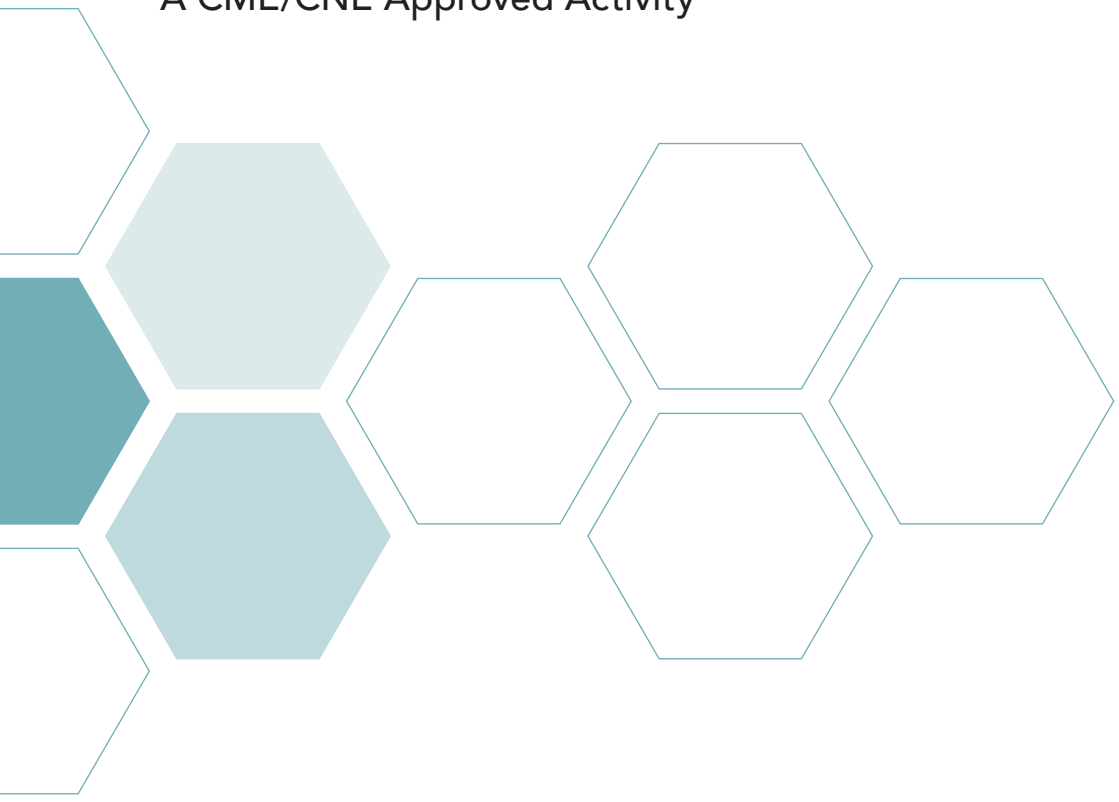
Novel Treatment Advances in the Management of Serious Gram-Negative Bacterial Infections:

Expert Strategies for Improved Patient Outcomes

A CME/CNE Approved Activity



JOURNAL of MANAGED CARE MEDICINE

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Instructions for CME/CNE: Activity is valid from February 1, 2019 to January 31, 2021.

A score of 70% must be achieved on the post-test to receive continuing education credits.
Read the monograph, answer the post-test, complete the evaluation form, and send completed post-test and evaluation to:

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Learning Objectives:
1. Explore the evolving prevalence and etiology of Gram-Negative bacteria and their impact on the spectrum of serious nosocomial infections.
2. Examine the efficacy and safety of current and emerging antimicrobials for serious infections caused by Gram-Negative bacteria.
3. Optimize clinical and economic strategies in the management of serious Gram-Negative infections.

Faculty Disclosure:
Dr. Muto has disclosed no relevant financial relationships.

All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacqueline Cole, RN, CPHQ, CMCN; and Jeremy Williams have no relevant financial relationships to disclose.

Accreditation and Designation
The National Association of Managed Care Physicians (NAMCP) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

NAMCP designates this enduring material for a maximum of 1 *AMA PRA Category I credits*™. Each physician should claim credit commensurate with the extent of their participation in the activity.
The American Association of Managed Care Nurses is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Nurses who complete this activity and achieve a passing score will receive 1 hour in continuing nursing credit. This activity has been approved by the American Board of Managed Care Nursing for 1.0 contact hours toward CMCN recertification requirements.

