Changing Treatment Paradigms in the Era of Resistance

An e-Bulletin on Meeting the Challenges in HABP/VABP

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

Upon completing this activity, participants will be able to:

- Discuss the impact of antimicrobial resistance on clinical and economic outcomes among severely ill patients with Gram-negative infections
- Identify strategies to include newer antimicrobial agents as part of a pathogen-specific approach when treating multidrug-resistant Gram-negative infections
- Explain advanced antimicrobial stewardship techniques that can be applied to patients with HABP/VABP

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Editor's Note

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. 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, including the use of antibiograms, rapid diagnostics, and newer antimicrobials in a pathogen-specific manner.

This bulletin is designed to complement the content and discussion from a virtual satellite symposium held recently as part of IDWeek 2020.

Consequences of Antimicrobial Resistance

Q1. What are the clinical and economic consequences of antimicrobial resistance among severely ill patients?

The threat of antimicrobial resistance among nosocomial pathogens has grown significantly over the past few decades. Though there is emerging evidence that the prevalence of certain problematic pathogens has started to plateau or decline, resistance remains elevated for pathogens frequently encountered in the ICU setting, including ESBL-producing Enterobacterales (formerly named Enterobacteriaceae), carbapenem-resistant Enterobacterales, and multidrug-resistant *Pseudomonas aeruginosa*. Resistance by *P. aeruginosa* is particularly troublesome in critically ill patients. A surveillance study of *P. aeruginosa* isolates from ICU patients with a bloodstream infection or pneumonia revealed susceptibility rates to commonly-used antimicrobials struggled to exceed 80% **(Table 1)**.[1] The highest susceptibility rates were for agents that are generally not preferred due to potential toxicity and serious adverse effects (i.e., amikacin [98.1% susceptibility], gentamicin [86.9%], and colistin [99.4%]).

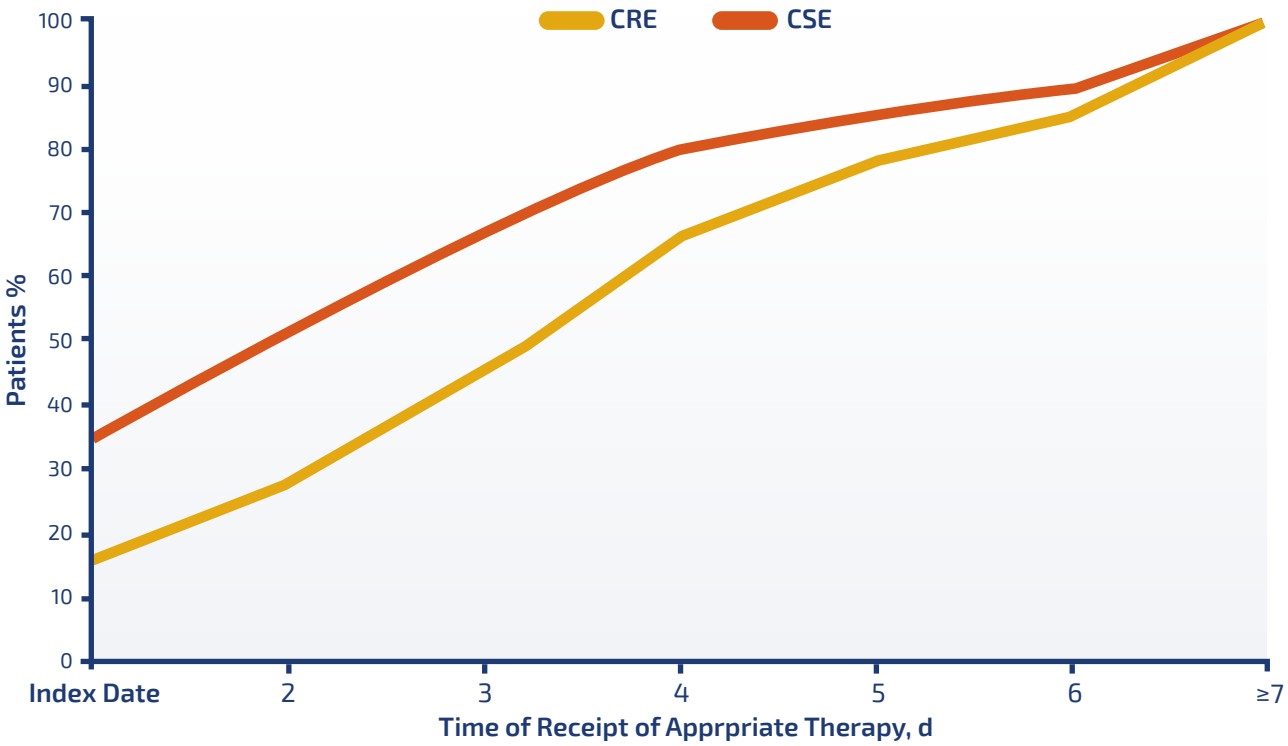
Table 1. *P. aeruginosa* Susceptibility from Pneumonia and Bloodstream Isolates in ICU Patients[1]

