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Antimicrobial stewardship programs (ASPs)

The devil is in the details

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Infectious disease clinicians traditionally have had the leadership role in recommending appropriate and optimal use of antibiotics in hospitals. This judicious and optimized use of antimicrobial agents is the central principle of antimicrobial stewardship. In addition to increased awareness among infectious disease experts, antimicrobial stewardship has become a national priority. Recently, the US Food and Drug Administration (FDA) promoted antimicrobial stewardship by creating incentives to encourage new anti-infective research. The Infectious Diseases of Society of America (IDSA) launched the campaign "Bad Bugs, No Drugs" to plead for the development of new systemic antibiotics.[1] While efforts at stewardship are important in their own right, the relative paucity of new agents and the spread of multidrug-resistant organisms have further emphasized the need for antimicrobial stewardship programs (ASPs) in order to preserve the antimicrobial agents that are currently available.

In this issue there are several important articles related to different aspects of ASPs. Andriy Nemchencko's infographic for this issue provides a visual overview of the key issues surrounding the need for effective ASPs as well as the overarching goals/benefits of effective stewardship programs.[2] Antimicrobial stewardship is a developing field, and every ASP must be tailored to its respective institution and each article has a distinctive focus and perspective. However, several common interventions and beliefs are shared among programs. For example, most ASPs include a restricted antimicrobial formulary that takes into account local resistance patterns. Additional important components of ASPs are the optimization of antibiotic dosing, administration of antimicrobials only for the shortest effective duration, and intravenous to oral conversion. Finally, ASPs have a significant educational mission as clinicians are asked to consider multiple aspects, such as: the efficacy profile, side effect profile, drug-drug interactions, potential for *Clostridium difficile* induction, effects on microbial resistance, etc.[3] ASPs should be funded from hospital revenues, partly thorough savings from implementation of key components of an ASP, such as an intravenous to oral conversion program, and the shortening of the duration of hospital therapy. As noted above, and since hospitals differ markedly by region, size, academic/community physician mix and hospital resistance problems, it is unreasonable to expect that one generic approach will be successful in all institutions. It is also unrealistic to think that each component of ASPs will be equally successful. Without careful/selective antibiotic formulary restrictions and an effective infection control program, the hospital's resistance problems will persist. However, any ASP should be considered successful if even a few key improvements are realized.

Importantly, an effective ASP is the result of the collaboration between a number of different groups including the hospital administration, infectious disease, infection control, pharmacy, microbiology and information technology groups.[4] The infectious disease group usually has the primary responsibility for assuring interdisciplinary cooperation/coordination of these key groups cited but a closely coordinated effort is essential since partial or misdirected measures will fail.[5]

Of note is that antimicrobial stewardship initiatives also have important pharmacoeconomic implications to the institution.[6] Antimicrobial cost is not simply a function of pharmacy acquisition costs. The total cost of antibiotic therapy is related to several indirect costs, e.g., intravenous antibiotic administration costs, antibiotic monitoring costs (drug levels, hepatic and renal function tests), cost of therapeutic failure/consequent re-treatment (usually with more expensive agents) and the economic burden of microbial resistance (increased length of stay, retreatment with effective, but more expensive drugs and the bed cost of cohorting patients with resistant organisms).[7,8] In order to assist in cost-containment, ASPs should include efforts to outline optimal antibiotic dosing regimens, shortest effective duration of antibiotic therapy, and intravenous to oral conversion.