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Post-Test Questions

1. Which of the following is NOT a commonly resistant bacteria?
   a. Klebsiella pneumoniae b. Pneumococcus
   c. Pseudomonas aeruginosa d. Escherichia Coli
2. Death from infection with resistant organisms is the _____ cause of death in the U.S.
   a Third b. Eighth c. Eleventh d. Twenty-fifth
3. Which of the following is the definition of a multi-drug resistant organism?
   a. An organism non-susceptible to one or more agents in three or more antimicrobial categories.
   b. An organism non-susceptible to at least one agent in all but two or fewer antimicrobial categories.
   c. An organism non-susceptible to all agents in all antimicrobial categories.
   d. An organism only sensitive to colistin.
4. Which of the following is the main reason why colistin should no longer be used as empiric therapy for suspected gram-negative bacterial infections?
   a. Level of known resistance.
   b. Cost compared to other agents.
   c. Toxicity, especially renal.
   d. Preserve it as a last resort antibiotic.
5 A Qualified Infectious Disease Product (QIDP) is an antibacterial or antifungal human drug intended to treat rare infections.
   a. True b. False
6. Which of the following is the best reason for aggressive empiric therapy in hospital acquired suspected gram-negative bacterial infection?
   a. The mortality rate
   b. Pathogenicity of gram-negative bacteria
   c. The costs to treat these infections
   d. All of the above
7. Which of the following is NOT a mechanism of antibiotic resistance in gram-negative bacteria?
   a. Loss of porins b. Efflux
   c. Enzymes d. Cell membrane lipid levels
8. Which of the following is first-line for carbapenemase-producing Enterobacteriaceae?
   a. Ceftazidime/avibactam b. Ceftolozane/tazobactam
   c. Meropenem/vaborbactam d. Colistin and meropenem
9. Which of the following is the least expensive (drug acquisition costs) for treating pseudomonas?
   a. Ceftazidime/avibactam b. Ceftolozane/tazobactam
   c. Meropenem/vaborbactam d. None of the preceding
10. Which of the following is the most comprehensive approach to reducing the spread of resistant bacteria in health care settings?
    a. Antibiotic stewardship program
    b. Enforced hand-washing
    c. Infection control procedures
    d. Ongoing clinician education program

Activity Evaluation and Improvement Process

Please rate this activity on the following scale:

4 - Excellent 3 - Good 2 - Fair 1 - Poor

1. Based on the content presented, I am better able to:

   Explore the evolving prevalence and etiology of Gram-Negative bacteria and their impact on the spectrum of serious nosocomial infections.

   4 3 2 1

   Examine the efficacy and safety of current and emerging antimicrobials for serious infections caused by Gram-Negative bacteria.

   4 3 2 1

   Optimize clinical and economic strategies in the management of serious Gram-Negative infections.

   4 3 2 1

2. The activity and presenters were free of bias.

   4 3 2 1

3. The activity was applicable to my position.

   4 3 2 1

4. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

5. Do you plan to change management strategies or patient care in your organization or practice based on the content presented?

   ☐ Yes ☐ No

6. If yes, what changes do you plan to implement in management strategies or patient care in your organization or practice?

   _____

   _____

   _____

   _____

7. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

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Richmond, VA 23255-1895
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fax (703) 997-5842

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GRAPHIC DESIGN
Douglas Murphy Communications, Inc.

ISSN: 1094-1525. The *Journal of Managed Care Medicine* is published by NAMCP Medical Directors Institute. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: P.O. Box 71895, Richmond, VA 23255-1895; Tel (804) 387-7580; Fax (703) 997-5842. Advertising offices: Sloane Reed, 4435 Waterfront Drive Ste 101, Glen Allen, VA 23060 Tel (804) 527-1905, Fax (804) 747-5316.

POSTMASTER: Send address changes to The Journal of Managed Care Medicine, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

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Journal of Managed Care Medicine

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Gram-Negative Bacterial Infections Monograph

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Carlene A. Muto, MD, MS

Introduction

Healthcare-acquired infections (HAIs) affect 5 to 10 percent of patients in acute care hospitals in the United States (U.S.) annually. This is nearly two million patients at a cost estimate of $5 to 10 billion. Approximately 99,000 people will die each year from HAIs, which is more deaths than those caused by breast cancer, colon cancer and stroke combined and is equivalent to one death every six minutes.

Approximately 20 percent of the two million HAIs annually are due to resistant organisms. The National Foundation of Infectious Diseases has estimated the cost of HAIs due to antibiotic-resistant organisms to be $4.5 billion annually. Approximately 19,000 deaths occur annually from these resistant organisms. Overall, death from resistant organisms is the eleventh leading cause of death in the U.S.

