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VOLUME 2 — ISSUE 8: TRANSCRIPT

Featured Cases: Multidrug-Resistant (MDR) Gram-Negative Pathogens

Our Guest Author is Lisa L. Maragakis, MD, MPH, Assistant Professor of Medicine Division of Infectious Disease at the Johns Hopkins University School of Medicine.

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

- Describe the risk factors and outcomes associated with multiple drug-resistant (MDR) *Acinetobacter baumannii* infections
- Explain the importance of controlling the source of completed infections, in conjunction with antibiotic selection, to prevent clinical failures and the emergence of antimicrobial resistant
- Discuss the clinical rationale for considering the use of extended infusion of beta-lactam antibiotics when treating MDR gram-negative infections

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to Multidrug-Resistant (MDR) in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 2, Issue 7 eInfections Review newsletter — [Multidrug-Resistant \(MDR\) Gram-Negative Pathogens](#).

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Unlabeled/Unapproved Uses: The author has indicated that this presentation will include off-label discussion meropenem infusion and dosing.

Faculty Disclosure

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

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MR. BOB BUSKER: Welcome to this *eInfections Review*[™] podcast.

eInfections Review[™] is presented by The Johns Hopkins University School of Medicine. This program is supported by an educational grant from AstraZeneca, Cubist Pharmaceuticals, and ViroPharma, Inc.

Today's program follows-up on our May 2010 newsletter topic: Multidrug-Resistant Gram Negative Pathogens.

Our guest is Dr. Lisa Maragakis from Johns Hopkins University.

This activity has been developed for primary care physicians, internists and infectious disease specialists caring for patients with infectious disease conditions. There are no fees or prerequisites for this activity.

The accreditation and credit designation statements can be found at the end of this podcast. For additional information about accreditation, Hopkins policies, expiration dates and to take the post-test to receive credit online, please go to our website newsletter archive, www.einfectionsreview.org, and click on the June 2010 podcast link.

Learning objectives for this program are that at the conclusion of this audio activity, participants should be better able to:

- Describe the risk factors and outcomes associated with multiple drug resistant *Acinetobacter baumannii* infections
- Explain the importance of controlling the source of complicated infections, in conjunction with antibiotic selection, to prevent clinical failures and the emergence of antimicrobial resistance, and
- Discuss the clinical rationale for considering the use of extended infusion of beta-lactam antibiotics when treating MDR gram-negative infections.

I'm **BOB BUSKER**, Managing Editor of *eInfections Review*. On the line we have with us Dr. Lisa Maragakis, Assistant Professor of Medicine in the Division of Infectious Disease at the Johns Hopkins University School of Medicine in Baltimore, Maryland.

Dr. Maragakis has disclosed that she has no relevant financial relationships with commercial supporters, and that her presentation today will include the off-label discussion of meropenem infusion and dosing.

Dr. Maragakis, welcome to this *eInfections Review* podcast.

DR. LISA MARAGAKIS: Thank you, Bob, it's my pleasure to be here today.

MR. BUSKER: To help us expand our understanding of multiple drug-resistant gram-negative pathogens, we've asked Dr. Maragakis to describe some typical case scenarios. So if you would, Dr. Maragakis.

DR. MARAGAKIS: Our first case is one of a 32 year old man with paraplegia caused by a remote gunshot wound. He is dependent upon mechanical ventilation. The patient is admitted to an acute-care hospital because of hypotension, increased oxygen requirements and sepsis. He transferred to the hospital from a long-term care facility, where he was on mechanical ventilation and was receiving wound care for a stage IV sacral decubitus ulcer. He also has a central venous catheter in place because of a recent course of broad-spectrum antibiotics for osteomyelitis.

On admission, the blood pressure is 60/40 and the chest x-ray showed multi-lobar consolidation consistent with pneumonia. The patient was treated with mechanical ventilation, oxygen, blood pressure support, and a carbapenem antibiotic agent. Blood and sputum cultures grow multidrug-resistant *Acinetobacter baumannii*, susceptible only to carbapenem antibiotics and colistin.