	MIC90, mg/L	% Susceptible
Aztreonam	>16	66.5
Cefepime	16	83.8
Ceftazidime	32	82
Ciprofloxacin	>4	73.9
Meropenem	8	76.3
Piperacillin-tazobactam	>64	77.1

While it is generally accepted that antimicrobial resistance among nosocomial isolates is high, the question remains as to the consequences of resistance. Several observational studies have evaluated the impact of resistance on clinical outcomes. A prospective study by Fisher and colleagues analyzed outcomes among ICU patients with respiratory failure and pneumonia.[2] Patients were divided into four microbiologic categories: pathogen negative, antibiotic-susceptible (as determined by ceftriaxone susceptibility), antibiotic-resistant, and viruses. When compared with patients who had antibiotic-susceptible infections, those with an antibiotic-resistant infection had nearly double the number of ventilator days (median of 7.5 vs. 4 days) and deaths (50% vs. 27%). These poorer outcomes were likely contributed to a higher rate of inappropriate initial antibiotic therapy (IIAT), which occurred in 21.2% of those with antibiotic-resistant infection compared with 3.2% of those with antibiotic-susceptible infection.

Other studies support the association of antimicrobial resistance with IIAT and poorer clinical outcomes. A study by Lodise et al. analyzed a large US hospital database to identify all admissions with a serious Enterobacteriaceae infection.[3] Outcomes were then compared among those with carbapenem-resistant Enterobacteriaceae (CRE) versus carbapenem-susceptible Enterobacteriaceae (CSE). Those with CRE were found to have a 2.2-fold higher risk of in-hospital death or discharge to hospice compared to those with CSE. Interestingly, timely appropriate therapy (within 72 hours) occurred in 67.5% of those with CSE, compared to only 44.6% with CRE ($p<0.01$) **(Figure 1)**. Regardless of CRE status, those who received delayed appropriate therapy had a longer duration of antibiotic therapy and LOS, higher costs, lower likelihood of discharge to home, and a greater likelihood of the composite mortality outcome.

Figure 1. Time to Receipt of Appropriate Therapy[3]



In addition to a higher clinical burden associated with resistant infections and delayed appropriate therapy, there is also an economic consequence, including longer LOS and higher hospital costs. A retrospective cohort study that utilized the Premier Research database that included 175 US hospitals identified over 40,000 patients with Enterobacteriaceae infection. Among those, 13.2% received inappropriate empiric therapy (IET), and it was determined that each day of IET resulted in an additional cost of $766 compared to those receiving adequate therapy.[4] A systematic review focusing on the economic burden of resistant pathogens determined infections caused by carbapenem-resistant *P. aeruginosa* resulted in 1.5-fold higher mean hospital costs and over 3-fold higher median total (direct and indirect) costs.[5]

These studies suggest that a major consequence of antimicrobial-resistant infections is a higher likelihood of inappropriate initial antimicrobial therapy. This often leads to poorer clinical outcomes, including higher mortality rates, as well as higher healthcare costs associated with prolonged LOS. Rapid diagnostics and newer antimicrobials can offer clinicians potentially new options to improve the likelihood of timely adequate initial therapy for patients at-risk of antimicrobial-resistant infections.

