Do we really understand what we want or need out of antimicrobial stewardship programs?

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"Maintaining our existing drug repertoire is the only strategy available for drug longevity but this will be difficult."

Infectious diseases are a global clinical entity and may be caused by bacteria, viruses, yeast/fungi, parasites and prions. Some infectious pathogens are more geographically restricted (i.e., *Plasmodium* spp. causing malaria) while others are not. While various chemical entities have been used throughout the years to treat infections, the era of modern day antimicrobial agents date to the latter part of the 1920s with the discovery of penicillin. Since then, the golden age of antimicrobial agents evolved primarily around the discovery and introduction of broader spectrum antibacterial drugs (extended-spectrum cephalosporins, quinolones and macrolides). On the other hand, antiviral drugs evolved at a different pace and against a limited number of viruses and, over the past 20 years, extensive investigation has led to newer antiyeast/antifungal drugs. Several elements are important for antimicrobial therapy of infectious diseases. These include (in no absolute order) clinical outcome, patient safety, optimization of therapy, controlling antimicrobial resistance, public health importance, and risk of communicability and cost – with cost being a nonscientific or clinical entity.

Increasing antimicrobial resistance with the declining development of new antimicrobial agents (along with cost) has driven the move toward antimicrobial stewardship programs [1]. Antimicrobial stewardship has arisen out of the need to improve the use of antimicrobial agents in hospitals; however, improvement in the outpatient setting is also critical given that more antimicrobial agents are used in this setting and antimicrobial resistance is now prevalent among community-acquired bacterial pathogens. As antimicrobial resistance results in increased morbidity, mortality and the cost of healthcare, initial attempts to develop guidelines for in-hospital drug use had limited success [2,3].

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Should there be 'testing ordering stewardship', 'infection control stewardship', 'microbiology stewardship', 'guideline stewardship', 'IT stewardship' or 'administrative stewardship'? Furthermore, is a multifunctional process involving key stakeholders, such as prescribers, pharmacists, microbiologists, infection control practitioners, information technology and administrators, the proper direction? In many instances, the goals of the various programs remain unclear; however, such programs are already or are becoming a requirement for accreditation.

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Improved patient outcomes (morbidity vs mortality)

There is no doubt that antimicrobial drugs impact morbidity by preventing clinical deterioration, symptom resolution, including improving infection-associated discomfort, and perhaps limiting spread of an infecting pathogen to other susceptible hosts [4,5]. Impacting mortality is an entirely different question and needs to be considered differently for patients with community-acquired mild-to-moderate disease versus moderate-to-severe or hospital-acquired infection in a critically ill patient. For some mild-to-moderate community-acquired bacterial infections being treated in the outpatient setting, clinical improvement would likely occur with or without antimicrobial therapy; however, antibacterial drugs clearly impact time to clinical response/recovery [6,7]. For more critically ill patients with infection, antibiotics impact mortality as well as morbidity [8].

Optimal antimicrobial therapy

Do we define optimal antimicrobial therapy as a goal of antimicrobial stewardship [9,10]? The approval of an antimicrobial agent for a specific clinical condition (i.e., respiratory tract infections) does not automatically mean that the drug is optimal against all (or any) of the pathogens potentially causing the infection. Defining what is meant by optimal therapy may have varying opinions, but should include a favorable clinical outcome while attaining necessary pharmacokinetic/pharmacodynamic/microbiological break points in order to prevent resistance from occurring. Traditionally, antimicrobial agents were approved for a specific clinical condition by proving noninferiority to a product already approved for that condition [11]. If clinical outcomes were not statistically different between both drugs then approval was likely, providing safety concerns were not identified. Such studies were designed and powered to show equivalency, so the outcomes were predictable. Study design chose an end point where differences between the two treatment regimens were unlikely, thereby ensuring equivalency or noninferiority. In addition, strict inclusion/exclusion criteria for patient enrollment/exclusion led to well-defined subjects in these studies and often they may not always represent real-world scenarios where considerable variability exists between patients (e.g., age, underlying medical conditions, overall health status and weight) seeking physician consultation for infection-related diseases. Such drugs were rarely evaluated in patients with a pathogen resistant to either compound – if such a scenario occurred during the trial, the patient was excluded from analysis. In addition, some drugs are recommended as a 'one dose fits all' rather than a mg/kg dosing [12], and weight alone clearly impacts dosing and achievable/sustainable drug concentrations. How, then, do we consider such drugs in real-world settings where the potential for drug resistance is prevalent and problematic and where optimization of therapy is desirable?

Restricting drug use

Restricting drug use or reducing drug use will save money, and if that is the aim of a stewardship program then so be it, but this does little to optimize therapy. In many instances, restricting one drug may be at the expense of increased use of another drug, perhaps at a lower price or simply a cost transfer. Antimicrobial restriction programs have not shown a consistently conclusive positive impact on antimicrobial resistance [13,14]; however, extensive restrictions reduced nosocomial plasmid-mediated cephalosporin-resistant *Klebsiella* infections and colonization [15]. In fact, it may have the opposite effect. The 2007 guidelines for the treatment of adult patients with community-acquired pneumonia suggested that if all else was equal, preference should be given to more potent drugs because of their potential benefit in restricting the development of resistance. Traditional thinking has trouble with this concept as it is felt that the more potent drugs should be reserved until 'needed'; however, the strategy of using

less active drugs in a stepwise fashion clearly cannot be an ideal strategy either, as resistance has escalated under this approach. The concept of 'best in class' deserves consideration, but the long-term consequences are unknown. In addition, Tillotson *et al.* questioned if hospital-based strategies for reducing antibiotic resistance have any relevance in the community [16].

