ANTIMICROBIAL STEWARDSHIP PROGRAM (ASP)

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INTRODUCTION

Dramatic changes in minimizing the transmission of infectious agents have been made with improved sanitation, purification of water and scientifically improved less crowded housing units. Regular large scale immunization and the discovery of antimicrobials further helped in mitigating the morbidity and mortality associated with such agents. However, the emergence of antimicrobial resistance (AMR) and global increase in such cases in the latter part of last century is a challenge that threatens to negate the gains made by the discovery of antimicrobial agents. Increasing resistance build up is due to widespread, irrational and indiscriminate use of antimicrobials. This causes bacterial genetic alterations due to selective pressure for survival and leads to the acquisition of newer resistance genes. These genes are subsequently transferred between bacteria. Coupled with poor infection control practices, this has resulted in the spread of multiply-drug resistant organisms (MDRO) between patients, intra- and inter-hospital. Furthermore, there is decline in the development of newer antimicrobial drugs.1,2

Antimicrobial resistance can lead to increased cost of drugs, longer expensive hospitalization and super infections with Enterococci spp. that are vancomycin resistant and, Staphylococcus aureus which are meticillin resistant. Among the gram negatives, increased prevalence of extended spectrum beta lactamases (ESBLs), AmpC Beta lactamase, quinolone resistance, Cabapenamase and the Metallo beta lactamase among Enterobacteriaceae, Pseudomonas spp. and Acinetobacter spp is seen with alarming rates.3,5

It is well known that areas within hospitals that have the highest rates of AMR are the various intensive care units (ICUs) and burn units. They also have the highest density of antimicrobial use. Moreover increase in the duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms endogenously and their propensity to spread to other patients and into the community as well upon their discharge.6

In the community, E coli and Salmonella strains resistant to third-generation cephalosporins and fluoroquinolones respectively have been associated with the unrestricted use and unregulated sale of antibiotics i.e. ‘over the counter’ drugs that are sold without prescription. In addition, use of antibiotics in animals for meat and poultry products in the retail food chain has also added to the problem of
AMR. This has further increased the selective pressure among these pathogens in the community. This problem continues to increase, despite recommendations from WHO and others to have this practice stopped, as it leads to organisms moving from animals to human and vice versa.\(^7\) These community pathogens have the potential of being carried to the hospital as well.

Physicians have had to resort to use of antibiotics with unfavourable toxicity profiles and limited pharmacodynamic guidance (eg, colistin), as well as, unconventional combinations of antibiotics that have not been investigated properly. Old ideas are being resurrected, such as the use of lytic bacteriophages, but with little evidence of clinical effectiveness. This leads to a pervasive belief in the scientific community that increasing resistance is the new norm. This is a misleading attitude and will prove costly in the long run, both in human and economic terms.

It was almost ten years ago that the WHO published its global strategy for containment of antimicrobial resistance. However effective stewardship practices for prevention of AMR were not implemented. Sensing this problem, this topic was announced as the theme for World Health Day in 2011.\(^8\)

It is now imperative for the clinicians to play a greater role in conserving the efficiency of the currently available agents for which containment of AMR is required.

**ANTIBIOTIC STEWARDSHIP PROGRAM**

An ASP should be designed to optimize antimicrobial therapy administered to hospitalized patients, to ensure cost-effective therapy, minimize collateral damage to other susceptible commensals causing a repopulation with drug resistant organisms and prevent other unintended consequences such as the toxicity of antimicrobial use. This would help improve patient outcome, contain the problem of bacterial resistance, and preserve the utility of the existing antimicrobials for a longer term.

The primary goal of ASP, also known as antibiotic management program is to raise awareness among health care workers about the escalating problem of AMR in healthcare and community settings. For it to be effective, the development of ASP and implementation of antimicrobial clinical practice guidelines should be comprehensive. ASP is a necessary element of a successful quality improvement program and measures the effectiveness of such a program.

The appropriate treatment options chosen need to be evidence based, with expert consultations and incorporation of local microbiology and resistance patterns (‘hospital antibiograms’), using the fewest formulary drugs that are necessary, with optimum dose, route, duration, side effects to provide cost-effective and, first, and alternate line options. There is evidence to show that the reduction in the use of antimicrobials also brings down the incidence of resistance. It then becomes possible to reduce antimicrobial use without compromising patient safety.

