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Multidrug-Resistant (MDR) Gram-Negative Pathogens

In this Issue...

Multidrug-resistant (MDR) gram-negative organisms are an important and rapidly emerging threat to patients in healthcare settings, and few antimicrobial treatment options remain for patients infected with the most resistant of these pathogens. Recent data shed light on the extent of the MDR gram-negative problem and suggest potential strategies to prevent transmission and improve clinical outcomes.

This issue discusses and examines the epidemiology of MDR gram-negative bacilli as a cause of healthcare-associated infections, recent guidance for control of carbapenemase-producing *Enterobacteriaceae*, risk factors for and clinical impact of carbapenemase-producing *Klebsiella pneumoniae*, and strategies to optimize existing antimicrobial treatment options for multidrug-resistant gram-negative infections.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe the emerging threat of increasing antimicrobial resistance among gram-negative bacteria in healthcare settings.
- Discuss some recommended strategies for the detection and control of MDR gram-negative bacteria transmission within healthcare settings.
- Identify treatment options, including new dosing regimens that may optimize existing antimicrobial therapy for patients infected with MDR gram-negative bacteria.

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- **Sara E. Cosgrove, MD, MS** – has disclosed that she has received grants or research support from Cubist, AdvanDX, and Astellas, and served as a consultant for Theravance/Astellas, Merck, and Forest.

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THIS ISSUE

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Lisa L. Maragakis, MD, MPH, has disclosed no relevant financial relationships.

Unlabeled/Unapproved Uses

The author has indicated that this presentation will include off-label discussion of colistin and meropenem dosing.

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NEWSLETTER ARCHIVE

COMMENTARY

The emergence of extensive antimicrobial resistance among gram-negative bacteria (GNB) poses a serious threat to patients in healthcare facilities. GNB cause a variety of healthcare-associated infections and are particularly problematic in severely ill patients in intensive care units. For decades, multidrug-resistant *Pseudomonas aeruginosa* and GNB producing extended-spectrum β-lactamase (ESBL) enzymes have posed treatment challenges, making the carbapenem class of antimicrobial agents the "drugs of last resort" for patients with these MDR GNB infections. More recently, MDR *Acinetobacter baumannii* has emerged as a formidable threat, with some isolates resistant to all clinically available antimicrobial agents.[1] Resistance to the carbapenems has continued to emerge in MDR *Pseudomonas*, *Acinetobacter* and more recently, among *Enterobacteriaceae* isolates producing carbapenemase-hydrolyzing enzymes (e.g. *Klebsiella pneumoniae* carbapenemases or "KPCs"). Unfortunately, this means that the carbapenem agents are no longer the saviors they used to be for patients with MDR GNB infections.

The study by Kallen and colleagues at the Centers for Disease Prevention and Control (reviewed herein) presents an analysis of the data on three gram-negative pathogens——*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* —— reported to the National Healthcare Safety Network (NHSN) in 2006-2008 as a cause of healthcare-associated infections. While other published reports have presented data on the proportions of various organisms that are resistant to individual antibiotic agents, the Kallen study provides insight into the extent and geographical distribution of gram-negative organisms resistant to <u>multiple</u> antimicrobial classes. Although the NHSN data is not entirely representative of every US healthcare facility, this report sounds an alarm that MDR GNB are relatively common and widespread.

The emergence of carbapenemase-producing *Enterobacteriaceae* over the past several years has also caused great concern. This type of antimicrobial resistance is carried on mobile genetic elements that are transmissible among bacterial species and can therefore spread rapidly.[2] As reviewed herein, the studies by Gasink et al and Hussein et al elucidate the risk factors for colonization and infection with these organisms, including receipt of broad-spectrum antimicrobial agents, severity of illness, and admission to an intensive care unit. The Gasink study also examines the association between these organisms and increased in-hospital mortality. A better understanding of these pathogens is urgently needed in order to prevent and control their spread. In response to this growing threat, the CDC recently issued guidance on the control of infections with carbapenemase-producing *Enterobacteriaceae* in acute care facilities. Although data are lacking on specific infection control precautions and strategies to prevent the spread of MDR GNB, this guidance builds upon the earlier CDC guideline for the control of multidrug-resistant organisms (MDROs) in healthcare settings[3] and offers important recommendations for detection, surveillance, and control of carbapenemase-producing *Enterobacteriaceae*.

