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Review Article

Antimicrobial Stewardship: A Need for Today for Safer Tomorrow

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ABSTRACT

Inappropriate empiric antibiotic therapy is widespread and is associated with increased mortality in critically ill patients. Antimicrobial Stewardship Programs (ASPs) promote the appropriate use of antimicrobials thus reducing antimicrobial resistance, health care costs and drug-related adverse events while improving clinical outcomes. Monitoring of adherence of the antimicrobial usage to the guidelines of antimicrobial stewardship program and also determination of sensitivity of the micro organisms towards different antimicrobials used, in the patients of community acquired infections and hospital acquired infections, can play a major role in improving patient outcomes and minimizing the untoward effects of antimicrobial agents including side effects as well as induction of resistance.

Keywords: Antimicrobial stewardship program, Community acquired infections, Hospital acquired infections.

INTRODUCTION

The discovery of penicillin by Alexander Fleming was a major breakthrough in the battle against infectious diseases. (Ho, PL *et al*., 2006). Antimicrobials are agents (as heat, radiation or a chemical) that destroy microorganisms that might carry disease. Patients admitted in tertiary care hospitals are often prescribed by multiple antimicrobials based on their provisional diagnosis. Patients admitted in the ICU are often prescribed multiple broad spectrum antibiotics at admission as they are more sick, exposed to multiple invasive procedures and vulnerable to multidrug resistant pathogens. However these prescriptions are often empiric and based on physician comfort and prior experience, often leading to overuse and misuse of antibiotics. This not only increases the burden of antibiotic resistance but also exposes the patients to the unnecessary side effects of these drugs besides increasing treatment cost. (Williams *et.al*, 2011). Today, antibiotics are the most widely prescribed drugs, yet their value is being threatened by an alarming increase in antibiotic-resistant bacteria. Multidrug-resistant strains of many commonly encountered bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella species*, *Neisseria gonorrhoeae*, and *Pseudomonas aeruginosa* have already emerged. (Ho, PL *et al*., 2006). Antimicrobial resistance is multifactorial, results in an increased length of hospital stay, increased mortality and increased cost of healthcare, and constitutes a major risk for human health. The emergence of antimicrobial resistance and transmission of antimicrobial-resistant pathogens in health systems may be addressed through antimicrobial stewardship in conjunction with infection prevention and control measures. (Martin *et.al.,* 2011).

Current Scenario of Antibiotic Resistance

Persistent indiscriminate use and rising antibiotic resistance world over may result in “Post antibiotic era” in 7-10 years from now. This is an emergency situation for public health care and calls for immediate redress. Implementation of effective antibiotic policy can be one significant step in this direction. There is a scarcity of quality literature on classified antibiogrammes from India, which is an impediment in formulating local, regional or national-level antibiotic policy. Anti-biogramme, prescription auditing and generation of drug resistance index (DRI) could take us a long way in looking at the control of resistance and rational use of antibiotics in our country. Overuse of antimicrobial agents has been described world over in both community and hospital settings. In addition to its effect on patients, antibiotic misuse can provoke emergence of bacterial resistance and increase healthcare cost. It is evident that optimizing antibiotic use is a challenge that deserves to be undertaken. It has been observed that the infectious disease physician plays a crucial role in controlling antibiotic use in the hospital, but a multidisciplinary team approach is known to do better. Though this is the scenario world over, particularly in intensive care units, in our country, we are more vulnerable due to the overwhelmingly indiscrete use and across-the-counter availability of antibiotics. (Wattal *et.al.*, 2012).

Antimicrobial Stewardship

The term '**steward**' is derived from the Old English word 'stigweard', combining 'stig' (hall) and 'weard' (keeper). Therefore, stewardship equates to 'the managing of'. Stewardship is the mantle under which many progressive causes operate, e.g., human rights, conservation, economic welfare, government reform and supervision, education, healthcare, disaster relief, animal welfare, mental health and efforts toward peace. MacDougall and Polk define an antimicrobial stewardship programme as an ongoing effort by a healthcare institution to optimise the use of antimicrobial agents among hospitalised patients in order to improve patient outcomes, ensure cost-effective therapy and reduce adverse sequel of antimicrobial use (including antimicrobial resistance). Antimicrobial management programmes have been pursuing such goals for decades, although the term stewardship has been applied only infrequently. (Allerberger *et.al.*, 2008). Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration. Antimicrobial stewards seek to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains.

