.3%, ranging from ≤0.3% in most countries to 13.0% in Thailand and 41.2% in Vietnam

✦SMART = Study for Monitoring Antimicrobial Resistance Trends

[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

Patient Stratification To Guide Therapy for *Pseudomonas,* ESBL, CRE Infections

Objective #3

- The importance of severity of illness
- The concept of "local validation"

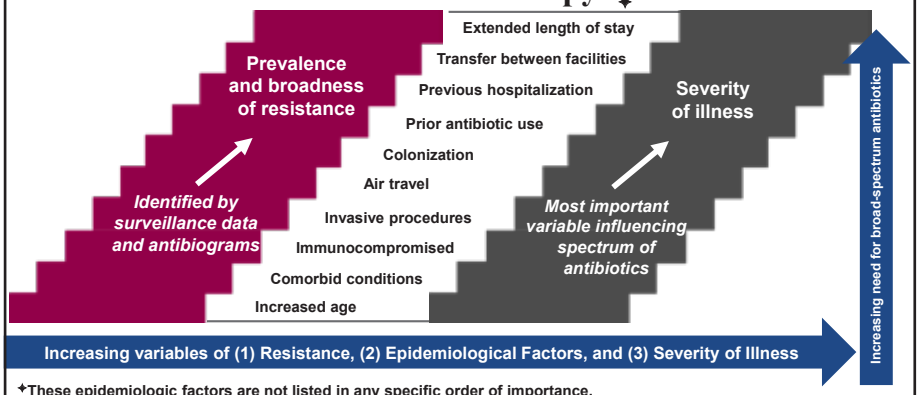
Approach to Stratification in the European Nosocomial Pneumonia Guidelines

Statement in Question 2: "We recommend broad-spectrum empiric antibiotic therapy targeting *P. aeruginosa* and extended-spectrum β-lactamase (ESBL)-producing organisms, and, in settings with a high prevalence of *Acinetobacter* spp., in patients with suspected early-onset HAP/VAP who are in septic shock, in patients who are in hospitals with a high background rate of resistant pathogens present in local microbiological data and in patients with other (non-classic) risk factors✦ for MDR pathogens." **Strong recommendation, low quality of evidence.**

- Risk factors for multidrug-resistant pathogens✦
  - Classic risk factors
    - HAP and VAP (≥5 days of hospitalization)
    - Previous antimicrobial therapy or hospitalization (≥2 days) in the preceding 90 days
  - Non-Classic risk factors
    - Severity of illness
    - High frequency of antibiotic resistance in the community or the specific hospital unit

Torres A, et al. *Eur Respir J.* 2017;50:1700582.

Variables Influencing Patient Stratification for Empiric Antibiotic Therapy✦



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

Karam G, Chastre J, Wilcox MH, Vincent J-L. *Crit Care.* 2016;20:136.

"Local Validation"

- Newly-termed concept in the 2019 CAP guidelines
  - "We propose that clinicians need to obtain local data on whether MRSA or *P. aeruginosa* is prevalent in patients with CAP and what the risk factors for infection are at a local (i.e., hospital or catchment area) level. We refer to this process as 'local validation'."
  - Is there the potential for a similar concept to influence antibiotic selection in the ICU?

Metlay JP, et al. *Am J Respir Crit Care Med.* 2019;200:e45–e67.

Back to Clinical Case

- A 37-year-old man with a 20-year history of fistulizing Crohn's disease was on business 6 weeks ago in Germany and developed fever and abdominal pain.
- Work-up was unrevealing for an etiology, but he responded to 5 days of therapy with meropenem.
- He returned to the United States one week later and did well until 2 weeks before the present admission, when he presented to the Emergency Department with an acute abdomen.
- At surgery, he was found to have a bowel wall abscess extending 16 cm and underwent a partial colectomy.
- His post-operative course was complicated by persistent fever and increasing shortness of breath, and he was empirically treated with piperacillin/tazobactam and linezolid.
- On post-op day 6, the patient acutely decompensated. Chest x-ray showed multilobar pneumonia.
- Over the next 12 hours, his respiratory status deteriorated, and he was moved to the ICU.

Clinical Case: What If…

- A 37-year-old man with a 20-year history of fistulizing Crohn's disease was on business 6 weeks ago in Vietnam and developed fever and abdominal pain.
- Work-up was unrevealing for an etiology, but he responded to 5 days of therapy with meropenem.
- He returned to the United States one week later and did well until 2 weeks before the present admission, when he presented to the Emergency Department with an acute abdomen.
- At surgery, he was found to have a bowel wall abscess extending 16 cm and underwent a partial colectomy.
- His post-operative course was complicated by persistent fever and increasing shortness of breath, and he was empirically treated with piperacillin/tazobactam and linezolid.
- On post-op day 6, the patient acutely decompensated. Chest x-ray showed multilobar pneumonia.
- Over the next 12 hours, his respiratory status deteriorated, and he was moved to the ICU.
- He subsequently developed hypotension refractory to fluids and required intubation and mechanical ventilation.

Summary

- Potential consequences of inadequate therapy and treatment failure
  - Mortality
  - Economy
  - Ecology
- Nosocomial pneumonia as a clinical example of an infectious process undergoing a paradigm shift
  - The importance of considering various forms of nosocomial pneumonia in decisions that can lead to heterogeneity in antibiotic prescribing
- Patient stratification to guide therapy for *Pseudomonas,* ESBL, CRE infections based on the IDSA guidance document
  - The influence of severity of illness
  - The reliance on local data to validate clinical decisions

Notes

A Review of the Clinical Evidence in HABP/VABP

Including Clinical Patient Case

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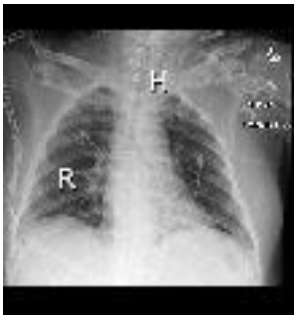
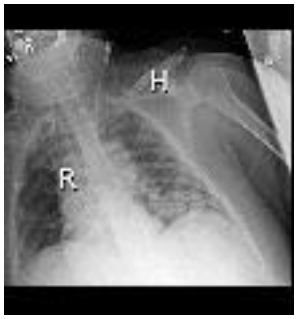
Washington University School of Medicine
Director, Critical Care Research
Director, Respiratory Care Services
Barnes-Jewish Hospital
St. Louis, MO

Patient Case:
Enterobacter VAP in 60-year-old Male With RCC and COVID-19



4/7/2020



4/13/2020

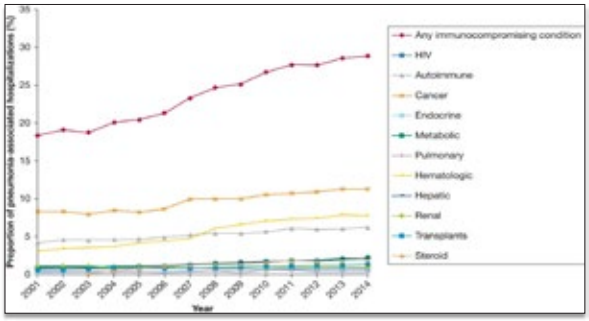
Tracheal aspirate culture >10^5 CFU/mL

Know Your Local Case Mix and Antibiogram!