MR. BUSKER: Let's focus first on risk factors, and let me start out by asking you about some of the pertinent risk factors for MDR, *Acinetobacter*, that this case illustrates.

DR. MARAGAKIS: This case highlights several of the associated risk factors for multidrug-resistant *Acinetobacter* and multi-drug resistant gram-negative bacteria, in general. These include prior exposure to health-care settings — in this case, prior exposure to a long-term care facility — and we believe probably a prior hospitalization because of the patient's history of osteomyelitis.

Other exposures to a health-care setting like dialysis or home care might also be important. Patients with severe underlying and chronic illnesses are also at risk of acquiring these organisms.

I think the case also illustrates two common health-care-associated infections that are frequently caused by these multidrug-resistant gram-negative bacteria, in this case central-line associated bloodstream infection and a ventilator-associated pneumonia.

Multidrug-resistant gram-negatives are prominent causes of both of these infections, and the presence of mechanical ventilation and a central venous catheter are both portals of entry for these bacteria and risk factors for these infections.

This case also shows that prior treatment with broad-spectrum antibiotics is a risk factor. This can lead to emergence of antimicrobial resistance and is a risk factor for acquiring these organisms. Finally, this case demonstrates that chronic wounds are also a risk factor, and patients with underlying severe illnesses and chronic wounds are often colonized with a variety of bacteria that may include these multidrug-resistant gram-negative organisms.

The colonization itself should not be treated with antibiotics, but colonization is a risk factor for proceeding to invasive infections. I think this case is important because it shows the increasing antimicrobial resistance that is seen among the gram-negative bacteria. Fortunately, in this patient the organism was susceptible to carbapenem agents, but others are really not so fortunate.

MR. BUSKER: The possible mechanisms that led to pneumonia and sepsis in this patient, what might those be?

DR. MARAGAKIS: There are several possible explanations. The multidrug-resistant *Acinetobacter*, either from this patient's own colonization or by transmission from another patient, may have contaminated the central line and caused a primary bloodstream infection.

It is also possible to imagine that the patient's colonization of the infected sacral decubitus wound might have directly entered the bloodstream and caused the bloodstream infection.

MR. BUSKER: All right, that would explain the sepsis, but where would the pneumonia have likely come from?

DR. MARAGAKIS: That's right, Bob, it explains the bloodstream infection, but not the pneumonia, and that's why I think in this patient it's most likely that multidrug-resistant *Acinetobacter*, again, either from inherent colonization or transmission from another patient, contaminated the endotracheal tube and caused a ventilator-associated pneumonia, which then led to a secondary bacteremia and sepsis.

In fact, we found that some types of wound care, such as pulsatile lavage debridement, can disperse pathogens in droplets that can be inhaled by patients and cause pneumonia.

MR. BUSKER: Talk to us, if you would, about the risks MDR *Acinetobacter* poses to this and other patients.

DR. MARAGAKIS: The crude mortality of this organism is very high. Estimates range anywhere from 26 to 68 percent. It's more difficult to know what the attributable mortality is, but MDR *Acinetobacter* infections are clearly associated with at least a two- to six-fold elevated risk of mortality and an estimated five to 13 additional days in the hospital.

As far as risk to other patients, this patient is a reservoir for potential transmission to other patients in the long-term care facility and in the intensive care unit in the hospital. Hand hygiene, contact-isolation precautions, cleaning and disinfection of the environment, and disinfection of equipment, are all essential to preventing this kind of spread.

MR. BUSKER: Just to round out this part of our discussion, what are some of the other types of resistant gram-negative bacteria that are clinically important?

DR. MARAGAKIS: I think there are five major types of multidrug-resistant gram-negative organisms with which we're dealing now. As illustrated in this case, multidrug-resistant *Acinetobacter* is one of them. For some time in the health-care setting, multidrug-resistant *Pseudomonas* has also been a problem.

