CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://zenodo.org/records/10697997

https://www.iajps.com/volumes/volume11-february-2024/01-issue-02-february-24/

Available online at: http://www.iajps.com Review Article

GUARDIANS OF RESISTANCE: A REVIEW OF ANTIMICROBIAL STEWARDSHIP AND IMPACT OF CLINICAL PHARMACISTS

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Abstract:
AMS is a crucial aspect of healthcare in hospitals, aimed at optimizing antimicrobial usage to enhance individual patient treatment while minimizing the risk of developing resistance. With the escalating AMR globally and a limited pipeline for new antimicrobial agents, it has become even more critical to have robust AMS programs to preserve the effectiveness of existing antimicrobials. It is essential to have interdisciplinary teams comprising infectious diseases specialists, clinical pharmacists, clinical microbiologists, and infection control experts to oversee these programs with support from the hospital leadership. Strategies for modifying antimicrobial prescribing practices include educating prescribers on appropriate antimicrobial utilization, establishing restricted antimicrobial formularies, and providing feedback to prescribers on their antimicrobial prescribing practices. The integration of clinical computer systems can facilitate the execution of these strategies by providing tailored patient data and recommendations at the point of care. Infection prevention plays a vital role in AMS efforts, and effective prophylactic strategies can decrease the incidence of hospital-acquired infections, thereby improving patient outcomes and reducing the need for unnecessary antimicrobial exposure.

Keywords: AMS, infection, intensive care unit, low and middle-income countries, AMR, antimicrobials, prescribing

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*Please cite this article in press J.S.Venkatesh et al., **Guardians Of Resistance: A Review Of Antimicrobial Stewardship And Impact Of Clinical Pharmacists**, Indo Am. J. P. Sci, 2024; 11 (02).*

INTRODUCTION:

AMR is a rising concern for patient safety and public health.[(1,2)] The development and spread of resistance are associated with exposure to antimicrobials, both at the population and individual level;[(3–8)] hence, it's essential to use these agents only when necessary and apply the shortest effective treatments. Even for the most critically ill patients, where immediate broad-spectrum therapy is crucial, daily review of these prescriptions and de-escalation to narrow-spectrum agents when feasible, are now considered standard practices, as stated in the Surviving Sepsis guidelines[9] and the English Department of Health Start Smart then Focus programme.[10]AMS programs strive to enhance individual patient outcomes while reducing unintended consequences, such as the creation of resistant organisms and adverse effects on the individual patient.[11] These programs usually involve evidence-based guidelines, educational initiatives, and regular feedback on antibiotic usage data to prescribers to encourage rational and evidence-based prescribing.[10] These stewardship practices are now part of the regulatory framework of the English Department of Health.[12] Clinical pharmacists play a vital role within hospitals as advocates of evidence-based medicine and cost-effective prescribing.[13] In England, hospital clinical pharmacy services often include daily ward visits, review of medication charts, provision of personalized recommendations on medication use, and participation in multidisciplinary ward rounds to offer expert advice on medication management. In light of the rising issue of antimicrobial resistance (AMR), it is recommended that bolstered clinical pharmacy interventions focusing on anti-infectives could play a vital role in refining treatment approaches, enhancing patient outcomes, promoting prudent prescribing practices, curtailing inappropriate usage, and potentially impeding the progression and dissemination of resistance. [(9,11,14–17)]

The creation and extensive use of antimicrobial agents has been one of the most significant public health measures in the previous century.[18] These agents, along with improved sanitation and widespread vaccination (where available), have significantly reduced infectious mortality.[19] Antimicrobials, which have been in the environment for thousands of years, are not a human invention. Humans have adopted the molecules that fungi, soil actinomycetes, and other microorganisms use to secure their ecological niche in a world full of competitors.[20, 22]

Shortly after the widespread medical use of natural antimicrobial products, human pathogens resistant to these agents were isolated. Resistance genes, which had likely been present for thousands of years, were quickly incorporated by human commensal and pathogenic flora.[21,23] It's remarkable how microorganisms have rapidly developed resistance to modified antimicrobials designed to evade original resistance mechanisms, as well as to new synthetic agents never before present in the environment. This is a testament to the impressive reproductive rate of most microorganisms, the enormous selective pressure applied by antimicrobial agents, and the vast number of uncultivable organisms in the environment that may serve as reservoirs of AMR genes.