Given the present lack of available treatment options for MDR GNB infections, and little anticipated in the future with no candidate agents in the pharmaceutical pipeline, we must optimize our use of the few available antimicrobial agents that remain. Two studies are reviewed herein that aim to use pharmacokinetic (PK) and pharacodynamic (PD) data to define more effective dosing regimens for existing antimicrobial agents to enhance clinical efficacy of the drugs in the face of antimicrobial resistance. Colistin, a polypeptide antibiotic initially introduced in the 1960's, but fallen from favor due to its toxicity profile, has been increasingly used in the last few years as one of the last lines of defense against the most resistant GNB infections. Little is known, however, about the PK/PD properties of colistin.[4] The study by Plachouras and colleagues presents important new data on the pharmacokinetics of colistin in a population of critically ill patients. Their analysis suggests that usual colistin dosing regimens may be inadequate and that new dosing regimens may be required to achieve therapeutic drug levels for MDR gram-negative infections. In a similar vein, the study by Roberts and colleagues examines current dosing regimens of meropenem, a carbapenem agent used to treat patients with MDR GNB infections, which may also be sub-optimal. These investigators found substantially higher plasma and tissue concentrations of the antibiotic when it was administered by extended or continuous infusion rather than by intermittent boluses, which may be an important consideration, especially when treating patients with severe GNB infections.

Infections due to MDR gram-negative bacteria now pose a serious threat to patients at many institutions and they will certainly be an increasingly encountered challenge to healthcare providers. Data and guidance published in the past year shed some light on the extent of the problem, providing important new information on improved methods of detection and control of transmission of these organisms, risk factors for and clinical impact of these infections, and potential strategies to optimize the few remaining antimicrobial treatment options. While this information should help healthcare providers recognize and combat these emerging pathogens, much further work is needed to elucidate ways to prevent, contain and treat MDR GNB infections.

Commentary References

1. Maragakis LL, Perl TM. Acinetobacter baumannii: epidemiology, antimicrobial resistance, and treatment options. *Clin Infect Dis.* 2008;46(8):1254-1263.
2. Schwaber MJ, Carmeli Y. Carbapenem-resistant Enterobacteriaceae: a potential threat. *JAMA.* 2008;300(24):2911-2913.
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MDR GRAM-NEGATIVE HEALTHCARE-ASSOCIATED INFECTIONS

Kallen AJ, Hidron AI, Patel J, Srinivasan A. **Multidrug Resistance among gram-negative pathogens that caused healthcare-associated infections reported to the National Healthcare Safety Network, 2006-2008.** *Infect Control Hosp Epidemiol.* 2010;31(5):258-532.

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The Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) is a national surveillance system that collects data from healthcare settings, including data regarding healthcare-associated infections.[1] Antimicrobial-resistant gram-negative bacilli are an emerging threat in the healthcare setting; they cause important infections such as pneumonia, wound and bloodstream infections, which are extremely difficult to treat given extensive antimicrobial resistance and few remaining treatment options. Kallen and colleagues evaluated NHSN data from January 2006 through December 2008 to determine the proportion of healthcare-associated *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* isolates that were multidrug-resistant (defined by the investigators as either 3-class resistant or 4-class resistant to the penicillin, cephalosporin, carbapenem, fluoroquinolone, and aminoglycoside antimicrobial classes).

