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A Debate on Dosing Considerations: Perspectives on Antimicrobials

Dr. Turck:
Critically ill patients suffering from infectious disease require unique approaches to all aspects of care, including medication dosing. So, how might we optimize antimicrobial dosing to improve care for these patients?

Welcome to the *IDSA Action Center* on ReachMD. I'm your host, Dr. Charles Turck. And joining us to talk about dosing considerations in infectious disease are Drs. Fatima Adhi and Mei Chang, both of whom recently spoke at IDWeek 2022. Dr. Adhi is an intensivist and infectious diseases specialist. She's also an Assistant Professor of Medicine at Baylor College of Medicine.

Dr. Adhi, welcome to the program.

Dr. Adhi:
Thank you so much for having me, Dr. Turck.

Dr. Turck:
And Dr. Mei Chang is a Clinical Pharmacy Manager of Infectious Diseases at the Montefiore Medical Center at the Weiler Division Einstein Campus.

Dr. Chang, thanks for being here today.

Dr. Chang:
It's my pleasure to be here. Thank you for inviting us.

Dr. Turck:
So, Dr. Chang, let's start by looking at patients undergoing renal replacement therapy, or RRT. What are the different forms of RRT? And are there any risks that need to be considered when patients undergoing RRT are prescribed antimicrobials?

Dr. Chang:
Sure. Other than the traditional intermittent three-times-a-week hemodialysis that many of us are familiar with, renal replacement therapy can also be applied as continuous, prolonged, intermittent, or through a peritoneal dialysis. So depending on the mode of renal replacement therapy, antibiotic molecules can be filtered and removed at different amounts and rates. The greatest risk to consider when patients are on renal replacement therapy is the possibility of underdosing antibiotics, particularly in septic patients with serious difficult-to-treat infections.

Dr. Turck:
And if we focus on one type of RRT in particular, continuous renal replacement therapy, or CRRT, what do we need to know about that? Are there any key considerations we should keep in mind when administering antibiotics to patients who are receiving CRRT specifically?

Dr. Chang:
Yes. So CRRT is expected to remove more antibiotics than all the other modes of renal replacement therapy. In fact, in the combined mode of continuous venovenous hemodiafiltrations set at higher rates, most antibiotics are dosed the same as those for patients with normal renal function. Otherwise, for continuous venovenous hemofiltration or continuous venovenous hemodiafiltration, we will generally expect antibiotics to be dosed at rates higher than those seen for traditional intermittent hemodialysis. And some of the key considerations that we should keep in mind when administering antibiotics to patients undergoing CRRT include the flow rates for blood, dialysate, effluent, replacement fluid, and ultrafiltration, if applicable. So the clearance of antibiotics are also dependent on the drug's

ability to cross the filter membranes, which we describe as the sieving coefficient or saturation coefficient. When this value is unknown, which happens occasionally, it can be estimated based on the degree of protein binding for that molecule. Using these values, pharmacists can use specific clearance equations to help estimate the expected antibiotic clearance.

Dr. Turck:
Turning to you, Dr. Adhi, let's talk about extracorporeal life support. What do we need to know about dosing and frequency of antimicrobials for patients undergoing that?

Dr. Adhi:
Absolutely. So, for clinicians, it's important to have a basic understanding of what extracorporeal life support is. As the name suggests, it's essentially life support supporting either the heart or the lungs on a continual basis, or both, depending on the pathology that the patient has. And because the function of the heart or lung is being performed outside the body by a machine, it's called extracorporeal. The most common form of ECLS by far that has increasingly widespread use is ECMO, or extracorporeal membrane oxygenation. And there are two basic kinds of that: venovenous ECMO, also known as VV ECMO, or venoarterial ECMO, also known as VA ECMO.

So, because this is a complicated circuitry, there are several factors affecting the concentration of any drugs, especially of antimicrobials. The extracorporeal factors include the sequestration of the drug by the circuit as the blood is flowing through the circuit. This is known as absorption phenomena, and it can occur within the circuit itself or within the membrane which is present in the oxygenator. The membrane characteristics also differ, but in general, because the membrane stays the same as long as the patient is on ECMO, unless there is an indication to change the membrane, the characteristics are therefore stable.

It is important to note that the volume of distribution is very high in these patients. So, in an adult patient at any given time, up to 25 percent of the volume on a patient on ECMO will be from fluids other than blood, like priming fluids, the replacement fluids, blood being transfused due to high amount of hemolysis through the pump, so hemodilution is a significant factor. The pulsatility differs. If the patient is on VV ECMO, usually the flow rate on ECMO is slow but the flow is still pulsatile, and therefore, the organs that are receiving the oxygen and the drug concentrations, they are receiving so in a pulsatile and normal physiological fashion, whereas on VA ECMO, this can be very different because the pump is pumping the blood, the heart is not functioning at all, and therefore, the flow is not pulsatile, so that can affect drug delivery as well. And then on top of all of this there are physiological changes, which change drug ionization and affect the free unbound antimicrobials available to perform the function that they are supposed to.