Empiric versus targeted therapy

Most antibacterial drugs are prescribed empirically, based on a syndromic approach. For example, many drugs are approved for the treatment of community-acquired respiratory tract infections and most have an antibacterial spectrum to include Gram positive (i.e., *Streptococcus pneumoniae*) and negative pathogens (i.e., *Haemophilus influenzae*) prevalent for this condition, and some drugs also have a spectrum to include atypical pathogens, such as *Mycoplasma* spp. and *Chlamydia* spp. van der Eerdan *et al.* reported no difference in efficacy between empiric versus pathogen-directed therapy for hospitalized patients with community-acquired pneumonia [17]. It has become clear that an antibiotic may be differentially active against various pathogens within its spectrum and, as such, may be less optimal for some bugs. Can this disproportionately contribute to resistance development? Recovery of a pathogen and tailoring therapy toward that bug (even if initially treated empirically) would allow for a greater likelihood for optimal therapy by considering drug potency against the pathogen and drug pharmacology. However, Montravers *et al.* showed that the choice and adequacy of initial empiric antibiotic therapy affected the outcome of postoperative peritonitis and that late changes in antibiotic therapy based on culture results did not affect outcome when the initial therapy was inadequate [18]. Such an approach is problematic as clinicians are reluctant to alter therapy in a patient responding favorably. Furthermore, the cost implications for the patient to have their prescriptions changed are barriers. In addition, mixed cultures or difficult-to-recover pathogens complicate this approach, as does access to timely results in rural geographic locations. Ideally, antimicrobial stewardship would promote such efforts to optimize therapy, despite such practical barriers.

Rapid diagnostic technology

Laboratory medicine is estimated to impact approximately 80% of patients, clearly not all related to infection. Several recent advances in clinical microbiology may impact favorably on a stewardship program and affect antimicrobial use in the hospital and in the community [19]. Molecular diagnostic technology (i.e., PCR) has already impacted the diagnosis of infection with key pathogens, such as methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, respiratory viruses including the influenza virus, and others. Such technology is based on amplifying a pathogen-specific unique segment of nucleic acids. Results can be generated in a matter of hours, a time frame that could impact antimicrobial treatment decisions (i.e., necessary or unnecessary). Unfortunately, the limitation is that such technology is restricted to larger medical centers and is, therefore, not uniformly available to all clinicians submitting patient specimens for analysis. Still, it is a start, and over time, this technology may become more broadly available to smaller centers. One can imagine a scenario where a patient presents with respiratory tract symptoms and it is unclear if this is a viral versus bacterial infection. A PCR assay, including a respiratory virus panel, could identify the specimen as positive for a viral pathogen and impact the decision to use (or not) an antimicrobial agent.

Mass spectrometry has recently been introduced to clinical laboratories in North America, but it has been in use in Europe for slightly longer. In this technology, the organism growing on an agar plate is transferred to a slide and placed in the instrument. The organism is blasted with a laser multiple times and a spectrogram of the protein profile is constructed. This profile is compared with a database of profiles and the organism is identified. In our laboratory, this technology has been successfully implemented and is transforming how we offer our services. Organism identification is normally complete in 3–5 min versus hours to days for other advanced technology or traditional microbiology. How can such technology impact a stewardship program in larger medical centers? There is no debate that empiric antimicrobial therapy is necessary in many patients – often with broad spectrum single agents or with combinations of agents; such treatments are recommended in numerous treatment guidelines. Once started, there is often a reluctance to alter therapy in a patient showing a favorable clinical response as mentioned above. This is often complicated

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by the time it takes to report the causative pathogen (if isolated) by the laboratory. Is this changing with the advancements in diagnostic laboratory technology? Nilsen reported on the automated pathogen identification directly from blood cultures [20]. Such data could facilitate early-targeted antimicrobial therapy. Stewardship programs might do well to insist a re-evaluation of the initial empiric therapy (once such organism information is available) and tailor therapy to optimize treatment for that specific pathogen. Such optimization would require more than casual knowledge of drug dosing and pharmacology. This is one potentially encouraging area that may positively serve an antimicrobial stewardship program.

"Let us identify our programs for what they are and, where necessary, transform them to what they need to be."

Comment

Curtailing antimicrobial resistance is of paramount importance as new antimicrobial development diminished substantially over the past decade and there are no signs that this is about to change. Regulatory hurdles in North America and Europe have not helped and may be too idealistic – time will tell! Niche drugs are needed and will be useful, however, only for limited clinical indications. Maintaining our existing drug repertoire is the only strategy available for drug longevity but this will be difficult. Restricting drug use to those that need antibiotics would be a good first step in reducing overuse and, therefore, the burden of antimicrobial selective pressure on resistance selection. If antimicrobial stewardship programs are to have any impact on antimicrobial resistance, then the priorities need to be less about saving money and more about optimizing therapy and reducing unnecessary drug use – hopefully impacting positively on antimicrobial resistance. Saving money is not a bad thing and we all have a responsibility in being stewards of our healthcare dollars. Let us identify our programs for what they are and, where necessary, transform them to what they need to be.

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