BJH 1350 Beds

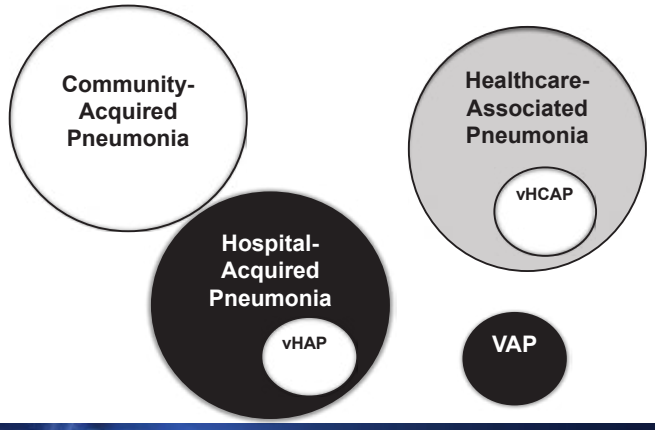
Parkland Health Center
Farmington, MO 130 beds

Burden of Pneumonia-Associated Hospitalizations: National Inpatient Sample (NIS) Data



Hayes BH, et al. *Chest.* 2018; 153:427-437.

What Constitutes Nosocomial Pneumonia?



Risk Factors For PES Pathogens In Severe CAP

Therapy-Related Risk Factors	Patient-Related Risk Factors	Antibiotic Selection Pressure
Hospitalization for more than 2 days in the past 90 days	Chronic lung diseases: bronchiectasis, severe COPD, tracheostomy	Systemic antibiotic in the past 3–6 months
Gastric acid suppression therapy	Poor functional status (Barthel's index <50, need for tube feeding, not ambulatory)	
Hemodialysis	MRSA colonization	
Immune suppressive therapy	*Pseudomonas aeruginosa* colonization	
Home wound care	Prior PES pathogen infection	
	Residence in LTAC	
	Recurrent skin infections	

PES = *Pseudomonas*, Enterobacterales, *S. aureus*
Torres A, et al. *Intensive Care Med.* 2019;45:159–171.

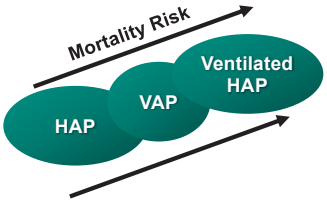
Forms of Nosocomial Pneumonia and Relative Mortality Risk

Hospital-Acquired Pneumonia (HAP)
- Occurs ≥48 hours after admission
- And was not incubating at the time of admission
- Not associated with mechanical ventilation

Ventilator-Associated Pneumonia (VAP)
- Arises ≥48 hours after mechanical ventilation

Ventilated HAP
- Patients with severe HAP who require mechanical ventilation
- Occurs ≥48 hours after admission
- And was not incubating at the time of admission
- Not associated with mechanical ventilation

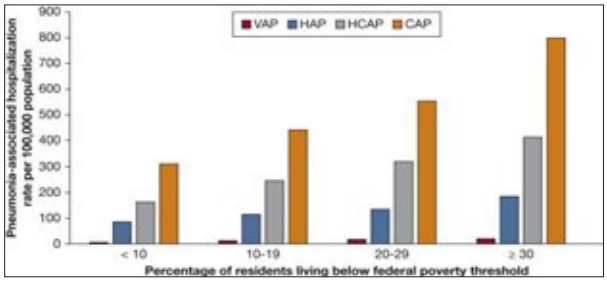
ICU HAP
- Occurs ≥48 hours after ICU admission



Ibn Saied W, et al. *Crit Care Med.* 2019;47:345-52.
Torres A, et al. *Eur Respir J.* 2017;50: pii: 1700582.
Kalil AC, et al. *Clin Infect Dis.* 2016;63:e61-111.

Pneumonia-Associated Hospitalizations According to Pneumonia Category

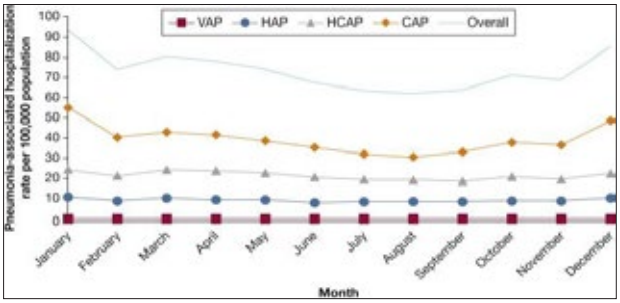
	All	CAP	HCAP	HAP	VAP
Overall	283,927 (100%)	154,158 (54.3%)	85,656 (30.2%)	39,712 (14.0%)	4,401 (1.2%)



New York City, 2010 to 2014

HCAP = recent hospitalization or antibiotics, admitted from nursing facility, dialysis
Corrado RE, et al. *Chest.* 2017;152:930-942.

Pneumonia-Associated Hospitalizations: CAP is Seasonal, HCAP is Not!



Corrado RE, et al. *Chest.* 2017;152:930-942.

Different Types of Pneumonia have Different Outcomes!

Outcomes	ALL	CAP	HCAP	HAP	VAP
Death during hospitalization					
Death	34,745 (12.2)	12,181 (7.9)	13,403 (15.6)	8,209 (20.7)	952 (21.6)
No death	249,182 (87.8)	141,977 (92.1)	72,253 (84.4)	31,503 (79.3)	3,449 (78.4)
LOS, days					
≤ 2	37,454 (13.2)	27,678 (18.0)	9,129 (10.7)	587 (1.5)	60 (1.4)
3-7	115,666 (40.7)	74,537 (48.4)	34,508 (40.3)	6,094 (15.3)	527 (12.0)
8-13	68,703 (24.2)	32,181 (20.9)	24,662 (28.8)	10,946 (27.6)	914 (20.8)
≥ 14	62,104 (21.9)	19,762 (12.8)	17,357 (20.3)	22,085 (55.6)	2,900 (65.9)
Readmission within 30 days					
Readmission	20,768 (7.3)	8,061 (5.2)	9,458 (11.0)	2,627 (6.6)	622 (14.1)
No readmit	263,159 (92.7)	146,097 (94.8)	76,198 (89.0)	37,085 (93.4)	3,779 (85.9)

Corrado RE, et al. *Chest.* 2017;152:930-942.

Case-Control Study Non-Ventilated HAP

Outcome	Cases - NVHAP n = 174	Controls w/o NVHAP n = 696	*P* Value
ICU admit, No. (%)	98 (56.3)	159 (22.8)	<0.01
MV, No. (%)	33 (19)	27 (3.9)	<0.01
Mortality, No. (%)	27 (15.5)	11 (1.6)	<0.01
Hospital LOS, d, range	15.9 (9.8–26.3)	4.4 (2.9–7.3)	<0.01
Readmit 30 d, No. (%)	37 (25.2)	145 (21.2)	0.29

Mortality Predictors

Variable	Adjusted OR	95% CI	*P* Value
HAP	8.4	5.6–12.5	<0.01
MV*	8.0	5.3–11.9	<0.01
Charlson Score (1-point increments)	1.2	1.1–1.2	0.01

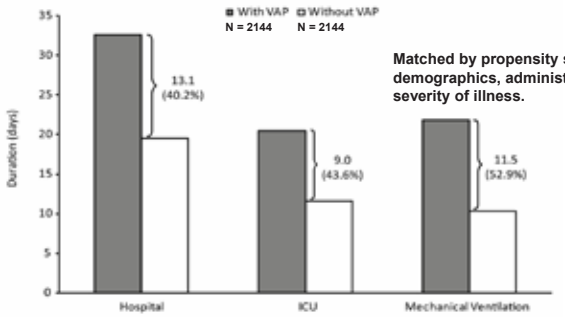
*Ventilated HAP

Micek ST, et al. *Chest.* 2016;150:1008-1014.

Respiratory viruses identified in 42 patients (24.1%).

VAP is Associated with Significant Resource Utilization Burden

Premier Database:
ICD-9 code 997.31 and ventilation charges for ≥2 calendar days: October 1, 2008 to December 31, 2009



Matched by propensity score based on demographics, administrative data, and severity of illness.