Pneumonia (mostly associated with ventilators) and surgical site infections are the most common type of HAI, followed by clostridium difficile infection and urinary tract infections. The top three pathogens in HAIs are gram-negative rods (*Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa*) and many of these are resistant organisms.

A multidrug-resistant organism (MDRO) is as an organism non-susceptible to one or more agents in three or more antimicrobial categories.[1] An extensively drug-resistant organism (XDRO) has non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories) and a pandrug-resistant organism (PDRO) has non-susceptibility to all agents in all antimicrobial categories.[1] These levels of resistance leave few available treatment options. Exhibit 1 lists the species most commonly multidrug-resistant organisms, which are also known as the ESKAPE organisms. For purposes of this article MDRO will be used to refer all three categories of drug resistance (MDRO, XDRO, and PDRO), unless otherwise specified.

The consequences of MDROs are significant. Adverse outcomes of MDRO infections include mortality and costs. Costs are related to increased hospital length of stay and the costs of the treatments. Until relatively recent antibiotic approvals, the primary treatment for MDROs was colistin, a polymyxin antibiotic, which is more toxic than other antibiotics and is costly. About one-third of patients treated with colistin develop renal insufficiency, requiring dialysis. Other antibiotics used for treating MDROs are also expensive.

As noted previously, gram-negative bacteria (GNB) are a common cause of HAIs. They cause pneumonia, sepsis, wound/surgical site infection, and meningitis in healthcare settings. The most common GNB are Enterobacteriaceae (*Klebsiella, Enterobacter, E. coli*) and *Pseudomonas aeruginosa*. GNB are intrinsically resistant to many drugs and increasingly resistant to even new antibiotics. Genetic materials can be easily passed among these bacteria via plasmids to create MDRO. Rates of multidrug resistance in GNB continue to increase in the U.S.

The median total hospital bill per day for resistant GNB infection is 1.5 times higher than at-risk patients without GNB infection and those with sensitive GNB infection. Median costs per day of antibiotics and laboratory investigations are also significantly higher for patients with resistant GNB infection. Empiric antibiotic therapy for suspected resistant GNB can cost more than $1,000 per day in just antibiotic acquisition costs.

GNB pathogenicity is related to lipid A endotoxin secretion, which leads to rapid illness, antigens found on the cell membrane (capsular and flagellar), and various virulence factors that allow for immune evasion. There is very little time before a hospital-acquired GNB infection makes the patient very ill. Starting with the more comprehensive, but more expensive empiric therapy, has been shown to be more efficacious. Delaying the start of effective antibiotics increases morbidity and mortality because of the pathogenicity of GNB. Mortality among patients with inadequate initial therapy increases for every hour therapy is delayed.[2] Only 50 percent of patients with septic shock received adequate therapy

Exhibit 1: Most Common Multi-Drug Resistant Organisms (ESKAPE)

- *Escherichia Coli/E. faecium*
- *Staphylococcus tenotrophomonas maltophilia/S. aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumanii*
- *Pseudomonas aeruginosa*
- *Enterobacter species*

within six hours of documented hypotension.[2] It is impossible to know immediately whether a patient has a resistant organism or not, so empiric therapy has to take into account known resistance patterns in the hospital (antibiogram) and the likely pathogen. Empiric therapy against the most likely infecting organisms must be instituted at the first signs of infection with a suspected GNB. Therapy can be de-escalated once culture and sensitivity results are available.

Antimicrobial resistance rates have increased because of underutilization of infection control procedures and overutilization of antibiotics (especially for GNB).[3] Lack of hand hygiene, ineffective cleaning of the environment, poor cleaning of common equipment, and lack of compliance with other infection control measures have all contributed. MDROs can be spread from patient to patient in healthcare settings, primarily on the hands, clothes, and equipment (e.g., stethoscopes) of healthcare workers. Fifty percent of antimicrobial use in hospitals is either unnecessary or inappropriate, especially the extensive use for upper respiratory colonization/infections.

Using antibiotics appropriately, appropriate isolation of patients with MDROs, infection control procedures with all patients, and administrative support are all needed to control spread of MDROs. There are patient and financial benefits in controlling MDROs. Many healthcare institutions have an antimicrobial stewardship program, which is a coordinated program that promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by MDROS.