Tools for Pathogen-Specific Therapy

Q2. How can clinicians utilize rapid diagnostics and newer antimicrobials in a pathogen-specific approach to therapy?

The past few years has seen a surge in antimicrobials approved for the treatment of HABP/VABP that target MDR Gram-negative pathogens. These include ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-cilastatin-relebactam, and cefiderocol. Appropriate utilization of these agents requires an ability to differentiate their pharmacologic and microbiologic properties. In particular, when implementing a pathogen-specific approach to treating MDR Gram-negative infections, it will be essential to select the agent that exhibits effective activity against that particular pathogen or resistance mechanism. This approach increases the chance of eradicating the infection while diminishing the risk of resistance emergence during therapy.

The expansion of rapid diagnostics has increased the ability to utilize a pathogen-specific approach to therapy. These advanced diagnostic approaches, such as the Biofire® FilmArray® System and the Verigene® Respiratory Pathogens Flex Test, are able to identify pathogens in a timely manner (within minutes to hours) rather than days. In addition to identifying bacterial species, rapid diagnostics can also detect the presence of resistance genes so as to help guide the selection of the most appropriate antimicrobial as well as de-escalate therapy when possible. Optimized treatment will require a comprehensive understanding of the microbiologic activity of available antimicrobials.

When comparing the microbiologic activity of the four newer antimicrobials against Gram-negative bacteria, there are distinct differences. A summary of the organisms approved by the FDA for the HABP/VABP indication for each agent is shown in **Table 2**. It is important to note that this list only reflects organisms that were found in sufficient numbers during the clinical trials to warrant approval by the FDA. The list also does not reflect resistance mechanisms that can be found in these organisms, such as ESBL production or carbapenemases.

Table 2. Bacteria Included in HABP/VABP Indications of Newer Antimicrobials[6-9]

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	●	●	●	●

In vitro microbiologic studies along with clinical trial data can offer a more comprehensive look at the activity of each of these agents against MDR Gram-negative bacteria. For example, in vitro studies demonstrate ceftolozane-tazobactam exhibits activity against *P. aeruginosa* isolates, including resistant and MDR strains.[1] This was supported with results from the phase III ASPECT-NP trial that demonstrated non-inferiority to meropenem for MDR *P. aeruginosa* in patients with nosocomial pneumonia **(Table 3)**.[10]

Table 3. Per-pathogen Clinical Cure at Test-of-Cure Visit (ASPECT-NP Trial)[10]

	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 (-19.3 to 10.7)
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)

A summary of the activity from newer antimicrobial agents is shown in **Table 4**. This can offer insights when selecting pathogen-specific therapy based on microbiologic findings. For example, treatment options for an infection caused by a KPC-producing Enterobacterales can include ceftazidime-avibactam or imipenem-relebactam. If an OXA-type carbapenemase is present, then ceftazidime-avibactam may be the most appropriate choice. Cefiderocol is the most recent agent to get HABP/VABP approval by the FDA and reports on its use in clinical practice will be important in determining its role in the management of HABP/VABP. However, in vitro activity suggests that this agent can be an important option when managing *Acinetobacter* infections or when certain metallo-beta-lactamases (e.g., NDM) are present.

Table 4. Activity of Newer Agents Against Problematic Pathogens[11,12]

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

The combination of rapid molecular diagnostics and the availability of newer antimicrobials that exhibit activity against problematic MDR Gram-negative bacteria can allow clinicians to utilize a pathogen-specific approach now more than ever before. Pathogen-specific therapy can also be an important aspect of antimicrobial stewardship as it optimizes antimicrobial selection based on the specific pathogen and/or resistance mechanism that is present. This approach potentially reduces the risk of resistance emergence and reduces the clinical and economic burden of infection.