The third category that has been problematic over the last several decades includes bacteria that produce ESBLs, or extended-spectrum beta-lactamases. These usually occur in *Klebsiella* species and *E. coli*.

We also have to contend with gram-negative bacteria that harbor an inducible AmpC beta-lactamase. This mechanism of resistance is important in *Enterobacter* species, as well as *Citrobacter*, and *ceracea* and others.

Finally, more recently, we are contending with carbapenemase-producing *Enterobacteriaceae*. These are organisms that produce enzymes that can hydrolyze some of our best antimicrobial agents, the carbapenems. They were first identified in *Klebsiella* species, and they are also seen in other species such as *Enterobacter*.

MR. BUSKER: I would like us to get a little deeper into the idea of source control, so if you would, Doctor, please present our next case.

DR. MARAGAKIS: All right, the second case is of a 40-year old diabetic, obese woman, who underwent elective bypass surgery for weight control. The abdominal surgical wound dehiscenced several weeks later, and imaging showed a surgical-site infection, as well as numerous intra-abdominal abscesses.

Over the ensuing several months the patient underwent multiple subsequent surgeries for resection of ischemic bowel and to drain the abscesses. She was also treated with broad-spectrum antibiotics, including third-generation cephalosporins, piperacillin, tazobactam, carbapenem, aminoglycosides, and colistin for the abscesses, as well as for recurrent bouts of bacteremia and sepsis.

Cultures of the wound, abscesses, and blood grew multiple organisms including *Enterobacter cloacae* and an *E. coli* that produced ESBL at various times during the hospital course. Increasing antimicrobial resistance was noted in these organisms over the course of the hospitalization.

MR. BUSKER: Talk to us about the pertinent factors about this case regarding source control, if you would.

DR. MARAGAKIS: I think this case is important because it illustrates the importance of controlling the source of infection. Lack of source control can lead to emergence of antimicrobial resistance, especially when patients are on long-term therapy with antibiotics. That happens because of continued replication of the bacteria in the presence of antimicrobial agents. That is why we really emphasize the importance of surgical debridement and control

of the source of infection when treating complicated infections. Antibiotics alone just can't get the job done.

Emergence of antimicrobial resistance caused by selective pressure from exposure to broad-spectrum antibiotics means that we really must choose and use antibiotics very carefully to avoid this phenomenon.

MR. BUSKER: This patient showed ESBL *E. coli*. What are some of the things clinicians should consider when selecting an antibiotic to treat these kinds of infections?

DR. MARAGAKIS: One of the main considerations must be that the extended spectrum beta-lactamase confers resistance to all penicillins, cephalosporins, and aztreonam. So that's very extensive antimicrobial resistance.

Fortunately, current microbiology testing guidelines from the Clinical Laboratory Standards Institute, CLSI, require that labs detect and report products of ESBL enzymes. ESBL-producing enzymes can appear to be susceptible to piperacillin and tazobactam, but remember, this agent is not a good therapeutic choice because of the production of the ESBL-mediated resistance. In this case, the beta-lactamase inhibitor, tazobactam, may not be able to overcome this type of beta-lactamase, especially in deep, complicated infections.

This means really that carbapenem agents are the drugs of choice for ESBL infections. I also wanted to note that CLSI testing guidelines are currently being revised. So we should watch for new testing and reporting algorithms on the horizon that may complicate this picture.

MR. BUSKER: What about infections caused by organisms like *Enterobacter cloacae*? What should the clinician consider when selecting an antibiotic to treat those?

DR. MARAGAKIS: The concern here is emerging resistance related to an inducible AmpC beta-lactamase enzyme. Production of AmpC beta-lactamase enzymes can be induced, particularly in *Enterobacter* species, also in *ceracea* and *Citrobacter* and others, in the presence of third-generation cephalosporin antibiotics. This may also apply to cefepime, but there are fewer data here.