Kollef MH, et al. *Infect Control Hosp Epidemiol.* 2012;33:250-6.

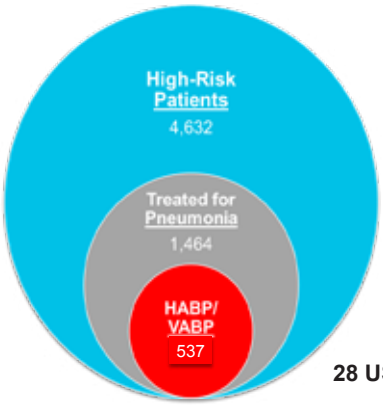
PROPHETIC: Prospective Identification of Pneumonia in Hospitalized Patients in the ICU

- Prospective cohort study involving ICUs from 28 US hospitals
- Included adults hospitalized for >48 hours and considered at high risk for pneumonia
  - Defined as treatment with invasive or noninvasive ventilatory support or high levels of supplemental oxygen
- Goal was to identify key patient characteristics and treatment exposures associated with nosocomial pneumonia development

Bergin SP, et al. *Chest.* 2020;S0012-3692(20)31825-0.

PROPHETIC: Patient Classification

VABP 394
HABP 143

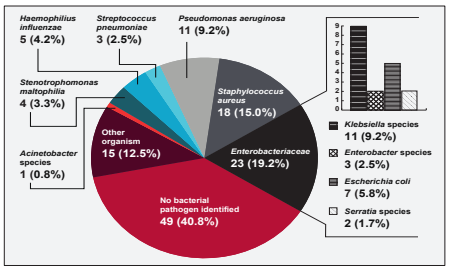


28 US Hospitals

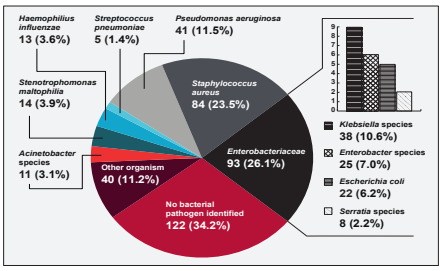
Bergin SP, et al. *Chest*. 2020;S0012-3692(20)31825-0.

PROPHETIC: Etiology of HABP/VABP

HABP

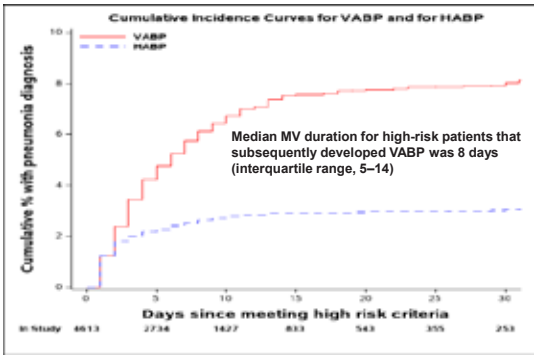


VABP



Bergin SP, et al. *Chest*. 2020;S0012-3692(20)31825-0.

PROPHETIC: Incidence of Pneumonia Over Time



Bergin SP, et al. *Chest*. 2020;S0012-3692(20)31825-0.

PROPHETIC: Risk Factors for Developing HABP/VABP in the ICU

Factor	Type 3 Wald Chi-Square	Beta Coefficient	Adjusted Odds Ratio (95% CI)	*P*-Value
ICU admission diagnosis	53.10			
Acute hypercapnic respiratory failure		-0.31	0.73 (0.38, 1.39)	0.336
Acute hypoxemic respiratory failure		0.13	1.14 (0.74, 1.76)	0.552
Acute myocardial infarction		0.12	1.12 (0.55, 2.28)	0.749
Altered mental status or seizures		-0.06	0.94 (0.57, 1.55)	0.815
Cerebrovascular accident		0.51	1.67 (0.95, 2.94)	0.073
Sepsis or septic shock		-0.12	0.88 (0.52, 1.49)	0.646
Trauma		1.16	3.19 (1.96, 5.20)	<.001
Shock (excluding septic shock)		0.06	1.06 (0.62, 1.83)	0.822
Other		0.10	1.11 (0.73, 1.68)	0.629
Planned post-operative ICU admission			reference	
Enteral nutrition	41.26	0.87	2.38 (1.83, 3.11)	<.001
Aspiration risk	39.18	0.74	2.10 (1.66, 2.65)	<.001
Systemic antibacterials within 90 days	16.78	0.44	1.56 (1.26, 1.92)	<.001
Admission source	13.53			
Skilled nursing, long term acute care		0.60	1.82 (1.17, 2.82)	0.007
Non-procedure; clinic or direct admission		0.19	1.20 (0.93, 1.55)	0.152
Scheduled procedure		-0.37	0.69 (0.45, 1.06)	0.089
Other		0.14	1.15 (0.83, 1.61)	0.396
Emergency department			reference	
Diabetes mellitus	6.44	-0.29	0.75 (0.59, 0.94)	0.011
Invasive mechanical ventilation	5.96	0.49	1.63 (1.10, 2.40)	0.015
Noninvasive mechanical ventilation	4.57	0.30	1.35 (1.03, 1.78)	0.032
Proton pump inhibitor therapy/H2-blocker therapy	4.36	0.27	1.30 (1.02, 1.67)	0.037
Blood product transfusion in the last 7 days	3.80	0.21	1.24 (1.00, 1.53)	0.051
Corticosteroids at current hospitalization	2.96	0.23	1.26 (0.97, 1.65)	0.086
Female sex	2.70	-0.16	0.85 (0.70, 1.03)	0.101
ICU length of stay (days), per 1-day increase	2.31	0.01	1.01 (1.00, 1.03)	0.128

Abbreviations: CI = confidence interval; ICU = intensive care unit; OR = odds ratio
Characteristics and treatment exposures recorded at time of high-risk population enrollment.
4613 patients included in analysis.
Risk factors selected using backward selection with α=0.1 for model inclusion and clinical expertise.
C-statistic: 0.709 (0.686, 0.731)

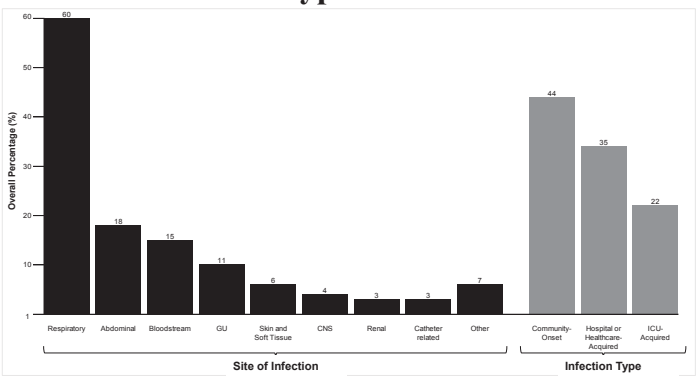
Bergin SP, et al. *Chest*. 2020;S0012-3692(20)31825-0.

EPIC:
Global Collection of Nosocomial Infection Data in ICUs

EPIC = European Prevalence of Infection in Intensive Care.
Vincent JL, et al. *JAMA*. 2020;323:1478-87.

EPIC III Participating Centers

EPIC III: Types of Infection



Of 7936 patients with infection, 2404 (30%) died in hospital, mortality was higher in patients with infection (2404/7936 [30%] vs 924/6883 [13%], p<0.001).

Vincent JL, et al. *JAMA*. 2020;323:1478-87.