The mass production of antimicrobials provided a temporary advantage in the battle against microorganisms. However, if the current rate of increase in resistance to antimicrobial agents continues, we may enter what some call the post-antibiotic era.[27] The introduction of new agents that evade resistance mechanisms has kept medicine one step ahead of resistance. However, the pace of antimicrobial drug development has significantly slowed in the last 20 years, with the approval of new antibacterial agents by the United States Food and Drug Administration decreasing by 56% from 1983 to 2002.[26]

Collaborative initiatives involving industry, academia, and government have been proposed to rejuvenate the development of antimicrobial drugs.[25] However, due to the time gap between the discovery of active molecules and their clinical application, we may face a decade or more with minimal introduction of new antimicrobial agents. Resistance to these new agents is expected to emerge once they are introduced into clinical practice. For instance, despite almost no resistance cases in clinical trials with the new antimicrobial daptomycin, resistance cases started appearing shortly after its limited clinical use.[24] Therefore, it's crucial to optimally use the currently available antimicrobials to ensure treatment options for infections.

AMS programs have been working towards this goal for years. These programs aim to ensure the correct use of antimicrobials to achieve the best patient outcomes, minimize adverse effects, enhance cost-effectiveness, and decrease or stabilize resistance levels. Until recently, the focus has been on the first three goals (patient outcome, toxicity, and cost). In the coming decade, the priority is likely to shift towards mitigating AMR. This review will discuss the rationale, structure, analysis, and outcomes of AMS programs, with a particular focus on their impact on AMR.

Serious infection often leads to ICU admission and necessitates the use of antimicrobial therapy. Given the limited number of new agents being developed, it's crucial to focus on proper antibiotic use and disease prevention. AMS refers to the careful selection, dosing, and duration of antimicrobials to achieve optimal clinical outcomes in treating or preventing infection while minimizing toxicity and resistance development.[28]

Background:
Historically, the role of pharmacists was primarily to dispense medications as prescribed by doctors.[32] However, over the past few decades, the field of pharmacy has evolved beyond just dispensing medications. Pharmacists have become integral members of clinical teams in hospital wards and have taken on management roles.[(23,33)] They are increasingly significant stakeholders in patient care, working alongside nurses and doctors, with a professional focus shifting towards pharmaceutical care and individual patients' drug therapy.[(34–36)] Recently, pharmacists have started to take on more responsibilities in the governance of antibiotics. This includes controlling the availability of drugs in the hospital[30], educating and raising awareness about AMR among nursing and medical staffs[31], and conducting audits and providing feedback on antibiotic use.[29]

Stewardship programs can aid in reducing improper prescriptions and the broad-spectrum use of antimicrobials, enhancing clinical outcomes for the entire population, slowing the rise of AMR, and preserving healthcare resources. Pharmacists are a crucial part of the stewardship team and play a significant role in addressing AMR.[81]

AMS strives to enhance patient care and mitigate the negative effects of antimicrobial overuse or misuse, such as reduced effectiveness, the rise of AMR, the onset of secondary infections, adverse drug reactions, extended hospital stays, and increased healthcare costs. Recent guidelines provide specific suggestions for creating institutional programs to boost AMS. Ideally, these programs should be all-encompassing, involve multiple disciplines, have the backing of hospital and medical staff leadership, and utilize evidence-based strategies that best suit local needs and resources.[78]

Association between Antimicrobial Use and Resistance:

A thorough grasp of the connection between antimicrobial usage and resistance is necessary for the best management of antimicrobial use to reduce resistance. This information includes the interactions between antimicrobial molecules and their microbial targets in vitro, the risks involved in giving an antimicrobial to a patient individually, and the ecological level, where studies of the combined effects of antimicrobial use are conducted using data from hospitals or the national government. Depending on the particular drug-bug combination, the nature of these drug-organism connections can vary significantly, while certain similar motifs might show up.[37] Even after a great deal of research, we still don't fully grasp these intricate relationships, particularly from an ecological standpoint.[(38, 39)]