**STRATEGIES OF ASP**\(^9\)

1. Multi disciplinary Committee: The first step in the development of antimicrobial guidelines is to establish a multidisciplinary committee. This should ideally consist of a core team of Infectious Disease physicians, clinical microbiologist, infection control professionals, hospital epidemiologist (optimal), clinical pharmacologist or pharmacist with infectious disease training. The addition of an information system specialist will help to develop guidelines measure audit and improve the ASP. Together they should develop an overall plan to identify the diseases that the guidelines can cover and determine appropriate treatment options. This will help the practitioners in making decisions about appropriate health care for specific clinical circumstances. There should be collaboration between the antimicrobial stewardship team, hospital intensive care therapist, pharmacy (formulary or essential drugs) and also commitment from the top management to keep patient safety as their first priority. Involvement of administrators and senior faculty members will add credibility to the ASP and improve its acceptability. Such collaboration would gain increased acceptance as consensus would generate ownership and thus better adherence Hospital administration should provide the desirable infrastructure support.

2. Education: A small pilot testing could be done and subsequently such collaboration can be scaled up. In addition, publication and dissemination of information, revision and updates would make the program user friendly. Education is an essential element that influences prescribing behavior and provides a foundation of knowledge. This will not only enhance but also increase the acceptance of ASP. Education along with incorporation of active interventions, have a significant impact on antimicrobial prescribing practices.

3. Evidence Based guidelines and clinical pathways: Multidisciplinary development of evidence based practice guidelines, incorporating local microbiology and resistant patterns, can improve antimicrobial utilization. Guideline adherent initial therapy has been shown to be clinically superior, with better survival, reduced length of hospital stay and less expense among patients who met the definition of HAP/VAP.\(^10\) The guidelines must be periodically updated otherwise they may become obsolete.

4. Antibiotic order forms: They can be an effective component of ASP and can facilitate implementation of practi-
cal guidelines. However it could also lead to inappropriate interruption in therapy due to automatic stop orders.

5. Prospective audit with intervention and feedback: The ASP team should be able to conduct prospective audit of the intervention and provide feedback as this is the more important and effective step. This can result in reduced inappropriate use of antibiotics. This was shown in a RCT conducted at a 600-bed tertiary teaching hospital. Inpatients who received suggestions from an infectious diseases fellow and a clinical pharmacist showed fewer days of parenteral therapy and cost savings versus those with no antimicrobial suggestions and with no adverse impact on clinical response, compared with the control group.11

6. Formulary restriction and preauthorization requirements for specific agents: Efforts must be made to limit inappropriate uses of antibiotic via formulary restriction and preauthorization requirements for specific agents. This may lead to immediate substantial reductions in antimicrobial use. However, on the downside, this may lead to increased staff requirements, perceived loss of prescriber autonomy and also may delay implementation of orders owing to delay in obtaining approval, potentially affecting patient safety. Evidence suggesting restriction of use of antimicrobials is appropriate since it is found to reverse the antimicrobial consumption eg: There was a return of Chloroquine (CQ) antimalarial efficacy in Malawi – 1993 by replacing this with Sulfadoxine-Pyrimethamine combination. Even the molecular marker of CQ-resistant P falciparum (PfCRT gene) declined and disappeared by 2001.Following this a RCT of CQ vs. Sulfapyridine in 210 children with uncomplicated falciparum malaria four years later, showed cumulative efficacy was CQ 99% compared to Sulfapyridine 21%.12

7. Monotherapy: It is equally effective with reduced risk of superimposed infections. Systematic plan to shift from a broad spectrum to specific narrow spectrum antibiotic and from parental to oral form would be useful

8. Combination therapy: It can prevent resistance development, but it is redundant and unnecessary, since there is insufficient data available demonstrating better clinical outcome or prevention of resistance. In critically ill patients with a risk of infections due to MDRO, increasing the breadth of coverage and the likelihood of appropriate empiric therapy may further exacerbate the problem.

9. Antimicrobial Cycling: Cycling is the scheduled rotation of one class of antibiotics with one or more different classes that have comparable spectra of activity, with the cycle repeated. It is a deliberate plan to change the routinely used antibiotics after a fixed period of time, like e.g. every 6 months. (“Mixing” is when you randomly change antibiotics on a continuous basis. It is not referring to “combination therapy” specifically although some people may initially assume this to be the case). There is insufficient data to recommend the routine use of antibiotic cycling as a mean of preventing or reducing antimicrobial resistance over a prolonged period of time. Substituting one antimicrobial for other may transiently decrease the selection pressure and reduce the resistance to the restricted antimicrobial. Unless the resistance is eliminated from the bacterial population, reintroduction of the original antibiotic is again likely to select for the expression of the resistant determinant in the exposed bacterial population.

10. Streamlining or de-escalation of therapy: Streamlining of empiric antibiotic therapy on the basis of culture results and elimination of redundant combination therapy or a narrow spectrum that is pathogen focussed is more effective. This results in decreased antibiotic exposure and substantial cost savings.