EPIC III: Infection with Resistant Organisms Associated with In-Hospital Mortality

Multilevel analysis patients with + isolates - hospital mortality dependent variable and resistant microorganisms as independent variables

Resistant microorganisms	OR (95% CI)	*P* value
S. aureus[a]	1.04 (0.76-1.44)	0.80
S. coagulase neg[b]	1.02 (0.70-1.49)	0.91
Enterococcus[c]	2.41 (1.43-4.06)	0.001
S. pneumoniae[d]	0.53 (0.10-2.69)	0.44
E. coli[e]	1.08 (0.78-1.49)	0.64
Klebsiella[e]	1.29 (1.02-1.63)	0.03
Pseudomonas[e]	1.16 (0.76-1.78)	0.49
Acinetobacter[f]	1.40 (1.08-1.81)	0.01
Candida[g]	1.40 (0.76-2.57)	0.28

a: resistant to methicillin, linezolid, or vancomycin; b: resistant to methicillin; c: resistant to vancomycin; d: resistant to macrolides; e: resistant to beta lactams or just carbapenems; f: resistant to carbapenems; g: resistant to azoles

Vincent JL, et al. *JAMA*. 2020;323:1478-87.

EPIC I, II, III: Microorganism Distribution (%)

	EPIC I	EPIC II	EPIC III
Year	1992	2007	2017
Number Infected Patients	4501	7087	8135
Gram-negative bacteria	---	62.2%	67.1%
Enterobacterales (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp.)	34.4%	35.7%	25.5%
Pseudomonas aeruginosa	28.7%	19.9%	16.2%
Acinetobacter	---	8.8%	11.4%
Gram-positive bacteria			
Staphylococcus aureus	30.1%	20.5%	9.6%
MRSA	---	10.2%	4.6 %
Fungi	17.1%	19.4%	16.4%
Viruses	0.2%	---	3.7%

Kollef MH, et al. *Crit Care Med*. 2020 (In Press).

Initial Empiric Therapy Recommendations

TABLE 4. INITIAL EMPIRIC THERAPY FOR HOSPITAL-ACQUIRED PNEUMONIA, VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS AND ALL DISEASE SEVERITY

Potential Pathogens	Combination Antibiotic Therapy[a]
Pathogens listed in Table 3 and MDR pathogens *Pseudomonas aeruginosa* *Klebsiella pneumoniae* (ESBL+)[f] *Acinetobacter* species[g]	Antipseudomonal cephalosporin (cefepime, ceftazidime) or Antipseudomonal carbepenem (imipenem or meropenem) or β-Lactam/β-lactamase inhibitor (piperacillin-tazobactam) *plus* Antipseudomonal fluoroquinolone[e] (ciprofloxacin or levofloxacin) or Aminoglycoside (amikacin, gentamicin, or tobramycin) *plus*
Methicillin-resistant *Staphylococcus aureus* (MRSA) *Legionella pneumophila*[f]	Linezolid or vancomycin[e]

HAP, VAP, HCAP Require Broad-Spectrum Empiric Therapy

→ Agent 1

+

→ Agent 2

+

→ Agent 3

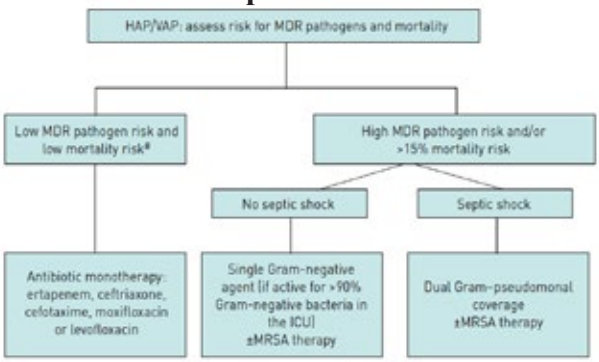
ATS/IDSA. *Am J Resp Crit Care Med*. 2005;171:388-416.

2016 ATS/IDSA: Empiric Antibiotic Therapy for HAP/VAP

Gram-Positive Antibiotics with MRSA Activity	Gram-Negative Antibiotics with Antipseudomonal Activity: β-Lactam-Based Agents	Gram-Negative Antibiotics with Antipseudomonal Activity: Non β-Lactam-Based Agents
Glycopeptides • Vancomycin 15mg/kg IV q8-12h (consider a loading dose of 25-30 mg/kg x 1 for severe illness)	Antipseudomonal pencillins • Piperacillin-tazobactam 4.5 g IV q6h	Fluoroquinolones • Ciprofloxacin 400 mg IV q8h • Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones • Linezolid 600 mg IV q12h	Cephalosporins • Cefepime 2 g IV q8h • Ceftazidime 2 g IV q8h	Aminoglycosides • Amikacin 15-20 mg/kg IV q24h • Gentamicin 5-7 mg/kg IV q24h • Tobramycin 5-7 mg/kg IV q24h
	OR	OR
	Carbapenems • Imipenem 500 mg IV q6h • Meropenem 1 g IV q8h	Polymyxins • Colistin 5 mg/kg IV x 1 (loading dose) followed by 2.5 mg x (1.5 x CrCl +30) IV q12h (maintenance dose) • Polymyxin B 2.5-3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams • Aztreonam 2 g IV q8h	

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

Empiric Antibiotic Algorithm for HABP/VABP: 2017 European Guidelines



#Low risk for mortality is defined as a ≤15% chance of dying, a mortality that has been associated with better outcomes using monotherapy than combination therapy when treating serious infection.

Torres A, et al. *EJR Open Res.* 2018;4(2):00028-2018.

Newer β-Lactam/β-Lactamase Inhibitor Combinations for Nosocomial Pneumonia

Ceftazidime-avibactam:
- 3rd-generation cephalosporin plus a novel β-lactamase inhibitor
- Dosed at 2.5 grams q8h for 7 to 14 days

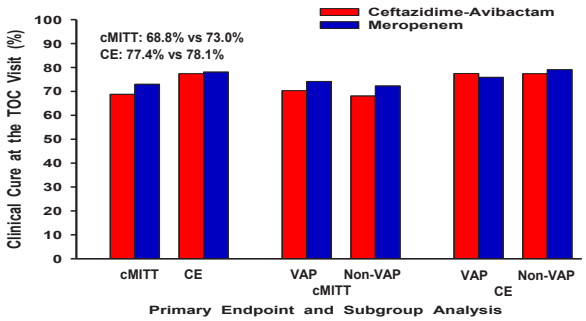
Ceftolozane-tazobactam:
- Novel cephalosporin plus an established β-lactamase inhibitor
- Dosed at 3 grams q8h for 8 to 14 days

Imipenem-cilastatin-relebactam:
- Carbapenem plus novel β-lactamase inhibitor
- Dosed at 500 mg/500 mg/250 mg q6h for 4 to 14 days

Poulakou G, et al. *Ann Transl Med.* 2018;6:423.

Ceftazidime-Avibactam for Nosocomial Pneumonia

Phase 3, Randomized, Multicenter Study (REPROVE)



TOC, test-of-cure ; cMITT, clinically modified intent-to-treat; CE, clinically evaluable; mMITT, microbiological MITT
Torres A, et al. *Lancet Infect Dis*. 2018;18:285-295.