Programs for managing antibiotics that are based on a partial knowledge of the connection between the use of antibiotics and resistance may be ineffectual or even harmful. Restrictions on the use of intravenous vancomycin were put in place following the sharp rise in vancomycin-resistant enterococci in the United States during the mid-1990s.[40] The biological plausibility of these suggestions was supported by early research indicating that the use of vancomycin was associated with an increased incidence of vancomycin-resistant enterococcal infections.[(41-44)] The main goals of many antimicrobial management strategies were to control and monitor the use of vancomycin.[45] Later research, however, indicated that intravenous vancomycin use was related to a significantly decreased risk of vancomycin-resistant enterococci, and when the strictest criteria were used, vancomycin was not linked at all.[46] Rather, the likelihood of isolating vancomycin-resistant enterococci appeared to be increased by drugs like clindamycin and broad-spectrum cephalosporins, with varying agents having varying impacts on acquisition, amplification, or transmission. Subsequent investigations using animal models have proposed explanations for the preventive effects of drugs such as piperacillin-tazobactam and the increased risk of vancomycin-resistant enterococci associated with cephalosporin usage.[47] Vancomycin use probably contributed to the formation of vancomycin-resistant enterococci, although other substances might be more important in keeping these resistant strains alive. Vancomycin-resistant enterococci have been successfully reduced by interventions to modify the use of these medications.[(48-50)] Fluoroquinolone use has been connected in several studies to the isolation of methicillin-resistant Staphylococcus aureus.[51,52] Other drugs inert against methicillin-resistant S. aureus do not exhibit the same degree of association, suggesting that the magnitude of the connection is more than what would be predicted by simple selection pressure.[53] Fluoroquinolones may have a special effect on the development of resistance factors and adherence determinants in staphylococci, according to in vitro research.[54,55] It is unclear if limiting the use of fluoroquinolones will contribute to a decrease in the amount of methicillin-resistant S. aureus that is found in hospital environments.

These illustrations show how important it is to continue researching the connection between antibiotic use and resistance in order to develop efficient AMS initiatives. It's also essential to follow good methodological guidelines when carrying out these kinds of investigations. For example, based on whether the research followed excellent epidemiologic criteria, distinct risk variables for vancomycin-resistant enterococci were reported, according to a meta-analysis.[56] The significance of appropriate study design, control group selection, and confounding factor adjustment has been underlined in recent reviews.[57] These standards were not met by a large number of frequently referenced research in the AMR literature. The necessity for methodologically solid research to direct the administration of antimicrobial drugs is paramount as we approach a time when AMS becomes vitally relevant.

Definition and Prevalence of AMS:

AMS programs, also referred to as antibiotic policies, management, or control programs, are crafted to oversee and guide the utilization of antibiotics within healthcare environments. Such initiatives encompass various activities, including intravenous-to-oral conversion protocols, pharmacokinetic consulting services, and drug substitution aimed at cost efficiency. Nonetheless, when these actions operate independently of broader programs, their influence on overall antibiotic usage or resistance may be limited.

During outbreaks of illnesses resistant to antibiotics, temporary bans on antibiotic usage may be implemented alongside heightened infection control measures. However, these interventions are secondary unless integrated into broader efforts to optimize antimicrobial use. AMS programs are defined as ongoing endeavors undertaken by hospitals and other healthcare institutions to optimize antibiotic utilization among hospitalized patients. The primary goals of such programs are to ensure cost-effective therapy, improve patient outcomes, and mitigate adverse effects like resistance.