Goals of Antimicrobial Stewardship Program

The primary goals of antimicrobial stewardship are to reduce patient morbidity and mortality, prevent or slow the emergence of antimicrobial resistance, and reduce adverse drug effects, including secondary infections, such as C difficile-associated diarrhoea. Secondary goals include a reduction in hospital length of stay and healthcare expenditures, without adversely affecting quality of care. Antimicrobial stewardship includes not only limiting inappropriate use but also optimising antimicrobial selection, dosing, route, and duration of therapy to maximise clinical cure or prevention of infection, while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and cost. Specifically, the goals of antimicrobial stewardship programmes are:

1. To ensure the best clinical outcome, for treatment or prevention of infection
2. To minimise unintended consequences of antimicrobial use including
   a. Adverse drug reactions
   b. Selection of pathogenic organisms e.g. *Clostridium difficile*
   c. Emergence of antimicrobial resistance
3. To minimise healthcare costs without compromising quality of care (Smyth *et.al.* 2009).

Guidelines for Antimicrobial Stewardship Program

Guidelines for developing an institutional program to enhance antimicrobial stewardship were published in 2007 by Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA). These guidelines call for a clinical pharmacist with infectious diseases (ID) training and an ID physician to serve as core members of a multidisciplinary antimicrobial stewardship team, with compensation provided for their time. According to the American Society of Health-System Pharmacists (ASHP) statement on the pharmacist's role in antimicrobial stewardship and infection prevention and control, pharmacists should assume a prominent role in antimicrobial stewardship because of their knowledge of and influence over antimicrobial use and membership on multidisciplinary committees in the institution. A clinical microbiologist, infection control professional, information system specialist, and hospital epidemiologist should be included in the antimicrobial stewardship program (ASP) core team, according to Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) guidelines (Martin *et.al.*, 2011).

- **Antimicrobial Stewardship Team and Administrative Support**
  antimicrobial stewardship team includes an infectious diseases physician and a clinical pharmacist with infectious diseases training and that both of these individuals are compensated appropriately for their time. Optimally, the team should include a clinical microbiologist who can provide surveillance data on antimicrobial resistance, as well as an information system specialist who can provide the computer support necessary for surveillance and implementation of recommendations.

- **Elements of an Antimicrobial stewardship Program**
  A comprehensive evidence-based stewardship program to combat antimicrobial resistance includes elements chosen from among the following strategies, which are based on local antimicrobial use and resistance problems, and on available resources that may differ depending on the size of the institution or clinical setting.

ANTIMICROBIAL STEWARDSHIP STRATEGIES (Dellit *et.al.*, 2007)

➢ **Active Antimicrobial Stewardship Strategies**

- **Prospective audit with intervention and feedback.** Prospective audit of antimicrobial use with direct interaction and feedback to the prescriber, performed by either an infectious diseases physician or a clinical pharmacist with infectious diseases training, can result in reduced inappropriate use of antimicrobials.

- **Formulary restriction and preauthorization requirements for specific agents.** Formulary restriction and preauthorization requirements can lead to immediate and significant reductions in antimicrobial use and cost and may be beneficial as part of a multifaceted response to a nosocomial outbreak of infection.

➢ **Supplemental Antimicrobial Stewardship Strategies**

- **Education**
  Education is considered to be an essential element of any program designed to influence prescribing behaviour and can provide a foundation of knowledge that will enhance and increase the acceptance of stewardship strategies.

- **Guidelines and clinical pathways**
  Multidisciplinary development of evidence-based practice guidelines incorporating local microbiology and resistance patterns can improve antimicrobial utilization.

- **Antimicrobial cycling and scheduled antimicrobial switch**
  "Antimicrobial cycling" refers to the scheduled removal and substitution of a specific antimicrobial or antimicrobial class to prevent or reverse the development of antimicrobial resistance within an institution or specific unit. Substituting one antimicrobial for another may transiently decrease selection pressure and reduce resistance to the restricted agent.