Ceftazidime-Avibactam for Nosocomial Pneumonia Per-Pathogen Results at Test-of-Cure (REPROVE)

Per-Pathogen Clinical Cure Rates & Favorable Microbiological Response 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)
Favorable Microbiological Response		
K. pneumoniae	78.4% (29/37)	79.6% (39/49)
P. aeruginosa	42.9% (18/42)	40.0% (14/35)

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

Ceftolozane-Tazobactam for Nosocomial Pneumonia (ASPECT-NP)

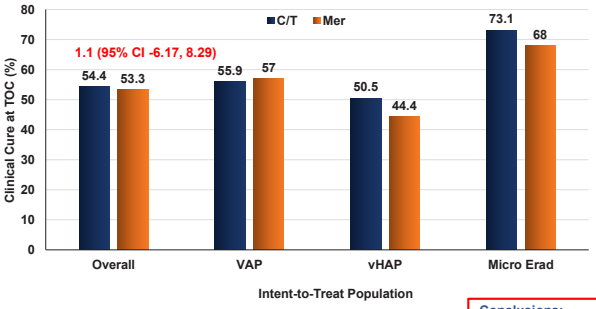
Randomized controlled, double-blind, phase III, non-inferiority trial comparing ceftolozane-tazobactam (3 g q8h) vs. meropenem (1 g q8h) for treatment of nosocomial pneumonia

- All patients were ventilated (71.5% with VAP and 28.5% with ventilated HAP)
- Mean APACHE II score: 17.5 (ceft-tazo) and 17.4 (mero)
- APACHE II score ≥20: 34% (ceft-tazo) and 32% (mero)

Baseline LRT pathogen (mITT population)	Ceftolozane-tazobactam N = 264	Meropenem 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;19:1299-1311.

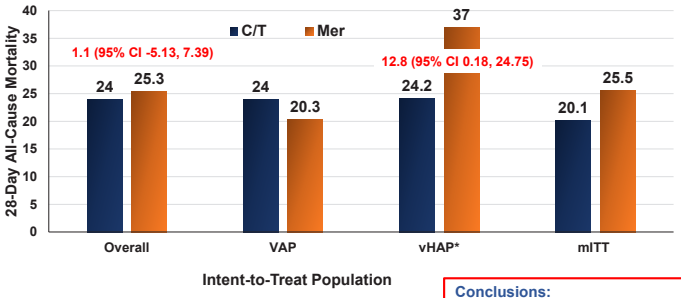
Ceftolozane-Tazobactam was Non-inferior to Meropenem Across Patient Populations (ASPECT-NP)



Conclusions:
- Non-inferior in all patient populations

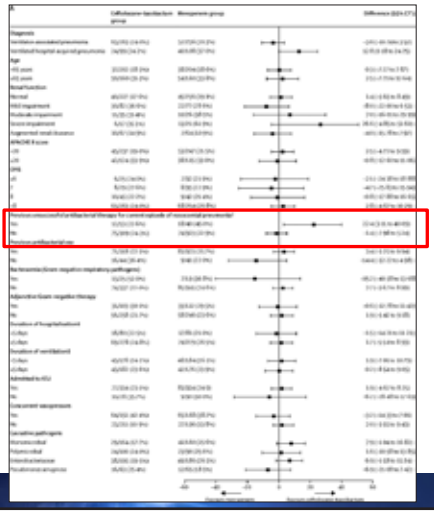
Kollef MH, et al. *Lancet Infect Dis.* 2019;19:1299-1311.

Ceftolozane-Tazobactam vs. Meropenem 28-Day All-Cause Mortality (ASPECT-NP)



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

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



ASPECT-NP: Ceftolozane-Tazobactam vs. Meropenem Sub-group Analyses

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

Ceftolozane-Tazobactam vs. Meropenem Results by Pathogen (ASPECT-NP)

Per-pathogen clinical cure TOC visit in mITT population

	Ceftolozane-tazobactam group	Meropenem group	% difference (95% CI)
Gram-negative pathogens	157/259 (60.6%)	137/240 (57.1%)	3.5 (-5.1 to 12.1)
Enterobacteriaceae	120/195 (61.5%)	105/185 (56.8%)	4.8 (-5.1 to 14.5)
ESBL-producing Enterobacteriaceae	48/84 (57.1%)	45/73 (61.6%)	-4.5 (-19.4 to 13.8)
P. aeruginosa	36/63 (57.1%)	39/65 (60.0%)	-2.9 (-19.4 to 13.8)
MDR *P. aeruginosa*	13/24 (54.2%)	6/11 (54.5%)	-0.4 (-31.2 to 31.7)
XDR *P. aeruginosa*	4/10 (40.0%)	2/5 (40.0%)	0.0 (-43.6 to 40.3)

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

Imipenem-Cilastatin-Relebactam vs. Piperacillin-Tazobactam in Adults With HABP/VABP (RESTORE-IMI 2 Study)

- Randomized, controlled, double-blind phase 3 trial
- Adult with HABP/VABP randomized 1:1 to:
  - Imipenem/cilastatin/relebactam 500 mg/500 mg/250 mg IV q6h for 7–14 days
  - Piperacillin/tazobactam 4 g/500 mg IV q6h for 7–14 days
- 537 patients randomized (531 in MITT population)
  - 48.6% had ventilated HABP/VABP
  - 47.5% with APACHE II score ≥15
  - 66.1% in ICU
  - 42.9% were ≥65 years of age

Titov I, et al. *Clin Infect Dis*. 2020;ciaa803, https://doi.org/10.1093/cid/ciaa803 [Online ahead of print].

IMI/REL Non-Inferior to PIP/TAZO for Primary and Key Secondary Endpoints in HABP/VABP (RESTORE-IMI 2)

Endpoint	IMI/REL, no./No. (%)	PIP/TAZ, no./No. (%)	Adjusted Difference, % (95% CI)
Day 28 ACM MITT	42/264 (15.9)	57/267 (21.3)	−5.3 (−11.9 to 1.2)
Favorable clinical response at EFU (MITT)	161/264 (61.0)	149/267 (55.8)	5.0 (−3.2 to 13.2)
Day 28 all-cause mortality (mMITT)	36/215 (16.7)	44/218 (20.2)	−3.5 (−10.9 to 3.6)
Favorable microbiologic response at EFU (mMITT)	146/215 (67.9)	135/218 (61.9)	6.2 (−2.7 to 15.0)
Favorable clinical response at EFU (CE)	101/136 (74.3)	100/126 (79.4)	−3.7 (−13.6 to 6.4)

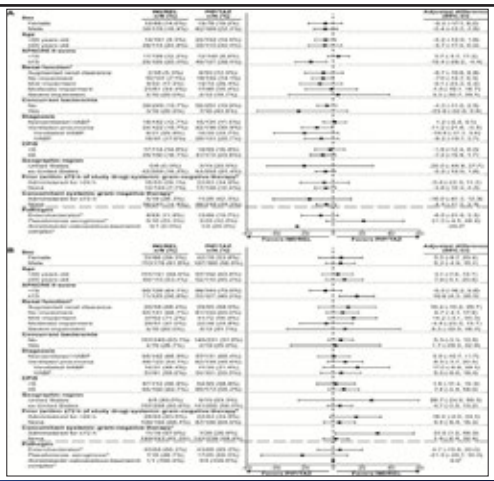
ACM, all-cause mortality; EFU, early follow-up visit
Titov I, et al. *Clin Infect Dis*. 2020;ciaa803, https://doi.org/10.1093/cid/ciaa803 [Online ahead of print].

RESTORE-IMI 2 Study Results by Randomization Stratum (28-day All-Cause Mortality)

Endpoint	IMI/REL n/N (%)	PIP/TAZ n/N (%)	Unadjusted Difference, %
Non-ventilated HABP with baseline APACHE II <15	10/102 (9.8)	6/102 (5.9)	3.9
Non-ventilated HABP with baseline APACHE II ≥15	7/45 (15.6)	12/43 (27.9)	-12.4
Ventilated HABP/VABP with baseline APACHE II <15	10/41 (24.4)	7/41 (17.1)	7.3
Ventilated HABP/VABP with baseline APACHE II ≥15	15/76 (19.7)	32/81 (39.5)	-19.8

Titov I, et al. *Clin Infect Dis*. 2020;ciaa803, https://doi.org/10.1093/cid/ciaa803 [Online ahead of print].