Several surveys have been conducted to assess the extent of AMS program implementation in healthcare institutions. A survey of 88 U.S. hospitals by Rifenburg et al. found that two-thirds had an antimicrobial formulary.[58] About 28% of hospitals required prior approval from an infectious diseases clinician before dispensing certain antimicrobials, and in 21% of cases, a clinical pharmacist's approval was needed. Larger hospitals were more likely to have antimicrobial restriction programs. A survey of 502 physician members of the Infectious Diseases Society of America's Emerging Infections Network revealed that 50% reported their practising hospital had an antimicrobial restriction program in place, with teaching hospitals significantly more likely to have such a program than non-teaching hospitals (60% versus 17%).[59] An examination of 47 hospitals engaged in the Centers for Disease Control and Prevention's Project ICARE revealed that each hospital acknowledged possessing an antibiotic formulary, with 91% implementing at least one additional antimicrobial management approach. Nonetheless, teaching hospitals demonstrated a notably higher tendency to enforce regulations on antimicrobial prescription compared to non-teaching hospitals.[60] Thus, teaching hospitals appear more likely to implement stringent antimicrobial control policies than non-teaching hospitals, possibly due to a higher perceived need for antimicrobial control, greater availability of resources and staff to administer the programs, or a lesser need to accommodate physician autonomy compared to non-teaching hospitals.

Roles of Clinical and Hospital Pharmacists in AMS Programs:

Many AMS programs originated as cost-saving measures initiated by pharmacy departments, placing pharmacists at the forefront of these programs.[61] Pharmacists, due to their role in processing medication orders and familiarity with hospital formularies, are well-suited for this task. Different pharmacists may play varying roles in these programs. Some pharmacists, whose primary role is processing medication orders and dispensing drugs, may note when restricted antimicrobials are ordered and inform the prescriber that authorization is required. However, these pharmacists may not have the time or specialized training in infectious diseases to provide recommendations for complex cases. Therefore, it's increasingly common to have a clinical pharmacist with specialized training in infectious diseases dedicated to administering the AMS program.

Formal training programs for clinical pharmacists in infectious diseases are expanding and becoming more standardized in the United States. This training typically involves at least two years of postgraduate work, with at least one year focusing on infectious diseases pharmacotherapy. Pharmacists who undergo such training acquire proficiency in microbiology, as well as in the pharmacokinetics and pharmacodynamics of antimicrobials, the pharmacotherapy of infections, and antimicrobial administration and oversight. When involved in AMS programs, these clinical pharmacist specialists share responsibility for various activities, including developing guidelines for antimicrobial use, educating healthcare professionals, reviewing hospital antimicrobial orders, administering restrictive strategies, providing pharmacokinetic consultation, and researching program outcomes.[62]

In 1997, the Infectious Diseases Society of America expressed concerns about hospital pharmacists providing therapeutic recommendations.[63] While no pharmacist, regardless of their training level, is qualified to practice medicine, properly trained clinical pharmacists can significantly impact patient care in various areas, including infectious diseases when working alongside physicians. [(64-66)]

Gross et al. implemented an AMS program at their teaching hospital, requiring physicians to get approval via a dedicated pager to use restricted antimicrobials.[67] A clinical pharmacist with infectious diseases training, supported by a senior infectious diseases physician as needed, managed the pager on weekdays, while infectious diseases physician fellows handled it on nights and weekends. The study compared the appropriateness of therapy and clinical outcomes from recommendations made by the pharmacist or the fellows. Recommendations made by the pharmacist were deemed appropriate by blinded physician review significantly more often (76%) than those made by the fellows (44%). Moreover, patients whose physicians received recommendations from the pharmacist were significantly more likely to achieve clinical or microbiological cure (49%) than those who received recommendations from the infectious diseases fellows (35%). Due to the need for midlevel practitioners to enforce AMS policies, clinical pharmacists are likely to become increasingly important partners to infectious disease physicians in implementing AMS programs in the coming decades.[68]

DISCUSSIONS:

It's been suggested that stewardship programs should be evaluated using a combination of process and outcome indicators.[69] Enhancements in AMS have been demonstrated to improve rational antibiotic prescribing and decrease Clostridium difficile infection rates. [(70,71)] The declining rates of C. difficile infection in England since 2005[72] may be associated with a decrease in the use of cephalosporins and fluoroquinolones due to AMS practices, along with factors like changing strain type epidemiology. A recent U.S. study showed that having a pharmacist on a multidisciplinary AMS team significantly reduced the use of fluoroquinolones, clindamycin, and ampicillin/sulbactam compared to when a pharmacist was not part of the team.[73] Moreover, providing prescribers with feedback on compliance data related to prescribing policies has been shown to enhance compliance. [(74,75)] This quality improvement methodology is used by some, but not all hospitals. Advances in hospital information systems and the implementation of electronic prescribing records could potentially improve the correlation between antibiotic use and patient outcomes.