- **Antimicrobial order forms**
  Antimicrobial order forms decrease antimicrobial consumption in longitudinal studies through the use of automatic stop orders and the requirement of physician justification.

- **Combination therapy: prevention of resistance versus redundant antimicrobial coverage**
  The rationale for combination antimicrobial therapy includes broad-spectrum empirical therapy for serious infections, improved clinical outcomes, and the prevention of resistance. Combination therapy does have a role in certain clinical contexts, including use for empirical therapy for critically ill patients at risk of infection with multi drug resistant pathogens, to increase the breadth of coverage and the likelihood of adequate initial therapy.

- **Streamlining or de-escalation of therapy**
  Streamlining or de-escalation of empirical antimicrobial therapy on the basis of culture results and elimination of redundant combination therapy can more effectively target the causative pathogen, resulting in decreased antimicrobial exposure and substantial cost savings.

- **Dose optimization**
  Optimization of antimicrobial dosing that accounts for individual patient characteristics (e.g., age, renal function, and weight), causative organism and site of infection (e.g., endocarditis, meningitis, and osteomyelitis), and pharmacokinetic and pharmacodynamic characteristics of the drug is an important part of antimicrobial stewardship.

- **Conversion from parenteral to oral therapy**
  Antimicrobial therapy for patients with serious infections requiring hospitalization is generally initiated with parenteral therapy. Enhanced oral bioavailability among certain antimicrobials—such as fluoroquinolones, oxazolidinones, metronidazole, clindamycin, trimethoprim-sulfamethoxazole, fluconazole, and voriconazole— allows conversion to oral therapy once a patient meets defined clinical criteria. This can result in reduced length of hospital stay, health care costs, and potential complications due to intravenous access.

- **Computer Surveillance and Decision Support**
  Computer-based surveillance can facilitate good stewardship by more efficient targeting of antimicrobial interventions, tracking of antimicrobial resistance patterns, and

identification of nosocomial infections and adverse drug events.

- **Microbiology Laboratory**
  The clinical microbiology laboratory plays a critical role in antimicrobial stewardship by providing patient-specific culture and susceptibility data to optimize individual antimicrobial management and by assisting infection control efforts in the surveillance of resistant organisms and in the molecular epidemiologic investigation of outbreaks.

- **Monitoring of Process and Outcome Measurements**
  In conjunction with developing local strategies for improving antimicrobial stewardship, programs must establish process and outcome measures to determine the impact of antimicrobial stewardship on antimicrobial use and resistance patterns.

Benefits of antimicrobial stewardship program

An Antimicrobial Stewardship Programme has several benefits. It reduces the use of targeted antibiotics and antimicrobial expenditure. Nonetheless crude or infection-related mortality rates, time to receipt of appropriate antibiotics, and length of hospitalisation are not affected by the implementation of ASPs. These findings are important because they indicate that patient safety is not compromised. At an institutional level, programmes designed to limit utilisation of agents that exert greater effect on the above have reduced specific resistance rates. Measurement and monitoring is an essential part of the programme. After an initial implementation of a restricted formulary and antimicrobial approval system, one should review the formulary, assess its effectiveness, provide and coordinate ongoing physician education, and analyse antimicrobial utilisation data within the hospital. The programme should be dynamic and continually reassessed, with new components added and unsuccessful components deleted (Ho, PL *et.al.*, 2006).

Disadvantages of antimicrobial stewardship program

The stewardship programme involves proactive monitoring and feedback. An alternative approach is 'no control' (i.e. only by passive means). Such an approach relies heavily on the distribution of national guidelines and has been shown not to work. Guidelines are seldom studied thoroughly by clinicians, and even if read, are unlikely to be incorporated into everyday practice. The perception of 'threatened physician autonomy' can be a significant hindrance. Another barrier to implementation is the perception that an ASP is solely cost-driven and patient safety may be compromised. For this reason, recent reports have emphasised the inclusion of quality indicators such as time to reception of appropriate empirical antibiotics. (Ho, PL *et.al.*, 2006).

Infection control and its measures

Infection is the invasion of a host organism's bodily tissues by disease-causing organisms, their multiplication, and the reaction of host tissues to these organisms and the toxins they produce. Infections are caused by microorganisms such as viruses, prions, bacteria, and viroids, and larger organisms like macro parasites and fungi. Hosts can fight infections using their immune system. Mammalian hosts react to infections with an innate response, often involving inflammation, followed by an adaptive response. Pharmaceuticals can also help fight infections (Patel, D., and MacDougall, C., 2010).