The study evaluated 13,003 gram-negative isolates reported to the NHSN as the causative agent of a central-line associated bloodstream infection, ventilator-associated pneumonia, catheter-associated urinary tract infection, or surgical site infection. The majority of isolates (67%) were seen in an intensive care unit setting. Of 6,489 isolates of *Pseudomonas aeruginosa*, 676 (10%) were found to be 3-class resistant. Of 4,527 isolates of *Klebsiella pneumoniae*, 679 (15%) were found to be 3-class resistant. A much larger proportion, 60% (1201 of 1987) of *Acinetobacter baumannii* isolates were resistant to at least 3 antimicrobial classes. Study results were not significantly different when large contributor facilities were excluded from the analysis. Antimicrobial-resistant gram-negative isolates were reported by at least 37 states. While the Northeast region reported the most multidrug resistance, all US regions reported antimicrobial resistant gram-negative isolates. Some differences in the proportions of MDR isolates causing each type of healthcare-associated infection were seen among the three pathogens. For instance, approximately 50% of the reported MDR *Acinetobacter baumannii* isolates caused ventilator-associated pneumonia while only 16% caused catheter-associated urinary tract infection. These proportions were reversed for MDR *Klebsiella pneumoniae*. Overall, MDR gram-negative pathogens were most prevalent as a cause of ventilator-associated pneumonia and least prevalent as a cause of surgical site infection.

The authors concluded that gram-negative antimicrobial resistance was relatively common and widespread in the US during the study period. The MDR gram-negative pathogens were not limited to large healthcare facilities or to any particular geographical region. Though less common than 3-class resistance, isolates with 4-class resistance were also seen in significant numbers and across regions. The widespread gram-negative antimicrobial resistance reported in this study is alarming because so few treatment options remain for patients with these infections and few new therapeutic options are currently in development. The authors note that the 4-class resistant isolates are analogous to "extensively drug-resistant" (or XDR strains) of other pathogens such as tuberculosis. Clearly this XDR level of antimicrobial resistance calls for urgent measures to prevent transmission in order to protect patients from acquiring these organisms. Study limitations include that data was provided only by facilities reporting to NHSN and so may not truly represent a cross-section of all US healthcare facilities, and that antimicrobial testing was performed at each reporting facility and was therefore not standardized. No antimicrobial susceptibility data was available for other antimicrobial agents such as colistin and tigecycline.

References

1. Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. *Am J Infect Control*. 2009;37(10):783-805.

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CONTROL OF CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

Guidance for control of infections with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae in cute are facilities *MMWR Morb Mortal Wkly Rep* 2009;58(10);256-260.

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Some bacteria from the *Enterobacteriaceae* family (e.g. *Klebsiella* spp, *Enterobacter* spp) commonly cause a wide range of infections in humans. These bacteria have become increasingly resistant to available antimicrobial agents over the past three decades, such that the carbapenem class of antimicrobials is one of the few remaining treatment options for many of these infections.[1] Increasing resistance to even the carbapenems has been rising among *Enterobacteriaceae* isolates, due in large part to the acquisition of β-lactamase hydrolyzing enzymes called carbapenemases. This type of antimicrobial resistance is of particular concern because the genes encoding the carbapenemase enzymes are contained on transmissible plasmids that carry a wide array of antimicrobial resistance genes which can be readily transferred among bacterial species.[1] In response to this emerging threat, the Centers for Disease Control and Prevention issued guidance for acute care healthcare facilities on appropriate control measures for carbapenemase-producing *Enterobacteriaceae*.

An earlier guideline, issued in 2006 by the CDC Healthcare Infection Control Practices Advisory Committee (HICPAC) puts forth evidence-based recommendations for the management of multidrug-resistant organisms (MDRO) in healthcare settings,[2] and forms the foundation for the current CDC recommendations that are specific to carbapenemase-producing *Enterobacteriaceae*. Appropriate laboratory detection of carbapenemase-producing *Enterobacteriaceae* is one especially important area that this guidance addresses. Detection of these organisms is complicated by the fact that they may appear to be carbapenem-susceptible on routine testing and therefore go unnoticed. These unrecognized patients colonized or infected with the organisms then become a reservoir for potential transmission to other patients. Correct identification of carbapenemase-producing *Enterobacteriaceae* requires that laboratories perform additional phenotypic testing, such as the modified Hodge test (MHT), for isolates that have elevated minimum inhibitory concentrations for carbapenems. Complete testing recommendations were updated in a recent Clinical and Laboratory Standards Institute (CLSI) guidance issued in January 2009.[3] Appropriate detection of these organisms will allow measures to be taken to prevent patient-to-patient transmission.