Antimicrobial Stewardship

Q3. What advanced antimicrobial stewardship strategies can be applied when managing patients with HABP/VABP?

Antimicrobial stewardship programs (ASPs) are now fully integrated into most, if not all, healthcare systems as a means to improve appropriate utilization of antimicrobials, decrease the risk of resistance emergence, and lower the clinical and economic burden of serious bacterial infections. When managing patients with HABP/VABP, antimicrobial stewardship techniques can be instrumental in ensuring optimal outcomes.

An important tool in antimicrobial stewardship is the utilization of antibiograms when selecting initial empiric antimicrobial therapy. Antibiograms offer clinicians a broad overview of the pathogens and susceptibility profiles that could potentially be causing a suspected or proven bacterial infection within an institution or medical ward.

Click here to listen to Dr. Keith Rodvold, discuss the importance and role of the institutional antibiogram in making therapeutic decisions.

There are various types of antibiograms that can be created based on the microbiological data available at an institution. The CLSI (Clinical & Laboratory Standards Institute) offers recommendations on how to develop an antibiogram that will provide the most useful data for clinicians, including stratifying antibiograms by medical unit, infection type, or patient characteristics, among others.

Click here to listen to Dr. Keith Rodvold, explain CLSI standards in creating an antibiogram and how to make the best use of the hospital microbiologic data to guide clinical decisions.

There is a growing body of evidence supporting the use of combination antibiograms, particularly when managing difficult pathogens that have low susceptibility to antimicrobial monotherapy. For these infections, such as those caused by *P. aeruginosa*, combination therapy is frequently administered to ensure at least one of the agents will exhibit adequate activity. A combination antibiogram takes into account the activity of two antibiotic combinations to help guide therapeutic selection.

A properly selected combination based on local susceptibility data will increase the likelihood that at least one agent will exhibit activity against the pathogen. This was illustrated in a study by Alnamnakani and Bosso who developed an institutional combination antibiogram to determine the most effective regimen for *P. aeruginosa* infections.[13] They examined beta-lactam plus aminoglycoside combinations and revealed that beta-lactam monotherapy resulted in susceptibility between 85% and 90% at their institution. By adding an aminoglycoside, susceptibility rates increased to over 95% in each case **(Table 5)**.

Table 5. Institutional Combination Antibiogram Example[13]

Number of Isolates	Most Active Combination	% Susceptibility Beta-Lactam	% Susceptibility Combination
298	Cefepime + Tobramycin	85.5	97
259	Piperacillin-tazobactam + Tobramycin	85.9	96.3
251	Meropenem + Amikacin	87.2	96.9

The authors were able to further stratify the data by days of hospitalization. For those who had a culture taken <3 days of hospitalization, the most effective combination was cefepime plus tobramycin (98.1% susceptible). However, for those whose culture was taken after 3 days or more of hospitalization, the most effective combination was meropenem plus amikacin (100% susceptible).

Other emerging stewardship techniques can involve the use of biological markers to help guide treatment decisions, particularly when to de-escalate or discontinue antimicrobial therapy. Serum procalcitonin is most often cited as a possible biomarker to determine when to discontinue therapy, with one international consensus panel offering an algorithm in interpreting procalcitonin levels to guide management decisions based on severity of illness and probability of bacterial infection.[14] Research is investigating the utility of other biomarkers to guide decisions aimed to decrease the inappropriate use of antimicrobials and improving patient outcomes.

Click here to listen to Dr. Melissa Johnson discuss the latest developments on the use of molecular biomarkers in the management of patients with pneumonia.

In addition to a greater use of institutional antibiograms and biomarkers, the future direction of antimicrobial stewardship will likely include a more expanded use of rapid diagnostics along with pathogen-specific approaches to antimicrobial selection. To achieve this, interprofessional collaboration will be essential in ensuring the optimal use of current and emerging tools to achieve improved patient outcomes among those with serious bacterial infections.

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