11. The duration of therapy can also be minimized. In a RCT conducted in 51 French ICUs, among patients with VAP; intervention of 8 day antibiotic regimen when compared with 15 day antibiotic regimen, 28-day mortality was similar.13

12. Dose Optimization: Optimization of antibiotic dosing based on individual patient characteristics, causative organisms, site of infections and PK-PD characteristics of drug is an important part of antibiotic stewardship. Systematic review of studies and several interventions that improved antibiotic prescription among in-patients; 81% showed significantly improved drug outcomes, 75% significantly improved microbiological outcomes, 33% significantly improved clinical outcomes.14 Antimicrobials active against the most likely organism, since most infections are monomicrobial, most likely to penetrate the involved tissue or cell should be chosen. The correct dose, route and duration to impact care and minimize resistance build up should be used.

IMPLEMENTATION OF ASP IN HOSPITALS AND IN COMMUNITY:

CAP guidelines are issued by several countries that focus on: choice of empirical antibiotics, diagnostic evaluation, criteria for admission to hospital and ICU. Besides this, a pathway should be devised which also includes guidelines for: admission and discharge, smoking cessation, preprinted orders with two choices of antibiotic therapy, assessment of pneumococcal and influenza vaccination and oxygenation assessment after admission. All this helps create a ‘halo effect’ in the ASP program that may lead to better outcomes.15,16

Adults with mild to moderate-severe CAP (pneumonia
severity index score ≤ 110), showed a better clinical success rate at day 10 and 28 after 3 days of treatment with intravenous amoxicillin when compared to placebo. Thus this RCT showed that discontinuing antibiotic treatment after 3 days is not inferior to stopping it after 8 days.17

The initial choice of antimicrobial therapy for common infections by empiric antibiotic treatment should be limited to conditions where early initiation of antibiotics has been shown to be beneficial eg. severe sepsis (sepsis-induced tissue hypoperfusion or organ dysfunction) and septic shock, acute bacterial meningitis, community acquired pneumonia, ventilator associated pneumonia and necrotizing fasciitis. Physicians should obtain cultures (two sets of separate blood cultures and other appropriate samples as clinically indicated e.g. normally sterile body fluids, deep pus etc.) before starting empiric antibiotic treatment. They should avoid sending cultures from superficial wounds, decubitus ulcers and chronic draining sinuses. Swab cultures are usually inadequate and provide misleading information regarding diagnosis.

The Ventilator Bundle is an excellent method to reduce VAP rates in ICUs. It contains four components, elevation of the head of the bed to 30-45°, daily ‘sedation vacation’ and daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, and deep venous thrombosis prophylaxis. It is aimed at improving outcome in mechanically ventilated patients. It should be modified and expanded to include specific processes of care that have been definitively demonstrated to be effective in VAP reduction or a specific VAP bundle created to focus on VAP prevention.18

MEASURING THE IMPACT OF ASP ACTIVITIES

It can be done by measuring antimicrobial use, auditing the quality of prescribing performance and monitoring process adherence to institutional guidelines, care bundles, and policies and procedures and cost analysis and outcome indicators such as clinical outcomes, antimicrobial resistance, and health care costs. Data on antimicrobial use and costs, current resistant rates of key sentinel pathogens from sentinel sites such as ICUs and surgical site infection and other hospital acquired infection rates, percentage reduction in ESBL prevalence, percentage decrease in pan resistance among bacteria and infection related quality indicators should be compared before and after ASP implementation. The trend should be monitored.19 Newer strategies such as biomarkers (e.g. Procalcitonin) can also be used to indicate duration of therapy. Institutional data also should be compared with benchmark data from local hospitals and published literature. Process indicators (key performance indicators or KPIs) such as rates of adherence to guidelines, appropriateness and timeliness of therapy for a given infection, advice acceptance rates and rates of concordance with susceptibility reporting can be measured.20

In conclusion, owing to the alarming decline in new drug development, we need antibiotic policies to promote their rational and reduced use so as to reverse/halt emergence of resistant pathogen which in turn helps to reduce cost and also improve patient outcomes. The guidelines for antibiotic use are easy to develop and have the potential to improve prescription practices and optimally use resources. But they are difficult to implement. A successful guideline should be dynamic, simple, credible and have same standards for all levels. It should provide it in the printed form in durable pocket manuals implementing and in electronic copies. There should be official launch of training (induction and in-service), monitoring and supervision programs. Community education on antibiotic use should continue. There should be constant interaction and update of antibiogram resistance monitoring between physicians, infection control team and microbiologist among different hospitals as well. These should help as patients will continue to be infected and physicians will need to treat them effectively with the agents available.

REFERENCES


