Antimicrobial Stewardship Programs (ASP): Perspective on Problems and Potential

CHESTON B. CUNHA, MD, FACP

Antibiotic Stewardship Programs (ASPs) are intended to optimize appropriate antibiotic use and decrease inappropriate or suboptimal antibiotic use. Infectious disease clinicians have traditionally held the role of antibiotic stewards.[1] Recently, the basic principles of optimal antibiotic use have been finalized in the Centers for Disease Control (CDC) ASP guidelines. The CDC guidelines consist of 7 principles that should be customized to the hospital's size, local epidemiology, resistance patterns, staff expertise and pharmacoeconomic considerations.[2] One size does not fit all, and effective ASP measures in one hospital may be ineffective or inappropriate in another.[3] Hospital differences may be evaluated using prospective audits to assess the effectiveness of ASP components in each hospital. (**Table 1**)

Table 1. Effective Antibiotic Stewardship Program (ASP): Core Elements

Leadership commitment from administration
A single ID Clinician/Leader responsible for outcomes
A single pharmacy leader who reports to the ID clinician
Tracking and reporting of antibiotic use
Reporting of antibiotic resistance
Educating providers on optimal use and resistance
Prospective antibiotic audits to measure appropriate use and specific improvement interventions

Adapted from: CDC ASP guidelines 2017

The CDC ASP guidelines consist of 7 practical ASP measures.[2] First, there must be administrative support to fund a dedicated infectious disease (ID) clinician team leader supported by a staff of ID-trained clinical pharmacists (PharmDs). Appropriate antibiotic use is the critical ASP tenet. Antibiotics should not be used to treat non-bacterial causes of fever, e.g., viral infections, drug fever, non-infectious febrile disorders. Furthermore, infection, not colonization, should be treated. The expertise of the ASP ID leader is critical as many non-ID physicians do not understand the importance of differentiating culture results that may represent either colonization (that should not be treated) or infection.[4]

These ASP principles of 1) not treating non-bacterial febrile disorders 2) not treating colonization are important cornerstones of effective ASPs. After selecting an antibiotic on the basis of appropriate spectrum, then tissue penetration (related to the site of infection) is an important consideration. Therapeutic serum levels have little relevance in treating non-serum site infections, e.g., meningitis, osteomyelitis, prostatitis.[4]

ASP programs should educate practitioners on optimal dosing based on pharmacokinetic (PK) and pharmacodynamic (PD) considerations. Dosing and duration of treatment are also important. Duration of therapy should be based on clinical response, and not a set number of days. Another key ASP objective is to further encourage IV-to-PO switch therapy or even better, oral (PO) therapy alone. Other ASP objectives are more challenging, especially the reduction of antimicrobial resistance (an institution-related problem). Antibiotic resistance is not necessarily volume/duration dependent and is not antibiotic class related. Resistance determinants are not well understood, but reducing "antibiotic tonnage" or "antibiotic cycling" often has little or no effect on resistance. Antibiotics are best viewed as being either "low or high resistance potential antibiotics." "Low resistance potential" antibiotics cause little/no resistance independent of volume or duration of use, e.g., nitrofurantoin, doxycycline, ceftriaxone. In contrast, "high resistance potential" antibiotics predispose to resistance even with little use, but resistance further increases with high volume use, e.g., gentamicin, ceftazidime, imipenem. As can be inferred from these "high resistance potential" antibiotics examples, antibiotic resistance is not related to antibiotic class since each antibiotic class has both "low and high resistance potential" antibiotics. Acquired resistance must not to be confused with clonal resistance, which is not related to antibiotic use. The spread of clonal resistance is a function of the effectiveness of infection control (IC) efforts to contain/limit the in-hospital spread of resistant strains. The ASP ID clinician should have a close working relationship with IC to be aware of outbreaks unrelated to antibiotic use.[5]

Another ASP problem is minimizing the potential of antibiotic collateral damage, e.g., adverse effects such as *C. difficile* diarrhea (CDD). Clinical education is critical to overcome long-held misconceptions. It is thought, "only antibiotics cause *C. difficile*." Certainly, clindamycin and most β-lactams can, e.g., piperacillin/tazobactam, but CDD is rare with many other antibiotics, e.g., macrolides, tetracyclines, azithromycin, aminoglycosides, TMP-SMX, tigecycline, daptomycin, linezolid, quniopristin/dalfopristin, colistin, polymyxin B, nitrofurantoin, fosfomycin. Quinolones and carbapenems alone may cause CDD, but CDD is much more likely if these drugs are used with proton pump inhibitors (PPIs).[6,7] Also, physicians need to be aware that non-antibiotic drugs are important causes of CDD, e.g., cancer chemotherapy, some psychiatric medications.

