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QUESTIONS & ANSWERS

Dr Lode: can each of you please highlight what we need to know and do with microbiological reports?

Dr Chastre: It is very important to be able to document the responsible microorganism, not only for epidemiological reasons, but also to help us use antibiotics wisely. This knowledge provides an essential framework for de-escalation. For example, there is no reason to continue vancomycin if methicillin-resistant *Staphylococcus aureus* is not isolated. Similarly, there is no reason to continue a broad-spectrum β-lactam if the responsible organism is highly sensitive to a narrow-spectrum agent. My recommendation is to isolate and determine the susceptibility patterns of the microorganisms involved.

Dr Drusano: I agree, but would describe the principle slightly differently. When you deal with a clinical situation, you either know what you are treating or you do not. In the first couple of days, you do not know what you are treating, which means that you have to try to kill everything to ensure you do not make a mistake.

After 3–4 days, you have two new pieces of information. One is the trajectory of the patient's clinical course; the other is the actual microbiology. If you have the microbiology, you can make a rational decision about chemotherapy and, in turn, make it more targeted.

The real problem for the clinician is too seldom mentioned: what do you do when the microbiology comes back and shows nothing? That is where the clinical trajectory becomes very important. If the patient is improving, or at least not getting worse, antibiotic therapy should be stopped very quickly.

The biggest problem is the group of patients whose clinical course worsens even though no microbial pathogen can be identified. In this case, I think you have to go back and re-evaluate all possible causes of the symptoms.

Dr Rello: Pneumonia is an acute infection accompanied by an inflammatory reaction to a bacterial pathogen. If after 3 days you do not have an inflammatory reaction, you conclude that there is no longer bacterial activity and no reason to prolong antibiotic use. In patients who exhibit persistent colonisation but do not show a resulting inflammatory reaction, their persistent colonisation is not treated. In most patients who fail clinical therapy, the inflammation persists independently of the initial therapy, and there is no rationale for continuing antibiotics.

Question: what is the importance of the epidemiological nature of sensitivity and resistance in the intensive care unit (ICU)? Do you recommend the use of fixed combinations based on epidemiology or do you change initial therapy regularly? If so, what is the interval between changes?

Dr Rello: I invite you to read our publication [1], in which we evaluated different antibiotic policies. During the first 10 months of our study, patient-specific antibiotic therapy was prescribed. For the next 24 months, 4-month rotation-cycle periods with various antimicrobial agents were implemented. During the final 10 months (mixing period), the first-line antibiotic for ventilator-associated pneumonia (VAP) was changed following a pre-established schedule to ensure maximum heterogeneity. Antibiotic consumption was closely monitored every month and antimicrobial resistance patterns were regularly assessed. The greatest heterogeneity of antibiotic use occurred during the patient-specific therapy approach (first 10 months), and the appearance of resistance was maximal during the 24-month rotation-cycle period. Therefore, regular, periodic change of antibiotic did not limit resistance.

Furthermore, empiric therapy is important during the first 2 days of treating a patient. Whether you treat susceptible *Pseudomonas aeruginosa* in non-neutropenic patients with one drug or 20, the result is exactly the same. We evaluated 200 patients in four Spanish hospitals with monomicrobial *P. aeruginosa* VAP. It did not matter how many antibiotics the pathogen was sensitive to: the administration of only one antibiotic during the initial period was inappropriate therapy and was associated with excess mortality. Therefore, initially, the broadest spectrum therapy should be used based on susceptibility data and microbiological analysis. After 2–3 days, the microbiological data will let you successfully continue using only one drug.

Dr Lode: I think, when you look at the American Thoracic Society/Infectious Disease Society of America guidelines, you have to distinguish between nosocomial and community-acquired pneumonia. If it is community-acquired, you are treating the most sensitive strains. However, for nosocomial pneumonia, you would like information about the local epidemiology, including the resistance patterns, in your hospital and ICU.

It makes no sense to change therapy every second or third day. Antibiotic cycling, which was favoured 3–4 yrs ago by some experts, did not produce good results. Therefore, a therapeutic orientation based on the patient's basic disease, risk factors and local epidemiology is what we are stressing here.

Dr Drusano: I agree. I have never been a big supporter of cycling for the basic reason that it is too complex. For example, if you start therapy with a quinolone, the efflux pumps are upregulated. There is a global regulon that upregulates efflux pumps and downregulates the outer membrane protein OprD2 at the same time, also causing resistance to carbapenems. Conversely, if you start with a cephalosporin, you can get stable AmpC derepression. In other words, when you consider what you start with and what you follow with, you can too easily make resistance worse.

I believe that there is no single regimen that is best for everyone. If you have an individualised programme with a certain amount of mixing, you avoid pressure on the organisms that can amplify clones with a single resistance mechanism, and the patient will be better off over a period of 3–6 months.

Dr Chastre: I completely concur. First, avoid using the same class of drug that the patient received a few days ago. Secondly, use surveillance microbiological results to select the initial antibiotic treatment. Thirdly, avoid giving the same class of antibiotic that other patients in the unit are receiving. This increases the heterogeneity of your antibiotic treatment and minimises the possible development of resistance.

Question: I treat cystic fibrosis and have many patients with multiple resistant pathogens. Dr Drusano, would you recommend using a bolus loading dose, followed by a continuous infusion? If there were a demonstrable benefit, I would consider trying it. Are you doing a clinical trial like that?

Dr Drusano: I propose prolonged infusion, not continuous infusion. Continuous infusions require another *i.v.* port in another *i.v.* line, which can be very painful and also increase the risk of a secondary infection. With a prolonged infusion, there are 4–5 h between infusions when other medications can be administered.

I would like to conduct a prospective study to demonstrate the benefits of prolonged infusion, but funding and permission are very difficult to obtain. The introduction of the automatic switch protocol in our hospital gave us the power to perform a retrospective study, and there was a salutary effect of prolonged infusion in sicker patients. The dynamically linked variable is the time that the plasma concentration of antibiotic is above the minimum inhibitory concentration. With prolonged infusion it is increased and a clinical advantage occurs.

Question: It appears that worse outcomes occur with combination therapy that includes a cephalosporin. Should we avoid the combination of a carbapenem with a cephalosporin? Are aminoglycosides still useful in combination therapy?

Dr Lode: It is not a good idea to combine a carbapenem with a cephalosporin. I would use a drug that has a different target or mechanism of action (not another β-lactam), such as a fluoroquinolone or an aminoglycoside.

Dr Chastre: I recommend using a combination that includes an aminoglycoside for 3–5 days, but no longer than that. There are good data supporting short periods of treatment using a broad-spectrum β-lactam with an aminoglycoside.

Dr Drusano: I think you have to be very careful. If you use fluoroquinolones, they do upregulate multidrug-resistance efflux pumps in Pseudomonas.

REFERENCE

1 Sandiumenge A, Diaz E, Rodriguez A, *et al.* Impact of diversity of antibiotic use on the development of antimicrobial resistance. *J Antimicrob Chemother* 2006; 57: 1197–1204.