RESTORE-IMI 2 Sub-group Analyses



Titov I, et al. *Clin Infect Dis*. 2020;ciaa803, https://doi.org/10.1093/cid/ciaa803 [Online ahead of print].

Cefiderocol: A Novel Cephalosporin

- A siderophore cephalosporin with a catechol moiety
  - Binds mainly to PBP-3 of Gram-negative bacteria
- A Canadian ICU study of 800 isolates of Gram-negative bacilli found all were susceptible to cefiderocol (MIC ≤4 µg/mL), including isolates of:
  - ESBL-producing Enterobacterales (*n*=40)
  - AmpC-producing Enterobacterales (*n*=6)
  - Carbapenem-nonsusceptible Enterobacterales (*n*=21)
  - Carbapenem-nonsusceptible *P. aeruginosa* (*n*=54)
  - MDR *P. aeruginosa* (*n*=29)
  - *Stenotrophomonas maltophilia* (*n*=66)
  - *Acinetobacter baumannii* (*n*=11)

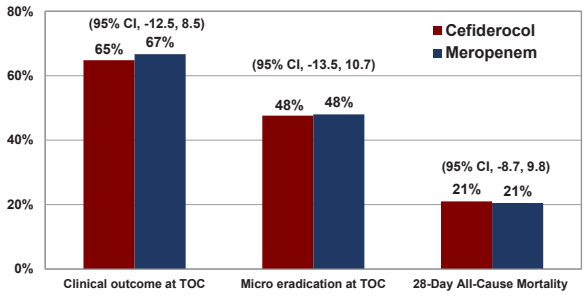
Golden AR, et al. *Diagn Microbiol Infect Dis*. 2020;97:115012.

Cefiderocol vs. Meropenem for Nosocomial Pneumonia (APEKS-NP)

- Multicenter, randomized, double-blind, parallel-group study of 300 hospitalized patients with pneumonia (HAP/VAP/HCAP) caused by Gram-negative pathogens
- Patients randomized 1:1 to receive:
  - Cefiderocol 2 g IV q8h for 7–14 days
  - Meropenem 2 g IV q8h for 7–14 days

Wunderink RG, et al. *Lancet Infect Dis*. 2020; DOI: https://doi.org/10.1016/S1473-3099(20)30731-3 (Online first).

Cefiderocol (CFDC) vs. Meropenem (MER) for Nosocomial Pneumonia (APEKS-NP)



Drug-related AEs:
- 9.5% (14/148) CFDC
- 11.3% (17/150) MER

TOC = test of cure

Wunderink RG, et al. *Lancet Infect Dis*. 2020; DOI: https://doi.org/10.1016/S1473-3099(20)30731-3 (Online first).

Cefiderocol vs. Meropenem for Nosocomial Pneumonia Clinical Cure per Pathogen (APEKS-NP)

Pathogen	Cefiderocol n/N (%)	Meropenem n/N (%)	Difference (95% CI)
K. pneumoniae	31/48 (64.6)	29/44 (65.9)	-1.3 (-20.8, 18.1)
E.coli	12/19 (63.2)	13/22 (59.1)	4.1 (-25.8, 33.9)
P. aeruginosa	16/24 (66.7)	17/24 (70.8)	-4.2 (-30.4, 22.0)
A. baumannii	12/23 (52.2)	14/24 (58.3)	-6.2 (-34.5, 22.2)

Wunderink RG, et al. *Lancet Infect Dis*. 2020; DOI: https://doi.org/10.1016/S1473-3099(20)30731-3 (Online first).

Summary

- Clinicians managing patients with HABP/VABP should be aware of local pathogens to guide medical decision-making
- Early pathogen-specific antibiotic therapy results in improved outcomes including lower mortality
- A multidisciplinary approach is essential in ensuring optimal management approaches and achieving favorable patient outcomes

Notes

Notes

Utilizing Stewardship to Optimize Diagnosis and Management for HABP/VABP

Including Institutional Experience

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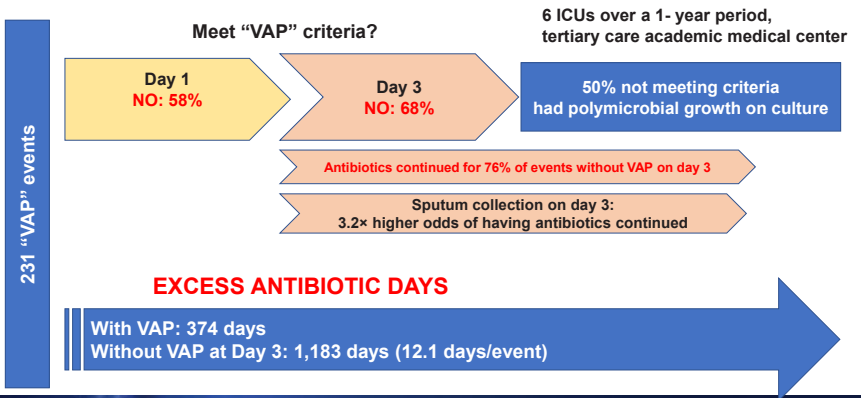
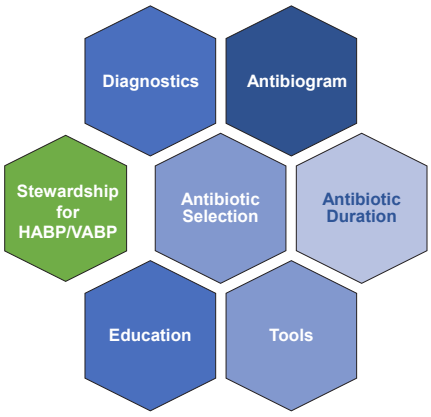
Durham, NC

Finding Opportunities for Stewardship



Nussenblatt V, et al. *Infect Control Hosp Epidemiol.* 2014;35:278-84.

Antimicrobial Stewardship: A Key Piece of the Puzzle



Challenges with Diagnostics in HABP/VABP

- Other diagnoses vs VAP
- Antibiotics prior to sampling
- Identification of multiple organisms
- Colonization vs infection
  - "normal respiratory flora"'
- Positive nucleic acid test, negative culture result
- Discrepant results

Kenaa B, et al. *Curr Infect Dis Rep.* 2019;21:50.

Antibiograms: Pitfalls, Limitations, and Optimizing the Data

- Review and understand limitations of automated susceptibility testing platform/cards
  - Reliable results/secondary methods needed for certain bug-drug combinations
- Single hospital antibiogram may not represent picture of HABP/VABP pathogens
  - ICU-specific, and respiratory specimens may be of interest
- Combination antibiogram for ICU pathogens may be helpful
  - "conditional" antibiogram

Institutional Experience: A Tale of Two Hospitals

Pseudomonas aeruginosa	Pip/Taz	Cefepime	Meropenem	Ciprofloxacin	Tobramycin	Aztreonam
Hospital A	95%	94%	90%	76%	98%	82%
Hospital B	79%	81%	88%	Levo: 65%	99%	N/A
Hospital B ICU	77%	74%	84%	Levo: 61%	97%	N/A

Unpublished data, Duke Antimicrobial Stewardship Outreach Network (DASON), 2020.