GNB develop antibiotic resistance easily. They have three primary mechanisms of resistance – loss of porins, efflux, and enzymes. Some antibiotics enter bacteria through porins; loss of porins prevents entry and thus causes loss of efficacy. GNB can pump antibiotics out of the cell through efflux. Exhibit 2 shows that many antibiotics are affected by efflux pumps in *Pseudomonas aeruginosa*.[4-7] GNB also make various enzymes such as beta-lactamases, which breakdown antibiotics. The enzymes which are problematic in clinical care are the extended-spectrum beta-lactamases, the AmpC beta-lactamases, and the carbapenemases. Extended-spectrum beta-lactamases (ESBLs) confer resistance to penicillins, cephalosporins, and the monobactam aztreonam. AmpC beta-lactamases convey resistance to penicillins, second- and third-generation cephalosporins, and cephamycins. Carbapenemases hydrolyze penicillin, cephalosporin, monobactam, and carbapenem antibiotics.

The carbapenemases are the most recently developed enzymes by GNB and include KPC (*Klebsiella pneumoniae* carbapenemase) and NDM (New Delhi metallo-β-lactamase). Bacteria that produce carbapenemases are referred to as carbapenem-resistant Enterobacteriaceae (CRE). Widespread use of carbapenem antibiotics (imipenem, meropenem, ertapenem, doripenem) for suspected ESBLs has contributed to resistance. CRE-producing organisms include *Klebsiella, Enterobacter, E. coli, and Serratia* species. CRE are typically seen in patients receiving long courses of broad-spectrum antibiotics with a prolonged ICU stay.

NDM CRE is still rare in the U.S., and infectious disease specialists would like it to stay that way. Thirty-four states have reported cases, as of December 2017.[8] Organisms with NDM are resistant to all antibiotics except colistin. It has been found more extensively in India, Pakistan, Bangladesh and Britain. Resistance can spread to other bacteria via a plasmid with incredible speed.

In 2006, CRE were reported in about 13 states; by 2014, CRE had been reported in almost all states.[8]

Exhibit 2: Agents Subject to Extrusion by Efflux Pumps in *Pseudomonas aeruginosa*[4-7]

MexAB-OprM*	MexCD-OprJ	MexEF-OprN	MexXY-OprM
Fluoroquinolones	Fluoroquinolones	Fluoroquinolones	Fluoroquinolones
Tetracycline	Piperacillin	Trimethoprim	Aminoglycosides
Chloramphenicol	Cefepime	Chloramphenicol	Piperacillin
Piperacillin	Meropenem		Cefepime
Cefepime			Meropenem
Aztreonam			Tigecycline
Meropenem			
Doripenem			

*Constitutively expressed in virtually all isolates

In 2012, CRE were reported in 4.6 percent of all healthcare facilities (3.9% of short stay, 17.8% of long-term care).[9] CRE can spread rapidly in healthcare settings. Invasive infections with CRE cause a greater than 40 percent mortality rate. Some CRE also frequently possess additional resistance mechanisms beyond the carbapenemases that render them resistant to most antimicrobials and are called pan-resistant CRE.

Until recently, the empiric antibiotic choice for suspected CRE was colistin and a carbapenem. The problem is the high rate of intolerance with colistin. Because of the toxicity, colistin really should not be used anymore, unless absolutely necessary.

A Qualified Infectious Disease Product (QIDP) is an antibacterial or antifungal human drug intended to treat a serious or life-threatening infection. The benefits of QIDP status are an expedited review by FDA and five extra years of marketing exclusivity. Drugs approved thus far as part of the QIDP program include dalbavancin (2014), tedizolid (2014), oritavancin (2014), ceftolozane/tazobactam (2014), ceftazidime/avibactam (2015), and meropenem/vaborbactam (2017). The last three are useful for resistant GNB.

Ceftolozane/tazobactam (Zerbaxa®) has broad-spectrum activity against GNB, including *Pseudomonas aeruginosa* and most ESBL-producing *Enterobacteriaceae,* but has no activity against CRE. Ceftolozane is a novel cephalosporin, whereas tazobactam is a beta-lactamase inhibitor that has been available for several years. In vitro studies show ceftolozane stability against the most common resistance mechanisms driven by mutation in *Pseudomonas aeruginosa* (overexpression of the chromosomal cephalosporinase AmpC, efflux pumps, and porin channel closure). FDA indications of this combination are complicated UTI and complicated intra-abdominal infection (in combination with metronidazole). *Pseudomonas aeruginosa* activity against cefepime, piperacillin/tazobactam, and meropenem-resistant strains occurs.[10,11] Tazobactam adds almost nothing for *Pseudomonas* activity, but it does for other bacteria. The current FDA approved dose is 1.5g Q8h, but higher doses (3g Q8h) have been studied for ventilator-associated penumonia.[12] Treatment of *Pseudomonas* infections and minimizing the development of cross-resistance and conserving activity against MDRO with other antipseudomonal agents are potential advantages of ceftolozane/tazobactam. Based on drug acquisition costs, it is the least expensive of the newer combinations with *Pseudomonas* activity (Exhibit 3).