In general, there is very little data about the dosing of antimicrobials in ECMO. A general way to approach this is to dose antimicrobials similarly to what we would for patients who are not on ECMO, which is keeping in mind their renal function and their nonrenal clearance as well. However, for hydrophilic antimicrobials, such as beta-lactams, carbapenems, linezolid, aminoglycosides, their volume of distribution is greatly increased, and so their peak concentrations are lower. Therefore, we advise increasing a loading dose as well as using therapeutic drug monitoring as much as we can.

Dr. Turck:
For those just tuning in, you're listening to *IDSA Action Center* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Fatima Adhi and Mei Chang about the importance of medication dosing considerations in patients who are critically ill with infectious diseases. Staying with you, Dr. Adhi, your presentation at IDWeek took a look at several patient case scenarios. What would you say are the key takeaways from those scenarios?

Dr. Adhi:
Yeah. So we talked about a variety of different case scenarios. We touched upon renal replacement therapy, whereas Dr. Chang mentioned the drug removal, the antimicrobial removal through renal replacement is usually the highest with the continuous form of CRRT, and especially in the case of antimicrobials, such as vancomycin for which the area under the curve over MIC monitoring is very important. It is recommended to use a much higher loading dose, up to 25–30 mg/kg, and then utilize frequent dose monitoring. For example, for vancomycin, check a level at least 24 hours after being on continuous renal replacement therapy so that you're not underdosing it. Similarly, for extracorporeal life support, we talked about utilizing therapeutic drug monitoring as often as we can.

We also talked about extended infusion of beta-lactams, which has been shown to be associated with improved drug concentration above the MIC and associated with improved clinical outcomes, especially in critically ill patients.

We also touched upon ceftriaxone, and we talked about using a higher dose of ceftriaxone, at least 2 grams every 24 hours in patients presenting with undifferentiated sepsis or patients who are critically ill because that allows the area under the curve to stay above the MIC for most pathogens at least initially when the exact pathogen and exact disease process is not known. And we talked about the higher doses of ceftriaxone up to 6 to 8 grams per day having been studied and having proven to be relatively safe and associated with the same level of side effects as with lower dosing.

Dr. Turck:
And if we take a moment to focus on collaborative management, Dr. Adhi, how can ID specialists and pharmacists best work together to manage dosing for patients with an infectious disease?

Dr. Adhi:
That's a great question. So, you know, medicine is a team support. I think critical care is probably the best example of that. And the role of a pharmacist in the ICU is absolutely critical. I think we rely heavily on our pharmacists to make sure that our dosing recommendations are appropriate. For the ID specialist as well, because they're not present at bedside throughout the day the role of the pharmacist becomes more important. Pharmacists are much more knowledgeable about the different ways of clearance of the drug, the PK/PD, as well as how to change the dosing based on the different renal replacement therapies or the changing hepatic or renal dysfunction.

So, as an intensivist, I will discuss all the medications every day on each patient, but especially antimicrobials, and make sure that we are having our pharmacist review the dosing recommendations. As an ID specialist, we sort of do the same thing and therefore, the pharmacist ends up being sort of the point person in making sure that the dosing recommendations are correct.

Dr. Turck:
Turning to you with the same question, Dr. Chang, how can pharmacists best collaborate with ID specialists to manage dosing?

Dr. Chang:
Sure. As Dr. Adhi mentioned, teamwork and collaboration is key. For pharmacists who are verifying antibiotic orders, they can check renal function and the mode of renal replacement therapy to determine what the optimal dose should be to help our ID specialists manage the dosing, and particularly in critically ill patients with fluctuating hemodynamics where the mode of renal replacement therapy and/or whether their need for ECMO may change frequently, it's imperative for clinicians to help each other out so we can keep track and make sure we dose optimize all of our patients' antibiotics.

Dr. Turck:
Those are great notes to end on as we come to the end of today's program. I want to thank my guests, Drs. Fatima Adhi and Mei Chang, for sharing their perspectives on antimicrobial dosing for critically ill patients with infectious disease. Dr. Adhi, Dr. Chang, it was great speaking with you both today.

Dr. Adhi:
It was a pleasure. Thank you for having us.

Dr. Chang:
Yes, thanks again for inviting us.

Dr. Turck:
I'm Dr. Charles Turck. To access this and other episodes in our series, visit ReachMD.com/IDSAActionCenter where you can be Part of the Knowledge. Thanks for listening.