In summary, to be effective, an ASP needs full administrative support, and ID ASP team leadership to educate the medical staff on the most important determinants of optimal antimicrobial therapy.[8,9] (**Table 2**)

Table 2. Antimicrobial Stewardship Principles and Practice: Beyond the Guidelines

Colonization vs. Infection
• Treat infection, not colonization. • Provide empiric coverage primarily directed against the most probable pathogens causing the infection at the body site. • Avoid "covering" or "chasing" multiple organisms cultured that are not (pathogens and non-pathogens) at the body site cultured. • Colonization of respiratory secretions, wounds, or urine with "water" (*S. maltophilia, B. cepacia, P. aeruginosa*) or skin organisms (MSSA, MRSA, CoNS, VSE, VRE) is the rule.
Narrow vs. Broad Spectrum Therapy
• Narrow vs. broad spectrum doesn't prevent resistance, e.g., in treating E. coli urosepsis switching from a carbapenem (broad spectrum) to ampicillin (narrow spectrum) may actually increase resistance potential. • Narrow spectrum vs broad spectrum may not be clinically superior to well-chosen broad spectrum therapy, e.g., switching from ceftriaxone (broad spectrum) to penicillin in treating *S. pneumoniae* has no clinical rationale or clinical advantage and has no effect on controlling resistance. • Antibiotic resistance is not related to spectrum narrowness or broadness, e.g., levofloxacin (broad spectrum but "low resistance potential") vs. ampicillin (narrow spectrum but "high resistance potential").
Antibiotic Resistance
• The best way to control resistance is a selectively restricted formulary; restricting "high resistance potential' antibiotics, e.g., imipenem (not meropenem or ertapenem), ceftazidime (not other 3rd of 4th GC), gentamicin/tobramycin (not amikacin). • Some antibiotics may be restricted for other reasons e.g., excessive vancomycin (IV not PO) use predisposes to VRE emergence and vancomycin may cause cell wall thickening in *S. aureus* resulting in permeability related resistance (to vancomycin and other antibiotics, e.g., daptomycin). • Over restriction of antibiotics may impair timely effective therapy and does not, per se, decrease resistance. • Preferentially select antibiotics (all other things being equal) with a "low resistance potential." Avoid, if possible, "high resistance potential" antibiotics, e.g., macrolides (for respiratory infections), TMP-SMX (for UTIs). • Since resistance is, in part, concentration dependent, subtherapeutic or low antibiotic tissue concentrations, (all other things being equal) predisposes to resistance. • Suboptimal dosing or usual dosing with inadequate tissue penetration, e.g., into the body fluids or undrained abscesses (source control is key) predisposes to resistance.
Monotherapy vs. Combination Therapy
• Preferably use monotherapy whenever possible to cover the most likely pathogen or cultured pathogen clinically relevant to the site of infection. • Combination therapy should be avoided if possible. Always try to preferentially use monotherapy. • Monotherapy is usually less expensive than combination therapy and has less potential for adverse effects and drug-drug interactions. • Combination therapy is often used for potential synergy (rarely occurs and if used must be based on microbiology laboratory synergy studies), to increase spectrum (preferable to use monotherapy with same spectrum), or to prevent resistance (except for TB).
PO and IV-to-PO Switch Antibiotic Therapy
• Wherever possible, treat with entirely oral antibiotic therapy instead of IV therapy. • Switch from IV-to-PO antibiotic therapy after clinical defervescence (usually < 72 hours). • Early IV-to-PO switch therapy eliminates phlebitis and IV line associated infections.
Antibiotic De-escalation
• De-escalation is problematic if based on microbiology data alone without site-pathogen correlation. • De-escalation is appropriate in the setting of broad spectrum coverage of "presumed urosepsis" which can be narrowed after the uropathogen is identified in blood/urine. • In intubated/ventilated patients, microbiology data from respiratory secretion cultures are usually misleading and not representative of NP or VAP lung pathogens. • In patients with NP or VAP, it is more prudent to treat the most likely pathogen, e.g., *P. aeruginosa* (even if not cultured from respiratory secretions) than to be misguided into treating multiple colonizing organisms in respiratory secretions. • De-escalation can be harmful if microbiology data is misleading, e.g., represents colonization rather than being reflective of the pathogen (underlying bone pathogen, not ulcer organisms), e.g., diabetic foot ulcers/chronic osteomyelitis or sacral ulcers/chronic osteomyelitis.
***C. difficile* Diarrhea/Colitis**
• Preferentially select antibiotics (all other things being equal) with low *C. difficile* potential. • Predisposing factors to *C. difficile* include relatively few antibiotics, e.g., clindamycin, β-lactams, ciprofloxacin. • Many antibiotics have little *C. difficile* potential, e.g., aminoglycosides, aztreonam, macrolides, TMP-SMX, colistin, polymyxin B, daptomycin, Q/D, doxycycline, minocycline, tigecycline, vancomycin, linezolid. • Some antibiotics are protective against *C. difficile*, e.g., doxycycline, tigecycline. • Always consider non-antibiotic factors that may predispose to *C. difficile*, e.g., cancer chemotherapy, anti-depressants, statins, PPIs. • Also consider person-to-person spread or acquisition for the environment.
Pharmacoeconomic Considerations
• The least expensive therapy is usually not the best therapy. • The least expensive antibiotic (acquisition cost) may, in fact, be expensive (re: total cost) when considering the cost implications to the institution of dosing frequency, *C. difficile* potential, resistance potential, and degree of activity against the known or likely pathogen, not to mention the cost of potential therapeutic failure vis-à-vis ↑ LOS and medicolegal costs. • Stewardship savings are best achieved by decreasing duration of antibiotic therapy, and by treating entirely with oral antibiotic therapy or early IV-to-PO switch therapy.