Ceftazidime-avibactam (Avycaz®) is another new antibiotic combination that is beneficial for GNB infections. The avibactam is the game-changer. Avibactam is a non-beta-lactam, beta-lactamase inhibitor that inhibits Ambler class A, C and some D beta-lactamases, so it works in ESBL, AmpC, OXA-48 type CRE, but has no metallo-beta-lactamase inhibition. It is much more active against *Enterobacteriaceae* compared to ceftazidime alone, and it is approximately four times as active for *Pseudomonas*.[13] This combination is now the first-line therapy for CRE.

Comparison of the two new combos against pseudomonas have found that about 70 percent of isolates of *Pseudomonas* are susceptible to these combinations.[14,15] Resistance to these two combinations is starting to be seen.[16-19] In a retrospective multicenter analysis of ceftolozane/tazobactam use for *Pseudomonas*, clinical success as monotherapy was found in 74 percent of cases; 11

Exhibit 3: Drug to Drug Comparison

	Ceftazidime/avibactam (Avycaz)	Ceftolozane/tazobactam (Zerbaxa)	Meropenem/vaborbactam (Vabomere)
FDA-approval	February 2015	January 2016	August 2017
Manufacturer	Allergan	Merck	The Medicines Company
Novel compound	Avibactam	Ceftolozane	Vaborbactam
FDA-indicated for cIAI	Yes (with metronidazole)	Yes (with metronidazole)	No
FDA-indicated for cUTI	Yes	Yes	Yes
Pseudomonas activity	Yes	Yes	Yes
Carbapenemase-producing Enterobacteriaceae activity (CRE)	Yes	No	Yes
MRSA activity	No	No	No
Usual dose	2.5 grams	1.5 grams	4 grams
Usual frequency	8 hours	8 hours	8 hours
Infusion duration	2 hours	1 hour	3 hours
Renal dose adjustment	CrCl < 50 mL/min	CrCl < 50 mL/min	eGFR < 50 mL/min
Hepatic dose adjustment	No	No	No
Cost per day	**$1,077**	**$310**	**$990**

cIAI = complicated intra-abdominal infection
cUTI = complicated urinary tract infection

percent of the isolates were already nonsusceptible.[16] In eight patients treated with ceftazidime/avibactam for multidrug-resistant infections there was a 50 percent clinical cure. Importantly, mortality is still an issue even with effective treatment; the 30- and 90-day mortality were 12.5 percent and 37.5 percent, respectively. No emergence of resistance was reported, but this was a very small clinical experience.[17] Given that resistance has already developed to these two new agents, appropriate use, like for all antibiotics, is important.

The most recently approved combination under the QIDP program is meropenem/vaborbactam (Vabomere®). Meropenem is a synthetic carbapenem antibacterial drug which has been available for several years, and vaborbactam is a cyclic boronic acid beta-lactamase inhibitor. This combination is effective for *Pseudomonas* and CRE and has similar costs to ceftazidime-avibactam. It is FDA approved for the treatment of patients 18 years of age and older with complicated urinary tract infections (cUTI). Exhibit 3 compares the three combinations discussed.

There are several antibiotics against GNB under investigation. These are a mix of agents in new classes (LpxC inhibitors and mono sulbactam) and old classes (tetracycline, aminoglycoside). Examples include omadacycline and plazomicin.

Conclusion

Multidrug-resistant gram-negative bacteria are increasing and treatment is limited and can be toxic if colistin is still used. There should be a change in the approach of empiric antimicrobial therapy when MDROs are suspected. Colistin should no longer be used. Ceftolozane/tazobactam and ceftazidime/avibactam may be useful for empiric therapy in patients with high risk of MDROs because they both have activity against MDR GNB, including *Pseudomonas aeruginosa*. Ceftazidime/avibactam is also active against CRE that produce Klebsiella

pneumoniae carbapenemases, except for metallo-beta-lactamases. Empiric therapy should be tailored to culture and sensitivity results as soon as possible to prevent overuse of these agents. Antimicrobial stewardship is essential to preserve the activity of these new agents.

Author Bio

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