The current CDC guidance calls for acute care facilities to utilize the CLSI guidelines for detection of carbapenemase-producing *Enterobacteriaceae*, and recommends that healthcare facilities manage all colonized or infected patients with contact precautions (e.g. gowns and gloves for patient care). In addition, the guidance recommends that facilities review microbiological results for the preceding year to look for previously unrecognized carbapenemase-producing *Enterobacteriaceae*. If any previously unrecognized cases are found, facilities are advised to perform point-prevalence culture surveys in high-risk units to look for additional cases. Ongoing surveillance of microbiology results and investigation of possible transmissions by active surveillance cultures is also recommended.

This guidance is important because it puts forth an aggressive infection control strategy to identify and contain the spread of these highly resistant gram-negative pathogens. However, for most facilities, implementation of the guideline will require additional resources for new microbiological testing protocols, infection control surveillance activities, point-prevalence surveys, isolation precautions, and other strategies to combat this growing threat.

References:

1. Schwaber MJ, Carmeli Y. Carbapenem-resistant Enterobacteriaceae: a potential threat. *JAMA.* 2008;300(24);2911-2913.
2. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in health care settings, 2006. *Am J Infect Control.* 2007;35(10 Suppl 2):S165-93.
3. Clinical and Laboratory Standards Institute. 2009 performance standards for antimicrobial susceptibility testing. *Nineteenth information supplement (M100-S19).* Wayne, PA: Clinical and Laboratory Standards Institute;2009.

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KPCS: RISK FACTORS AND CLINICAL IMPACT

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

Gasink LB, Edelstein PH, Lautenbach E, Synnestvedt M, Fishman NO. **Risk factors and clinical impact of Klebsiella pneumoniae carbapenemase-producing K. pneumoniae.** *Infect Control Hosp Epidemiol.* 2009;30(12):1180-1185.

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Hussein K, Sprecher H, Mashiach T, Oren I, Kassis I, Finkelstein R. **Carbapenem resistance among Klebsiella pneumoniae isolates: Risk factors, molecular characteristics, and susceptibility patterns.** *Infect Control Hosp Epidemiol.* 2009;30(7):666-671.

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Klebsiella pneumoniae is a common cause of healthcare-associated infections and has been a problem gram-negative pathogen for decades due to production of extended-spectrum β-lactamase enzymes (ESBLs) that confer resistance to all β-lactam antimicrobial agents (except cephamycins and carbapenems). More recently, the organism has increasing resistance to these classes of antimicrobial agents as well, due to production of the class A carbapenemase enzymes that have been named after it, termed "*Klebsiella pneumoniae* carbapenemases" (KPCs). Hussein and colleagues in Israel, and Gasink and colleagues in Pennsylvania, aimed to elucidate the risk factors for and clinical impact of these organisms among hospitalized patients.

In the Hussein article, the investigators conducted a case-control study comparing 88 patients with carbapenem-resistant *K. pneumoniae* infection to 373 control patients with carbapenem-susceptible *K. pneumoniae* infection. They found that prior treatment with fluoroquinolones (OR=1.9,95% CI 1.07-3.26; P=.026), receipt of carbapenems (OR=1.8,95% CI 1.02-3.27; P=.042), and admission to an ICU (OR=4.27, 95% CI 2.49-7.31; P<.001) were significant risk factors for carbapenem-resistant *K. pneumoniae* infection. In this study, 90% of the tested isolates contained the gene encoding a KPC and almost of the isolates were resistant to all antimicrobial agents except colistin, gentamicin, and tigecycline.

The article by Gasink et al reports on a case-control study comparing 56 case patients infected or colonized with KPC-producing *K. pneumoniae* to 863 control patients with carbapenem-susceptible *K. pneumoniae* . These investigators also conducted a cohort study to evaluate the association between KPCs and in-hospital mortality. On multivariable analysis, they found that severity of illness (adjusted OR=4.31, 95% CI 2.3-8.3;P<.001), prior fluoroquinolone use (adjusted OR=3.39, 95% CI 1.5-7.7;P=.003), and prior extended-spectrum cephalosporin use (adjusted OR=2.6, 95% CI 1.2-5.5;P=.02) were significant risk factors. KPC-producing *K. pneumoniae* was independently associated with in-hospital mortality (adjusted OR=2.3, 95% CI 1.2-4.4;P<.02).