BILIARY TRACT INFECTION AND ASP ANTIBIOTIC SELECTION: A PRACTICAL ANTIBIOTIC STEWARDSHIP VIGNETTE

Infectious Disease physicians have been the leaders in optimal antibiotic use.

Optimal antibiotic selection is based on an accurate presumptive clinical diagnosis. Without the correct diagnosis, antibiotic therapy is necessarily suboptimal. The first critical step in antibiotic selection is to identify the likely source of infection, which determines the pathogen at the site of infection. For example, in cholecystitis or cholangitis the usual pathogens are *E. coli*, *Klebsiella pneumoniae*, or vancomycin susceptible enterococci (VSE). In the absence of associated bacteremia that would identify the pathogen, therapy should be directed against all three of the usual pathogens. Therefore, the first consideration in antibiotic selection is spectrum (based on the usual pathogens at the site of infection). Any antibiotic that covers these pathogens is appropriate in terms of spectrum. Biliary tract bacteremias are caused by single organisms (vs. polymicrobial infections from the colon) but since any one of these are the pathogen, all three should be covered until or if the single pathogen is identified.

When using an antibiotic, it is important to equally consider what organisms to cover, as well as what not to cover. Non-biliary pathogens that do not require coverage empirically are *B. fragilis*, MSSA/MRSA. Using biliary infection as an example, the next ASP consideration is to select not only an antibiotic with the correct antibiotic spectrum, but the antibiotic must also penetrate the site of infection, e.g., bile and gallbladder wall in therapeutically effective concentrations. Antibiotics with therapeutic serum levels may be completely ineffective in biliary sepsis if not able to penetrate adequately into the bile/gallbladder wall. To further illustrate the importance of pharmacokinetic (PK) considerations in the biliary tract, it is assumed the common bile duct (CBD) is unobstructed (an obstructed CBD would further limit antibiotic penetration). Antibiotic selection solely based on penetration into an obstructed CBD with the requisite PK properties, but not the proper spectrum makes little sense, e.g., clindamycin penetrates even with an obstructed CBD, but doesn't have proper spectrum/activity against *E. coli*, *K. pneumoniae*, or VSE.