While control of antimicrobial resistance is among the most frequently cited goals of ASPs, it clearly is the most ambitious and difficult to quantify.[8] Without a clear understanding of the key determinants of resistance, resistance control efforts are unlikely to work. For example, the failures of well-intended antibiotic cycling programs are a testimony to the challenges associated with programs lack of understanding of resistance determinants. Furthermore, resistance problems are often institution-specific and effective solutions must be tailored to the institutional needs. Evidence-based guidelines concerning antibiotic resistance are inadequate and contradictory.[4-6]

One aspect of resistance has to do with preventing/minimizing antibiotic resistance in the hospital; the other aspect has to do with containing resistant organisms and preventing their spread within the institution. As the primary goal of most ASPs is to decrease inappropriate antibiotic use, and by extension, antibiotic resistance will be decreased, but decreasing antibiotic usage alone has little if any effect on resistance. In the literature, antibiotic usage is expressed as DDD (defined daily dose/1,000 patient days). DDDs may be a good index of antibiotic use/cost, but it

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cannot be directly linked to antibiotic resistance. A corollary of this notion is that broad spectrum therapy should be narrowed to prevent resistance, which is not the case. For example, changing therapy to penicillin after *Streptococcus pneumoniae* is identified as the pneumonia pathogen, while intuitively appealing, has no basis in limiting resistance.[9]

Experience-based guidance adapted to the hospital's particular resistance problems is preferable to being misguided by poorly designed contradictory evidence-based studies. ASP efforts to decrease antibiotic consumption are worthwhile to decrease costs, decrease duration of therapy and decrease potential side effects/drug-drug interactions, but will not, per se, affect hospital resistance. Decreasing inappropriate or unnecessary antibiotic therapy is a worthy clinical goal, but it is unreasonable to expect that this will have any appreciable effect on resistance.[10-12] Independent of volume of use, some antibiotics such as nitrofurantoin, amikacin, doxycycline and ceftriaxone are unlikely to result in resistance and may be termed "low resistance potential antibiotics." In contrast, antibiotics that may result in resistance even with limited use may be termed "high resistance potential antibiotics" such as imipenem, ciprofloxacin, gentamicin and ceftazidime.[13]

It is a common misconception that acquired resistance is a class phenomenon. For example, the high resistance potential of ceftazidime is not shared by the other third generation cephalosporins such as cefotaxime, ceftizoxime, cefoperazone and ceftriaxone.[14] Also, acquired resistance is usually limited to relatively few organisms, as such, ceftazidime retains its activity against most Gram-negative bacillary pathogens and resistance is largely limited to few bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.[15] This has important implications in interpreting and applying resistance literature. Articles that attempt to relate resistance to volume of use by antibiotic class rather than analyzing each antibiotic within the class could lead to erroneous conclusions. ASPs that restrict certain antibiotic classes, such as third generation cephalosporins, quinolones and carbapenems, will miss the mark of impacting on resistance. A restricted formulary that limits "high resistance potential antibiotics" is the key to minimizing antibiotic resistance.[16,17]

Looking into more detail in the papers included in this issue, Chung et al., from the National University Health System in Singapore, review the difficulties and controversies in applying prospective audit and feedback to ASPs.[18] The authors make the point that a carefully considered antibiotic restricted formulary has been shown to be effective. However, formulary restrictions must be preceded by physician education to assure understanding and support. Overall, the concept of audits that can improve performance is well intentioned, but, as discussed in the article, there is no agreement as to what should be measured in ASP audits.

Reed et al. discuss the pros and cons of their formulary restriction and prior authorization programs at the Ohio State University.[19] While most would agree that formulary restriction is fundamental in trying to limit acquired resistance, the problem is which drugs should be restricted? A restricted formulary should combine restriction of "high resistance potential antibiotics" with the unrestricted use of "low resistance potential antibiotics." Evidence-based medicine can fail if it is misapplied. What is the benefit of restricting all third generation cephalosporins when only ceftazidime has been shown to be responsible for most resistance related to third generation cephalosporins? Why and on what basis should prior authorization be needed to use cefotaxime, ceftizoxime or ceftriaxone? Certainly, the described model works in their institution, but others should take care in customizing, not copying, their approach to each hospital's particular resistance problems.