Both groups of investigators concluded that KPC-producing *K. pneumoniae* poses a significant clinical threat to patients, and that effective strategies to prevent transmission and contain this pathogen are urgently needed. Both studies also highlight the need for antimicrobial stewardship, since treatment with broad-spectrum antimicrobial agents was a significant risk factor for acquiring KPCs. However, the retrospective, observational nature of both studies precludes drawing conclusions about causality. In addition, both groups studied patients with carbapenem-susceptible organisms as controls, which can lead to overestimation of the association with antimicrobial agents.[1] Despite these limitations, both articles highlight KPC-producing organisms as important emerging pathogens that require urgent attention to infection control, and antimicrobial stewardship strategies to protect patients in the healthcare setting.

References

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OPTIMIZING TREATMENT OF MDR-GNB INFECTIONS

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

Roberts JA, Kirkpatrick CMJ, Roberts MS, Robertson TA, Dalley AJ, Lipman J. **Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution.** *J Antimicrob Chemother.* 2009;64;142-150.

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Plachouras D, Karvanen M, Friberg LE, at et. **Population Phamacokinetic Analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria.** *Antimicrob Agents Chemother.* Aug 2009;53(8);3430-3436.

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Increasing antimicrobial resistance among gram-negative bacteria means increasing numbers of patients are infected with organisms for which there are few, if any, treatment options. Unfortunately, there are not many new agents in the drug-development "pipeline" to rescue us from this dilemma any time in the near future. This means that we must optimize the way we use the available antimicrobial agents that remain. Colistin, a polypeptide antibiotic developed in the 1960's, is now being used to treat patients with extensively resistant gram-negative infections. Little is known, however, about its pharmacokinetic (PK) and pharmacodynamic (PD) properties, or optimal dosing for these infections.

Plachouras and colleagues aimed to characterize the PK parameters of colistin in a population of critically ill patients with MDR gram-negative infections. The investigators administered the intravenous form of colistin methanesulfonate (CMS) at a dose of 3 million units every 8 hours, measured plasma CMS and colistin concentrations, and performed population PK analysis. In the second study, Roberts and colleagues aimed to compare plasma and subcutaneous tissue levels of meropenem when administered by intermittent bolus versus extended or continuous infusion methods in order to recommend ways to optimize dosing regimens against resistant gram-negative infections.

In the Plachouras study, investigators found that the estimated half-life of colistin was 14.4 hours and the predicted maximum plasma concentrations were 0.60 mg/liter after the first dose and 2.3 mg/liter at steady state. The authors concluded that the initial plasma level of colistin was insufficient and well below the minimum inhibitory concentration breakpoint of 2.0 mg/liter for gram-negative pathogens, and that it remained so for several days until a steady state is reached. Even at steady state, the plasma levels in this study were found to be below some MDR gram-negative organism breakpoints. The prolonged time at low plasma levels of colistin essentially delays initiation of appropriate antimicrobial therapy, which can lead to increased mortality in critically ill patients. From these data, the authors concluded that current colistin dosing regimens may be inadequate and suggested that a 9-12 million unit colistin loading dose followed by 4.5 million units every 12 hours may help achieve therapeutic concentrations faster to optimize colistin therapy. This is analogous to a similar circumstance seen years ago with aminoglycoside agents, for which under dosing due to concern for toxicity resulted in increased mortality among critically ill patients with gram-negative bacteremia.[1]

In the meropenem study, Roberts and colleagues found that all three methods of administration——intermittent bolus, extended infusion, and continuous infusion—— achieved plasma and subcutaneous target levels against gram-negative pathogens. However, extended or continuous infusions led to higher plasma and tissue concentrations than intermittent dosing. The authors concluded that meropenem administration by extended or continuous infusion may help to optimize use of this antimicrobial agent against gram-negative infections with reduced antimicrobial susceptibility.

Both the Plachouras and Roberts studies are important because they illustrate ways that currently available antimicrobial agents may be optimized to improve therapy of patients with MDR gram-negative infections. More investigation is needed to determine if the dosing regimens suggested by these studies lead to improved clinical outcomes.

References

1. Moore RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. *J Infect Dis.* 1984;149(3):443-448.

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