Clinically, this means that isolates initially appear to be susceptible to the third-generation cephalosporins on susceptibility testing. They also appear to be susceptible to cefepime, but then they may show resistance if these agents are used. Therefore, in general, we should avoid third-generation cephalosporins and probably cefepime, too, and choose other agents such as quinolone agents or carbapenems when treating infections caused by these organisms, especially if there is a deep-seated infection and poor source control, like this example of intra-abdominal abscesses.

Severe multidrug-resistant gram-negative infections, including those caused by organisms that produce ESBL, carbapenamases and AmpC beta-lactamases are best managed with the help of an infectious diseases specialist, in my opinion.

MR. BUSKER: What are the risks that these infections pose to patients like the one we've been talking about, as well as other patients in the ward?

DR. MARAGAKIS: Like the multi-drug resistant *Acinetobacter*, the mortality in cases like this is exceedingly high. Like the previous case or any involving multidrug-resistant organisms, the patient represents a reservoir of potential transmission to other patients, especially if infection-control practices are not followed precisely. And the long duration of hospitalization that most of these patients endure amplifies the risk of transmission and offers more opportunities to transmit the organism.

MR. BUSKER: We'll return in a moment with Dr. Maragakis from Johns Hopkins.

DR. PAUL AUWAERTER: Hello, I'm Dr. Paul Auwaerter, from the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. I'm one of the program directors for eInfections Review.

eInfections Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews current literature in areas of importance to infectious disease specialists, primary care physicians, and other clinicians caring for patients with infectious diseases.

These podcasts, which are also available as downloadable transcripts, provide case-based

scenarios to help bring new information into practice in both the exam room and at the bedside.

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MR. BUSKER: Welcome back to our June 2010, eInfections Review podcast. I'm Bob Busker, Managing Editor of eInfections Review. My guest is Dr. Lisa Maragakis, Assistant Professor at the Johns Hopkins University School of Medicine, and our topic is multidrug-resistant gram-negative pathogens.

We've been bringing the data presented in our May 2010 newsletter into clinical practice via case scenarios. So if you would, Dr. Maragakis, let's continue with another case.

DR. MARAGAKIS: This case is of a 60-year-old man with a history of a renal transplant and numerous hospitalizations for management of rejection. The patient is transferred from one hospital to another for management of ventilator associated pneumonia and sepsis. Cultures of sputum and blood grow multidrug-resistant *Klebsiella pneumoniae* resistant to many antimicrobial classes but susceptible to carbapenem agents.

He is treated with meropenem, an antimicrobial from the carbapenem class of agents, but the patient does not respond to therapy as expected and remains gravely ill.

MR. BUSKER: What are some of the important factors about this case?

DR. MARAGAKIS: This case also illustrates prior health-care exposure and invasive procedures and devices as risk factors for multidrug-resistant gram-negative organisms.

This case is important because the patient is not responding as expected to the antimicrobial agent that was chosen based on routine culture and susceptibility results.

There could be other explanations for this failure of clinical response, but in this case it is likely that additional phenotypic testing in the microbiology lab would identify the *Klebsiella* isolate as a carbapenemase producing *Enterobacteriaceae*, for example, a KPC producer that is actually resistant to the carbapenem agent that is being used for therapy.

MR. BUSKER: Help us out with a definition here, what is meant by carbapenemase-producing *Enterobacteriaceae*?

DR. MARAGAKIS: Well, Bob, organisms of the *Enterobacteriaceae* family such as *Klebsiella* and *Enterobacter* species, can produce carbapenemase enzymes that are capable of hydrolyzing carbapenem antibiotics. This, unfortunately, confers resistance to all penicillins, cephalosporins, carbapenems, and aztreonam.