The current interest in hospital based ASPs is based on the notion that ASPs can prevent/control antibiotic resistance problems, i.e., methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), multidrug-resistant (MDR) Gram-negative bacilli, as well as minimizing *C. difficile* infection.[20] The article by Landelle et al. from Geneva, Switzerland and Bolzano, Italy correctly distinguishes between preventing/controlling resistant organisms from containing the spread of resistant organisms.[21] While it is not always possible to prevent exposure of antibiotics that predispose to resistance (from outpatient offices/clinics, chronic care facilities or other hospitals) even in the worst case scenario, infection control is the best defense against patient to patient spread. Infection control containment measures have long been the bulwark against highly lethal/untreatable viral outbreaks/epidemics.

Sanjay Bhattacharya from Tata Medical Center in Kolkata, India discusses the clinical value of rapid identification/reporting of resistant pathogens.[22] ASPs should try to educate the medical staff on the pitfalls of relying on susceptibility data without taking into account the clinical context of the patient. In critically ill patients, empiric therapy is based on the clinical syndrome and most likely pathogen, taking into account local resistance patterns. For example, if someone is admitted to the ICU with a new heart murmur and Gram-positive cocci in clusters in blood cultures, it is likely empiric therapy will be directed against MRSA. Since MRSA drugs also cover MSSA, the patient is appropriately covered. If the Gram-positive cocci are later identified as MSSA, therapy may be continued or changed to an anti-MSSA antibiotic. Similarly, with Gram-negative bacilli, if multidrug-resistant organisms (MDROs) are endemic to the hospital, then empiric therapy with a carbapenem will certainly hold the line pending susceptibility results. Differentiating colonization from infection is critical. Rapid susceptibility results on a colonizing organism may result in unnecessary treatment. Each ASP must decide whether rapid testing is cost-effective for each pathogen relevant to the institution.[23]

Ian Gould from Aberdeen and Abhijit Bal from Kilmarnock (both in Scotland) argue for the development of new agents to treat resistant organisms.[24] Two key concepts deserve commentary. First, new agents do not always fulfill their expectations, such as gatifloxacin, trovafloxacin, telithromycin and moxalactam. Second, until new agents are available for clinical use, ASP efforts should re-review the use of selected older agents, e.g., fosfomycin, doxycycline, minocycline, chloramphenicol alone or in combination, that may be efficacious in treating some MDROs.[25]

As with antibiotic resistance, antibiotics predisposing to *Clostridium difficile* are often as misunderstood as an antibiotic

exposure problem. How many times, when *C. difficile* is in the differential diagnosis of acute diarrhea, do you hear asked, "Was the patient on antibiotics?" Clearly, clindamycin and β lactams are potent inducers of *C. difficile* infection. However, there are many antibiotics that have a low *C. difficile* potential, such as aminoglycosides, trimethoprim-sulfamethoxazole (TMP-SMX), aztreonam, doxycycline, minocycline, daptomycin, linezolid, quinupristin/dalfopristin, vancomycin, macrolides (non-*Clostridium difficile* diarrhea), chloramphenicol, fosfomycin, nitrofurantoin, tigecycline, etc. As with antibiotic resistance, containment of spread of *Clostridium difficile* is an important hospital infection control function.[26]

The article by Céline Pulcini from the University of Nice, France and Inge Gyssens from the Radbourd University Medical Center in the Netherlands provides a perspective on prudent prescribing.[27] They focus on the dual effect of antimicrobial therapy on colonizing flora and the potential for inducing resistance. No one would disagree that inappropriate and unnecessary antibiotic therapy should be discouraged. As discussed above, resistance problems relate to specific antimicrobials independent of volume of use. The problem is who should teach and what should be taught. Evidence based approaches are either conflicting or non-existent. Misinformation and misconceptions are often the rule rather than the exception, and the authors highlight that the primary determinant of resistance is the use of "high resistance potential antimicrobials" over time.