Combination Antibiograms to Guide Empiric Therapy Selection: An Institutional Example

Number of Isolates	Most Active Combination	% Susceptibility Beta-Lactam	% Susceptibility Combination
298	Cefepime + Tobramycin	85.5	97.0
259	Piperacillin-tazobactam + Tobramycin	85.9	96.3
251	Meropenem + Amikacin	87.2	96.9

<3 Days of Hospitalization

Number of Isolates	Most Active Combination	% Susc Beta-Lactam	% Susc Combination
120	Cefepime + Tobramycin	86.9	98.1
120	Meropenem + Tobramycin	88.1	97.5
120	Piperacillin-tazobactam + Tobramycin	88.1	96.9

≥3 Days of Hospitalization

Number of Isolates	Most Active Combination	% Susc Beta-Lactam	% Susc Combination
114	Meropenem + Amikacin	86.2	100
114	Piperacillin-tazobactam + Amikacin	83.31	99.3
114	Cefepime + Amikacin	84.1	99.2

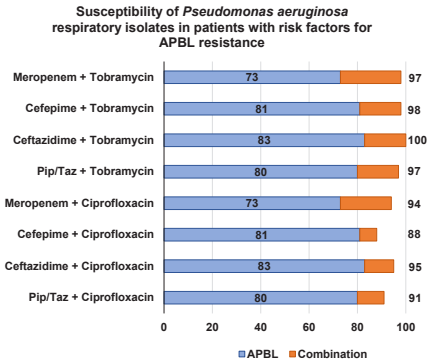
Alnamnakani B, Bosso JA. *J Clin Lab Med.* 2016;1(1): doi http://dx.doi.org/10.16966/2572-9578.105

Risk Scores and Combination Antibiograms: A Case-Control Study

- Aimed to identify risk factors for pneumonia due to beta-lactam–resistant *P. aeruginosa*

Risk Factor	OR (95% CI
Bronchiectasis	8.3 (1.7-46.6)
APBL use within 3–30 days	7.7 (3.4-17.9)
Prior airway colonization with APBL-R PA within 12 months	14.9 (2.0-312.9)

- APBL susceptibility was ≥95% in the absence of these risk factors



APBL = antipseudomonal beta-lactam
Al-Jaghbeer MJ, et al. *Infection.* 2018;46:487-94.

Microbiology Comment: "Nudge" to Improve Antibiotic Prescribing for Pneumonia

Respiratory cultures with no dominant organism growth and no *Pseudomonas* spp. or *Staphylococcus aureus*

Comment:
"commensal respiratory flora only: No *S. aureus*/MRSA [methicillin-resistant *Staphylococcus aureus*] or *P.* [*Pseudomonas*] *aeruginosa*"

De-escalation: odds ↑ 5.5-fold (aOR, 5.5; 95% CI: 2.8–10.7)
Acute kidney injury: ↓ (31% pre vs. 14% post, *p*=0.003)
All-cause mortality: no significant difference (30% pre vs post 18%, *p*=0.052)

Musgrove A, et al. *Open Forum Infect Dis*. 2018;5(7):ofy162.

Microbiology Comment: "Nudge" to Improve Antibiotic Prescribing for Pneumonia

Respiratory cultures with no dominant organism growth and no *Pseudomonas* spp. or *Staphylococcus aureus*

Alternative comment:

"No predominant pathogen identified. Please consider de-escalating antimicrobial therapies, including those targeted at MRSA and *P. aeruginosa*."

Rapid Diagnostics: Comparison of Bacteria Detected by Multiplex Pneumonia Panels

Specimen Types		Streptococcus agalactiae	S. aureus	Streptococcus pyogenes	S. pneumoniae	Citrobacter freundii	E. cloacae complex	E. coli	K. aerogenes	K. pneumoniae	Proteus spp.	K. oxytoca	Serratia marcescens	K. variicola	Morganella morganii	Moraxella catarrhalis	Pseudomonas aeruginosa	Acinetobacter baumanii complex	Stenotrophomonas maltophilia	Legionella pneumophila	Haemophilus influenzae	Mycoplasma pneumoniae	Chlamydia pneumoniae	Viruses	
Biofire Pneumonia	BAL, mini-BAL, sputum, tracheal aspirate	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	-	✓	-	✓	✓	✓	8
Unyvero LRT	BAL, mini-BAL	✓		✓		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-
Unyvero LRT	tracheal aspirate	✓		✓		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	-
Unyvero HPN	Sputum, BAL, tracheal aspirate	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-
		Gram +					Enterobacterales												Nonfermenters			Others			

Rapid Diagnostics: Comparison of Resistance Genes Detected by Multiplex Pneumonia Panels

Specimen Types		Mec A	Mec C	MREJ	KPC	NDM	Oxa-23	Oxa-24/40	Oxa-48-like	Oxa-58	VIM	IMP	CTX-M	esm-B	TEM	SHV	SUL-1	6yrA93	6yrA87
Biofire Pneumonia	BAL, mini-BAL, sputum, tracheal aspirate	✓	✓	✓	✓	✓			✓		✓	✓		✓					
Unyvero LRT	BAL, mini-BAL	✓			✓	✓	✓	✓	✓	✓	✓	✓		✓			✓		
Unyvero LRT	tracheal aspirate	✓			✓	✓	✓	✓	✓	✓	✓			✓			✓		
Unyvero HPN	Sputum, BAL, tracheal aspirate	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓
		Methicillin-Resistance			Carbapenemases									ESBL	Macrolide	Penicilin	Sulfonamide	Fluoroquinolone		

Challenges with Rapid Diagnostics for Pneumonia

- Don't cover all organisms
- Identification of multiple organisms
  - Sputum and endotracheal aspirates >3× as likely to have multiple organisms identified
- Positive nucleic acid test, negative culture
- Genotypic vs phenotypic resistance?
  - CLSI M-100 Appendix H for guidance

CLSI. M100: Performance Standards for Antimicrobial Susceptibility Testing, 30th Edition. 2020.

Potential Benefits of Rapid Diagnostics

- May identify pathogens not recovered on culture, due to prior antibiotic exposure
- Facilitate antibiotic optimization
  - 71% of patients in a recent study using BAL or min-BAL

Potential modification	No. of antimicrobials	No. (%) of patients	No. of hrs
Appropriate de-escalation/discontinuation	206	122 (48.2)	18,284.07
Appropriate escalation/initiation	11	11 (4.3)	184.66
Inappropriate de-escalation/discontinuation	4	4 (1.6)	
Inappropriate escalation/continuation	42	42 (16.6)	
No change		74 (29.2)	
Unable to assess[a]		16	

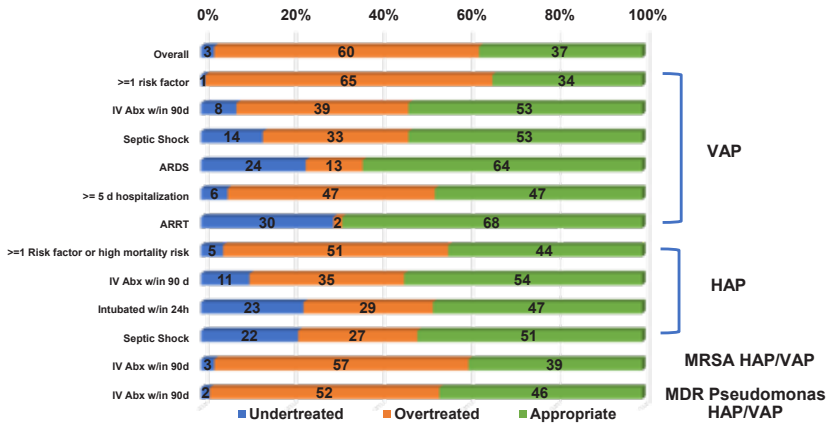
Buchan BW, et al. *J Clin Microbiol.* 2020;58(7):e00135-20; DOI: 10.1128/JCM.00135-20.