Some of these enzymes are termed KPCs, named for the first identified enzyme in *Klebsiella pneumoniae*, but the KPCs in other carbapenemase enzymes are highly transmissible and can appear in many bacterial species.

MR. BUSKER: Thank you. I think a logical question is, why wasn't this level of resistance detected by routine susceptibility testing?

DR. MARAGAKIS: The carbapenemase-producing *Enterobacteriaceae* can initially appear susceptible to carbapenem agents on routine testing, but they usually give us some clue by having elevated minimum inhibitory concentrations, or MICs, or reduced disk-diffusion zone sizes on susceptibility testing. That can be a clue that additional phenotypic testing is required to detect the production of the carbapenemase enzymes.

CLSI recommends a phenotypic test, the Modified Hodge test, for isolates with elevated carbapenem MICs.

MR. BUSKER: What can you tell us about the CDC's recent recommendations regarding control of these organisms in acute-care facilities?

DR. MARAGAKIS: The CDC is very concerned about transmission and spread of these emerging pathogens. They recommended several things. First, that clinical microbiology labs follow the CLSI

guidelines for testing and detecting these organisms using phenotypic tests like the Modified Hodge test.

Institutions are also advised to review at least six to 12 months of microbiology data, looking for previously unrecognized cases and to use contact-isolation precautions for any patients who are infected or colonized with these organisms.

The CDC also recommends performing active surveillance cultures and point-prevalence culture surveys in high-risk units and in any patients who have epidemiologic links to identified cases of carbapenemase-producing *Enterobacteriaceae*.

MR. BUSKER: I would like us to focus now on extended infusion of beta-lactam antibiotics. So if you would, Dr. Maragakis, please take us to another case.

DR. MARAGAKIS: This is a case of a 72-year old man in the intensive care unit after repair of an abdominal aortic aneurysm. The patient develops severe ventilator-associated pneumonia, and sputum cultures grow multidrug-resistant *Pseudomonas aeruginosa* with an intermediate susceptibility to meropenem and amikacin, but resistant to all other clinically available antibiotics.

MR. BUSKER: Given the extensive resistance of this pathogen, what antimicrobial treatment options are left for this patient?

DR. MARAGAKIS: Two of the only options that are left are carbapenem agents and aminoglycosides. And given that both of these are only in the intermediate category, I would suggest using a combination of carbapenem and aminoglycoside, both at traditional dosing regimens.

You could also escalate and treat the patient with colistin and verify that the organism was susceptible by additional susceptibility testing in the lab.

Finally, a combination of carbapenem and aminoglycoside agents could be used, but using an extended infusion of the meropenem to optimize use of this agent. An example would be giving 2 grams intravenously every eight hours, but infusing it over three hours instead of a more traditional 30 minutes.

MR. BUSKER: Talk to us now, if you would, about the rationale for considering extended or continuous infusion of beta-lactam antibiotics.

DR. MARAGAKIS: Beta-lactam antibiotics are time-dependent agents. That means they are most effective when the concentration of drug is kept above the MIC of the infecting pathogen. Bacteria resume multiplying when their concentration falls below the MIC of the organism.

Physiologic changes and invasive interventions in severely ill patients can actually lead to lower drug concentrations, and elevated MICs of multidrug-resistant pathogens further compromise the effectiveness of normal dosing regimens.

So the idea of extended or continuous infusion aims to optimize the pharmacokinetic and pharmacodynamic parameters of the antibiotic agent. In this case we're trying to achieve higher trough concentrations and increase the time spent above the MIC of the organism by infusing the meropenem over a longer time period.

MR. BUSKER: In what circumstances should a clinician consider an extended or continuous infusion strategy?

DR. MARAGAKIS: This strategy can be considered in seriously ill patients who have severe infections with multidrug-resistant gram-negative organisms. This can be considered particularly when the MIC of the pathogen is elevated to the only available antimicrobial agent, and the strategy should be considered when there is concern about how effectively the antibiotic can penetrate to the infected tissue.