The contributors of this Special Focus are to be commended for grappling with such thorny aspects of ASPs in their articles. In order to preserve the effectiveness of antimicrobial agents, efforts should be directed at prudent use. Kent Sepkowitz has put this in historical perspective, "Somehow, however, in our re-coil from the mess around us, we seem to have become overly apologetic, lamenting the terrible curse that our improvident stewardship of Alexander Fleming's gift has brought down on human-kind. We insist that it's all our fault—the superbugs and the *Clostridium difficile* and the 100,000 persons reportedly killed each year by a lethal blend of ineptitude, greed, and heartless decision making.... Rather than our current attitude of self-pity and gnawing regret, we should adopt Finland and Weinstein's cautious optimism about what lies before us: as they predicted, antibiotics will continue to provide us with many challenges and problems but also with far more miraculous cures."[28] Over time, as experience is accrued by ASPs, hopefully more clinically relevant data will be reported to help further refine what has been learned, but not yet applied. With ASPs, it may certainly be said, the devil is in the details.

References

1. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:1-12; PMID:19035777; http://dx.doi.org/10.1086/595011
2. Nemchenko A. Infographic: Antimicrobial Stewardship. Virulence 2013; 4; In press; PMID:23324540; http://dx.doi.org/10.4161/viru.23630
3. Johannsson B, Beekmann SE, Srinivasan A, Hersh AL, Laxminarayan R, Polgreen PM. Improving antimicrobial stewardship: the evolution of programmatic strategies and barriers. Infect Control Hosp Epidemiol 2011; 32:367-74; PMID:21460488; http://dx.doi.org/10.1086/658946
4. Owens RC Jr., Shorr AF, Deschambeault AL. Antimicrobial stewardship: shepherding precious resources. Am J Health Syst Pharm 2009; 66(Suppl 4):S15-22; PMID:19502223; http://dx.doi.org/10.2146/090087c
5. Lesprit P, Brun-Buisson C. Hospital antibiotic stewardship. Curr Opin Infect Dis 2008; 21:344-9; PMID:18594284; http://dx.doi.org/10.1097/QCO.0b013e3283013959
6. Allerberger F, Mittermayer H. Antimicrobial stewardship. Clin Microbiol Infect 2008; 14:197-9; PMID:18190577; http://dx.doi.org/10.1111/j.1469-0691.2007.01929.x
7. Septimus EJ, Owens RC Jr. Need and potential of antimicrobial stewardship in community hospitals. Clin Infect Dis 2011; 53(Suppl 1):S8-14; PMID:21795728; http://dx.doi.org/10.1093/cid/cir363
8. Ohl CA, Luther VP. Antimicrobial stewardship for inpatient facilities. J Hosp Med 2011; 6(Suppl 1):S4-15; PMID:21225949; http://dx.doi.org/10.1002/jhm.881
9. Berrington A. Antimicrobial prescribing in hospitals: be careful what you measure. J Antimicrob Chemother 2010; 65:163-8; PMID:19884120; http://dx.doi.org/10.1093/jac/dkp399
10. Bevilacqua S, Demoré B, Boschetti E, Doco-Lecompte T, May I, May T, et al. 15 years of antibiotic stewardship policy in the Nancy Teaching Hospital. Med Mal Infect 2011; 41:532-9; PMID:21907511; http://dx.doi.org/10.1016/j.medmal.2011.08.001
11. Rattanaumpawan P, Morales KH, Binkley S, Synnestvedt M, Weiner MG, Gasink LB, et al. Impact of antimicrobial stewardship programme changes on unnecessary double anaerobic coverage therapy. J Antimicrob Chemother 2011; 66:2655-8; PMID:21803769; http://dx.doi.org/10.1093/jac/dkr321
12. Griffith M, Postelnick M, Scheetz M. Antimicrobial stewardship programs: methods of operation and suggested outcomes. Expert Rev Anti Infect Ther 2012; 10:63-73; PMID:22149615; http://dx.doi.org/10.1586/eri.11.153