The next consideration in antibiotic selection, using the biliary tract sepsis example, is to understand the "resistance potential" of the antibiotics being considered. Antibiotics may be classified as either "high or low resistance potential" drugs. It is a popular misconception that antibiotic resistance is primarily related to volume or duration of use, which is not the case. Excluding clonal resistance spread, "low resistance potential" antibiotics, for unclear reasons, cause little or no resistance after high volume/prolonged use. Doxycycline, a "low resistance potential" antibiotic has been used extensively worldwide for decades and has few resistance problems. Similarly, in terms of volume of use, the "low resistance potential" antibiotic ceftriaxone has caused virtually no clinically relevant resistance problems after decades of use worldwide. In contrast, "high resistance potential" antibiotics, e.g., ceftazidime, causes widespread resistance even with minimal use, and major resistance problems with high volume use. Resistance is also not an antibiotic class phenomenon since within each class there are "high and low resistance" potential antibiotics, e.g., among carbapenems imipenem (high resistance potential) vs. meropenem, doripenem (low resistance potential).

Taking into account resistance potential, if empiric selection between levofloxacin monotherapy vs. cefazolin plus ampicillin therapy, from a resistance potential alone, levofloxacin would be preferable since ampicillin is a "high resistance potential" antibiotic.

Other considerations include side effects or adverse events, e.g., *C. difficile* potential. In selecting levofloxacin for biliary sepsis, it has the proper spectrum (*E. coli*, *K. pneumoniae*, VSE), penetrates into bile in an unobstructed biliary tract, and has a "low resistance potential." Furthermore, without concomitant PPI use, it has a relatively low *C. difficile* potential. In contrast, cefazolin and ampicillin are β-lactams which, after clindamycin, have a relatively high *C. difficile* potential.

Levofloxacin has the additional advantage of being one drug and has a PO formulation for oral or IV-to-PO switch therapy which shortens hospital length of stay (LOS) and permits earlier discharge.[1,2]

The above biliary sepsis example is illustrative of the practical considerations of antibiotic selection taking into account ASP principles.

References

1. Cunha CB. Principles of Stewardship. In: LaPlante K, Cunha C, Morrill H, Rice L, Mylonakis E (eds.): *Antimicrobial Stewardship: Principles & Practice,* CABI Publishers, London, 2017.
2. CDC ASP Guidelines Elements. https://www.cdc.gov/antibiotic-use/healthcare/pdfs/core-elements.pdf
3. Cunha CB, Varughese CA, Mylonakis E: Antimicrobial Stewardship Programs (ASPs): The Devil is in the Details. *Virulence* 4:147-149, 2013.
4. Cunha BA, Hage JE, Schoch PE, Cunha CB, Bottone EJ, Torres DC. Overview of Antimicrobial Therapy. In: Cunha CB, Cunha, BA (eds.): *Antibiotic Essentials* (15th Edition). Jaypee Brothers Medical Publishers Ltd, New Delhi, 2017.
5. Cunha BA: Effective Antibiotic-resistance Control Strategies. *Lancet* 28:1307-8, 2001.
6. Bouza E: Consequences of *clostridium difficile* infection: understanding the healthcare burden. *Clinical microbiology and infection* 18:5-12, 2012.
7. Dubberke ER, Wertheimer AI: Review of current literature on the economic burden of *Closdtridium difficile* infection. Infection Control and Hospital Epidemiology. 30: 57-66, 2009.
8. Restrepo MI, Frei CR. (2010) Health economics of use fluoroquinolones to treat patients with community-acquired pneumonia. *American Journal of Medicine*. 123, S39-46.

9. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, Keohane C, Denham CR, Bates DW. (2013) Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Internal Medicine.* 173, 2039-46.

Author

Cheston B. Cunha, MD, FACP, Assistant Professor of Medicine, Alpert Medical School of Brown University; Medical Director, Antimicrobial Stewardship Program (Rhode Island Hospital and Miriam Hospital), Providence, RI.

Correspondence

Cheston B. Cunha, MD, FACP
Division of Infectious Disease
Rhode Island Hospital
593 Eddy Street
Physicians Office Building Suite # 328
Providence, RI 02903
401-444-4957
Fax 401-444-8179
ccunha@lifespan.org