Recommendations for Empiric Antibiotic Selection

- **IDSA/ATS guidelines**
- **European guidelines**
- **LOCAL epidemiology & resistance patterns**

Kalil AC, et al. *Clin Infect Dis.* 2016; 63(5):e61-111.
Torres A et al. *Eur Resp J.* 2017;50:1700582.
Ekren Pk et al. *Am J Resp Crit Care Med.* 2018;197(6):828-30.

Evaluation of Empiric Antibiotic Coverage if IDSA/ATS Guidelines Followed



Kalil AC, et al. *Clin Infect Dis.* 2016; 63(5):e61-111.
Torres A, et al. *Eur Resp J.* 2017;50:1700582.
Ekren PK, et al. *Am J Resp Crit Care Med.* 2018;197(6):826-30.

Utilizing a Treatment Pathway for HABP/VABP: Institutional Example

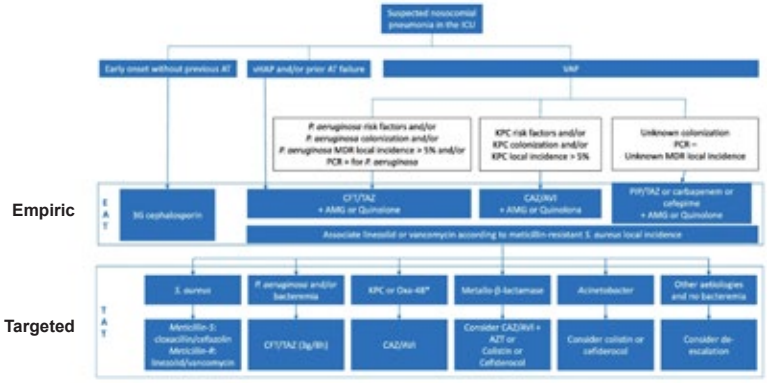
"Hospital A"

Hospital-acquired pneumonia (HAP) or Ventilator-Associated Pneumonia (VAP)	
No risk factors for MDR GN	Cefepime 1 g IV q6h or Piperacillin-tazobactam 4.5 g IV q6h +/- vancomycin IV (pharmacy to dose)
Severe (ventilator support and/or septic shock), Risk factors for MDR GN	Piperacillin/tazobactam 4.5 g IV q6h +/- tobramycin (pharmacy to dose) +/- vancomycin IV (pharmacy to dose)
Severe penicillin allergy	Aztreonam 2 g IV q8h plus tobramycin

Note: Hospital reports 95% of *P. aeruginosa* susceptible to piperacillin/tazobactam, 98% susceptible to tobramycin, 76% susceptible to ciprofloxacin.

Example: DASON Hospital, 2019.

Utilizing a Treatment Pathway for HABP/VABP: Institutional Example



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

2020 IDSA Guidance: Treatment of MDR Gram-Negative Infections

Preferred Treatments (If Susceptible) for Infections Outside the Urinary Tract		
ESBL-Producing *Enterobacterales*	DTR-*Pseudomonas aeruginosa*	Carbapenem-Resistant *Enterobacterales*
meropenem imipenem-cilastatin ertapenem	ceftolozane-tazobactam ceftazidime-avibactam imipenem-relebactam	**R to Erta/S to Mero (CPE test – or N/A):** meropenem* (EI) **R to Erta/Mero (CPE test – or N/A):** ceftazidime-avibactam meropenem-vaborbactam imipenem-relebactam
		KPC: ceftazidime-avibactam meropenem-vaborbactam imipenem-relebactam
		MBL (VIM,IMP, NDM): ceftazidime-avibactam + aztreonam cefiderocol
		OXA-48-like: ceftazidime-avibactam

DTR = "difficult-to-treat" resistance, defined as non-susceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin; EI = extended infusion

Adapted from: Tamma PD et al. Infectious Diseases Society of America Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections, 2020. https://www.idsociety.org/practice-guideline/amr-guidance/

Stewardship Approaches: Duration of Therapy/De-escalation

- Evidence supports 7 days of therapy (IDSA recommendations) & de-escalation
  - Need more data on outcomes of de-escalation, duration for MDRO infections
- Can use PCT + clinical criteria to guide discontinuation
  - International consensus panel, adults with severe illness in ICU: recheck PCT q24-48h and discontinue once PCT <0.5 μg/L or decreases by 80%
- De-escalation based on MRSA nares testing
  - Negative nasal swab in ICU: NPV 99.4% for subsequent MRSA infection during admission
  - Reduction in mean duration of anti-MRSA therapy by 46.6h with pharmacist-driven protocol in patients with suspected pneumonia, without negative impact on clinical outcomes

Kalil AC, et al. *Clin Infect Dis*. 2016;63(5):e61-111.
Chotiprasitsakul D, et al. *Infect Control Hosp Epidemiol*. 2018;39:290-6.
Schuetz P, et al. *Clin Chem Lab Med*. 2019; 57(9): 1308-18.
Baby N, et al. *Antimicrob Agents Chemother*. 2017;61:e02432-16.

Barriers to IDSA/ATS Guideline Adherence

Barrier	Agree/ Strongly Agree
Multiple physician groups managing patients	67.3%
Variation in VAP management depending on ICU service	64.3%
Renal failure in ICU patients complicating antibiotic selection/management	57.4%
Variation in VAP management between attending physicians	56.8%
Variation in VAP management between attending physicians and house staff	52.6%

Safdar N, et al. *BMC Infect Dis*. 2016;16:349.

Selected Top Facilitators of Guideline Adherence

Selected Facilitators	%
Pharmacist participation on rounds is beneficial	98.6%
Nurse participation on ICU rounds is beneficial	98%
Respiratory Therapist participation on rounds is beneficial	96.7%
I can readily access orders written for my ICU patients	92.6%
RT services are readily available on my ICU	92.3%
Multidisciplinary management of patients occurs on my ICU	91.9%
Nurses consistently participate on ICU patient rounds	90.3%
Physicians are receptive to pharmacist input on ICU care	89.7%
Pharmacists on my ICU effectively monitor antibiotic use	89.3%
Pharmacists participation promote appropriate antibiotic ordering	89%
Using VAP management guidelines helps me to manage VAP patients in the ICU	86.7%
I can appropriately manage ICU patients with VAP	83.1%

Safdar N, et al. *BMC Infect Dis*. 2016;16:349.

Additional Stewardship Techniques

- **Antibiotic Time-out**
  - Provider-driven time-out on days 3–5 did not result in a change in overall antibiotic utilization (days of therapy/admission), but increased appropriateness of antibiotics by ~25%
- **Prospective Audit and Feedback (PAF) vs Pre-authorization**
  - More de-escalation with PAF
- **"Handshake Stewardship"**
  - Sustainable decrease in overall hospital antimicrobial utilization
- **Multidisciplinary rounding**
  - Reduction in antibiotic utilization and *C. difficile* rates
- **Prevention… is worth a pound of cure**

Thom KA, et al. *Clin Infect Dis*. 2019;68:1581-84.
MacBrayne CE, et al. *Clin Infect Dis*. 2020;70:2325-2332.
Anderson DJ, et al. *JAMA Netw Open*. 2019; 2(8):e199369.
Davis A, et al. *Open Forum Infect Dis*. 2016;3(Suppl 1):977.

Stewardship: Looking Into the Future

- Expanded rapid diagnostics
- Pathogen-specific approaches
- TDM to optimize antibiotic dosing
- Artificial intelligence techniques
- Behavior change approaches

Abdul-Aziz MH et al. *Intensive Care Med*. 2020;46:127-53.
Chumbita M, et al. *J Clin Med*. 2020;9:248.
AHRQ Pub. No. 17(20)-0028-EF 2019; https://www.ahrq.gov/antibiotic-use/acute-care/improve/behavior-changes.html.

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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 HABP/VABP.

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.