13. Cunha BA. Effective antibiotic-resistance control strategies. Lancet 2001; 357:1307-8; PMID:11343730; http://dx.doi.org/10.1016/S0140-6736(00)04527-X
14. Aldeyab MA, Harbarth S, Vernaz N, Kearney MP, Scott MG, Darwish Elhajji FW, et al. The impact of antibiotic use on the incidence and resistance pattern of extended-spectrum beta-lactamase-producing bacteria in primary and secondary healthcare settings. Br J Clin Pharmacol 2012; 74:171-9; PMID:22150975; http://dx.doi.org/10.1111/j.1365-2125.2011.04161.x
15. Rice LB. Mechanisms of resistance and clinical relevance of resistance to β-lactams, glycopeptides, and fluoroquinolones. Mayo Clin Proc 2012; 87:198-208; PMID:22305032; http://dx.doi.org/10.1016/j.mayocp.2011.12.003
16. Doron S, Davidson LE. Antimicrobial stewardship. Mayo Clin Proc 2011; 86:1113-23; PMID:22033257; http://dx.doi.org/10.4065/mcp.2011.0358
17. Ohl CA, Dodds Ashley ES. Antimicrobial stewardship programs in community hospitals: the evidence base and case studies. Clin Infect Dis 2011; 53(Suppl 1):S23-8, quiz S29-30; PMID:21795725; http://dx.doi.org/10.1093/cid/cir365
18. Chung GW, Wu JE, Yeo CL, Chan D, Hsu LY. Antimicrobial stewardship: A review of prospective audit and feedback systems and an objective evaluation of outcomes. Virulence 2013; In press; PMID:23302793; http://dx.doi.org/10.4161/viru.21626
19. Reed EE, Stevenson KB, West JE, Bauer KA, Goff DA. Impact of formulary restriction with prior authorization by an antimicrobial stewardship program. Virulence 2012; In press; PMID:23154323; http://dx.doi.org/10.4161/viru.21657
20. Höjgård S. Antibiotic resistance - why is the problem so difficult to solve? Infect Ecol Epidemiol 2012; 2: ; PMID:22957126; http://dx.doi.org/10.3402/iee.v2i0.18165
21. Landelle C, Pagani L, Harbarth S. Is patient isolation the single most important measure to prevent the spread of multidrug-resistant pathogens? Virulence 2013; In press; PMID:23302791; http://dx.doi.org/10.4161/viru.22641
22. Bhattacharya S. Early diagnosis of resistant pathogens: How can it improve antimicrobial treatment? Virulence 2013; In press; PMID:23302786; http://dx.doi.org/10.4161/viru.23326
23. Jonas D, Speck M, Daschner FD, Grundmann H. Rapid PCR-based identification of methicillin-resistant Staphylococcus aureus from screening swabs. J Clin Microbiol 2002; 40:1821-3; PMID:11980967; http://dx.doi.org/10.1128/JCM.40.5.1821-1823.2002
24. Gould IM, Bal AM. New antibiotic agents in the pipeline and how they can help overcome microbial resistance. Virulence 2013; In press; PMID:23302792; http//dx.doi.org/10.4161/viru.22507
25. Cunha BA. Oral doxycycline for non-systemic urinary tract infections (UTIs) due to P. aeruginosa and other Gram negative uropathogens. Eur J Clin Microbiol Infect Dis 2012; 31:2865-8; PMID:22767268; http://dx.doi.org/10.1007/s10096-012-1680-0
26. Talpaert MJ, Gopal Rao G, Cooper BS, Wade P. Impact of guidelines and enhanced antibiotic stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of *Clostridium difficile* infection. J Antimicrob Chemother 2011; 66:2168-74; PMID:21676904; http://dx.doi.org/10.1093/jac/dkr253
27. Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. Virulence 2013; In press; PMID:23361336; http://dx.doi.org/10.4161/viru.23706
28. Sepkowitz KA. Finland, Weinstein, and the birth of antibiotic regret. N Engl J Med 2012; 367:102-3; PMID:22784113; http://dx.doi.org/10.1056/NEJMp1205847