Masks, respiratory protection, eye protection, face shields and gowns must be worn in specific conditions. Specific measures must also be carried out with regard to patient care equipment, linen and laundry, dishes, glasses, cups and eating utensils (Foucault, F. and Brouqui, P., 2007).

Infections can be classified as

I: Community Acquired Infection and
II: Hospital Acquired Infection.

- **Community-acquired infections**
  Community-acquired infections are acquired anywhere other than in a healthcare facility, in settings such as schools, exercise facilities, or any place you come in contact with other people or with surfaces that have been contaminated. (Maya *et.al.*, 2010).

Some of the most common community-acquired infections

- ***Staphylococcus & Methicillin Resistant Staphylococcus Aureus(MRSA)***
- ***Clostridium difficile***
- ***Vancomycin-Resistant Enterococci***
- ***Noroviruses***

- **Healthcare/ Hospital Acquired Infections**
  Hospital-acquired infections (HAIs) (also called "nosocomial infections" or "health-care-associated infections") are infections that a patient acquires while in hospital being treated for some other condition. They have a significant impact on both patients and the province's health system. (ISBN 978-1-4249-7835-9 (PDF))

1.9.2.1 Escape Pathogens

***E**nterococcus faecium*, ***S**taphylococcus aureus*
***C**lostridium difficile*, ***A**cinetobacter baumannii*
***P**seudomonas aeruginosa*, ***E**nterobacteriaceae*

(includes *Enterobacter* species, *Klebsiella pneumoniae, Escherichia coli*). The majority of hospital-acquired infections are caused by a small group of bacteria with increasing resistance to currently available antimicrobial agents. The acronym ESKAPE has been used for these pathogens—*Enterococcus faecium, Staphylococcus aureus (S. aureus), Klebsiella pneumoniae (K. pneumoniae), Acinetobacter baumannii, Pseudomonas aeruginosa (P. aeruginosa),* and *Enterobacter* species—because of the high likelihood of their escape from the effects of antimicrobial therapy. These agents are now referred to as ESCAPE pathogens (Table 1) with C for *Clostridium difficile* replacing K for *K. pneumoniae* and E for Enterobacteriaceae (which include *Enterobacter* species, *K. pneumoniae, Escherichia coli*, and other pathogens) instead of *Enterobacter* species, to reflect recent increases in antimicrobial resistance in and the impact of hospital-acquired infections caused by these organisms. (Martin *et.al.,* 2011).

Factors influencing the development of nosocomial infections (Ducel, G. *et.al.*, 2002)

i. **The microbial agent** Contact between the patient and a microorganism does not by itself necessarily result in the development of clinical disease.
ii. **Environmental factors**
Health care settings are an environment where both infected persons and persons at increased risk of infection congregate. Patients with infections or carriers of pathogenic microorganisms admitted to hospital are potential sources of infection for patients and staff.
iii. **Patient susceptibility**
Patients with chronic disease such as malignant tumours, leukaemia, diabetes mellitus, renal failure, or the acquired immunodeficiency syndrome (AIDS) have an increased susceptibility to infections with opportunistic pathogens.
iv. **Bacterial resistance**
Many patients receive antimicrobial drugs. The widespread use of antimicrobials for therapy or prophylaxis (including topical) is the major determinant of resistance.

CONCLUSION

Antimicrobial stewardship will demarcate the sensitivity of the antimicrobials towards community-acquired infections as well as the hospital-acquired infections and suggest the measures for reducing cause of morbidity and mortality associated with it. Infections caused by resistant or MDR (multi drug resistance) pathogens are associated with increased mortality, longer length of hospital stay, and higher healthcare costs. The prevalence of these dangerous bacteria will affects antimicrobial choices across a wider range of patients, particularly when choosing empiric therapy. Together with infection control, antimicrobial stewardship is an attractive solution to the challenges posed by antimicrobial resistance. Emphasis must be given on the de-escalation of therapy than escalation of therapy which helps in decreased risk of bacterial resistance.

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