For example, it is harder to achieve target drug levels in a peritoneal exudate than it might be in serum for a bloodstream infection.

MR. BUSKER: What might the potential downsides of this strategy be?

DR. MARAGAKIS: Several things have to be considered. The first thing is chemical stability of the infused agent. Some agents, like imipenem, have limited chemical stability at room temperature and are really not amenable to this strategy.

Infusion of the agent over a long period of time also occupies venous access for a longer period of time, and this can potentially complicate administration of fluids or other medication. So implementing the strategy requires

excellent communication and coordination among treating physicians, nursing staff, and the pharmacy to assure that everything happens as planned, without unintended complications.

MR. BUSKER: From your clinical experience, Dr. Maragakis, is there anything else to note about the treatment of MDR *Pseudomonas* infections?

DR. MARAGAKIS: I think another thing to mention is the concept of double coverage of gram-negative infections, or treating these serious infections with two or more antimicrobial agents. There are no data that this is an effective strategy, and that's concerning because it leads to more antimicrobial use and potentially more resistance. But for these extensively MDR *Pseudomonas* infections with few treatment options, extended beta-lactam therapy is best combined with an aminoglycoside agent or with colistin to improve the chances for clinical success.

I would also call to mind that tigecycline has offered some therapeutic options for some MDR gram-negative infections, but we have to remember that it does not have activity against *Pseudomonas*.

MR. BUSKER: I think we have time to discuss one more case, so if you would, Doctor.

DR. MARAGAKIS: An otherwise healthy 38-year old woman presents to an outpatient clinic with signs and symptoms of a urinary tract infection. She is empirically treated with oral trimethoprim sulfamethoxazole and urine is sent for culture.

The urine culture grows multidrug-resistant ESBL-producing *E. coli* resistant to trimethoprim sulfa, fluoroquinolones, cephalosporins, and piperacillin, and tazobactam. The organism is susceptible only to carbapenem agents and aminoglycosides.

MR. BUSKER: Talk to us about the antimicrobial treatment options for a patient with such an extensively resistant pathogen.

DR. MARAGAKIS: It is important to note that this is an otherwise healthy outpatient woman with a relatively common mild urinary tract infection, and the prospect of having only intravenous carbapenem antibiotics as a treatment option for this woman's urinary tract infection is a frightening scenario of the future of emerging multidrug resistance among gram-negative bacilli.

I would say we have to remember in this case to consider oral fosfomycin, which still does have activity against many of these multidrug-resistant gram-negative bacteria. Fosfomycin is a synthetic broad-spectrum bactericidal agent, it has in vitro activity against many gram positive and gram-negative bacteria; it does not have activity, though, against *Acinetobacter*.

In the United States fosfomycin is only available in an oral formulation and it has convenient one-time dosing, but we do need to remember it only achieves adequate concentrations in the urine, so it is only for treatment of UTI. The dose in this case would be 3 grams, or one sachet orally once, and you could repeat it if there were a complicated infection and request susceptibility testing for fosfomycin to confirm that the organism was susceptible.

The other options are somewhat limited or not very pleasant. An aminoglycoside can be given intramuscularly, for example, 80 milligrams twice a day or three times a day for the three days of therapy. Ertapenem can also be administered intramuscularly. Outside of these agents, the last resort would be to place a central venous catheter to administer intravenous carbapenem or aminoglycoside for this patient's outpatient urinary tract infection.

MR. BUSKER: Dr. Lisa Maragakis, Assistant Professor, Division of Infectious Diseases at the Johns Hopkins University School of Medicine in Baltimore, thank you for participating in this eInfections Review podcast.

DR. MARAGAKIS: You're welcome, Bob, it was my pleasure. Thank you.

MR. BUSKER: This podcast is presented in conjunction with eInfections Review newsletter, a peer-reviewed CME accredited literature review emailed monthly to clinicians treating patients with infectious diseases.

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