Critical proactive tactics, supported by evidence, include prospective audits, interventions, feedback mechanisms, formulary restrictions, and preauthorization measures. Additional approaches encompass personalized education, tailored guidelines, and informatics aiding clinical decision-making. The overarching objectives of interventions are to minimize unnecessary antimicrobial initiations, promptly refine or scale back therapy, transition from intravenous to oral administration, optimize dosages and ascertain the correct duration of treatment.[78]

The clinician-led and clinical pharmacist-driven AMS has proven to be effective in implementing lasting change in LMICs like India, where there is a significant shortage of infectious diseases physicians. The multidisciplinary model in this hospital has the potential to be expanded to other hospitals in India and LMICs.

Pharmacist-driven AMS models have also yielded positive results in other LMIC settings. For instance, a study on a pharmacist-driven AMS program across 47 hospitals in South Africa demonstrated a significant decrease in inappropriate antibiotic use.[76] Similarly, pharmacist-led antimicrobial audits and feedback in a referral hospital in Ethiopia resulted in a reduction in antimicrobial consumption.[77]

AMS is a critical component in the fight against AMR, aiming to optimize the use of antimicrobials to improve patient outcomes and reduce negative consequences such as resistance and adverse drug reactions. Clinical pharmacists play an integral role in these programs across various healthcare settings.

Since most antibiotic prescriptions in outpatient care occur there, clinical pharmacists play a critical role in AMS initiatives.[78] By decreasing unnecessary medications, enhancing therapeutic results, and preserving healthcare expenditures, pharmacists help AMS.[79] The creation of comprehensive, professional curricula facilitates the education of pharmacists who specialize in antimicrobial therapy, improving their capacity to provide efficient AMS.[80] Clinical pharmacists in emergency care oversee AMS programs, with a particular emphasis on culture follow-up for patients who are released from the ER.[81] Clinical pharmacists with training in infectious illnesses are advised to be essential members of the multidisciplinary team in inpatient AMS programs.[82] To maximize the prescription of antibiotics, hospital AMS programs are becoming more and more significant. Clinical pharmacists should be a part of these programs' interdisciplinary teams.[83] The role of pharmacists in AMS in English hospitals has expanded, with a significant increase in specialist antimicrobial pharmacists and their involvement in stewardship activities.[84] Pharmacists face interprofessional and resource constraints in their antibiotic governance roles, but their expertise is critical for optimizing antibiotic use.[85] In LMICs, clinical pharmacists are the key to the operational delivery of stewardship interventions, demonstrating increased appropriateness and compliance with antimicrobial prescriptions.[86] Engaging pharmacy students, residents, and fellows in AMS can help address the shortage of formally trained pharmacists in stewardship roles.[87]

These studies suggest that clinical pharmacists, especially those with infectious diseases training, are integral to AMS programs across various healthcare settings, contributing to optimized prescribing, improved patient outcomes, cost reduction, and combating AMR, although their impact may be influenced by interprofessional dynamics and resource availability.

CONCLUSION:

If adequately resourced, most community hospitals should be capable of successfully implementing an AMS program. Evidence indicates that effective AMS can result in reduced overall and inappropriate use of antimicrobials, decreased drug-related expenses, a decrease in Clostridium difficile-associated disease, and in some research, a reduction in the emergence of AMR.[78]

Clinical pharmacists play a vital role in AMS and can effectively drive sustainable changes in LMICs like India, where there is a significant shortage of infectious disease physicians. A multidisciplinary approach to AMS has the potential to be expanded to other hospitals in India and other LMICs, where professional boundaries currently limit the integration of pharmacists into clinical services.[88]

In conclusion, clinical pharmacists are indispensable in the implementation and success of AMS programs. Their expertise in medication management, ability to guide appropriate antimicrobial use, and participation in multidisciplinary teams are pivotal in curbing AMR and improving patient care.

Abbreviations:

AMR Antimicrobial resistance
AMS Antimicrobial stewardship
LMICs Low and middle-income countries

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