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Original Research Paper

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ANTIMICROBIAL STEWARDSHIP: A POTENTIAL TOOL FOR RESTRICTING RESERVED ANTIMCROBIALS USE, COMBATING THE ANTIBIOTIC RESISTANCE, ADVERSE DRUG REACTIONS AND SAFE DRUG ADMINISTRATION IN PATIENT CARE

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ABSTRACT Ensuring the safety of drugs constitutes a critical component of healthcare, focusing on the detection, assessment, and prevention of adverse drug reactions (ADRs). Antibiotics are among the most precious and they have finite source, different from the other drugs. Antibiotics are the only drugs that do not directly affects the patients, instead they affect the growth and ecology of the pathogens that invade and also to the commensals flora. The therapy of antibiotics mostly depends on clinical conditions of the patients and the drug, however, it also depends on characterstics of organisms and the resident flora. But because of improper use of antibiotics, specially the reserved antibiotics, antibiotic resistance cases have been increasing along with serious adverse reactions while patient care. So to overcome this problems most of the hospitals have established antimicrobial stewardship programs, to optimize the beneficial effects of antibiotics as well as minimise the negative consequences for both patients and community. The Pharmacovigilance program seeks to involve diverse stakeholders, including healthcare professionals, pharmacists, and the public, in the reporting of ADRs. Nevertheless, in developing nations such as India, there is a noticeable lack of public participation in reporting ADRs. The objective of this paper is to raise awareness about drug safety and adverse drug reactions , antibiotic resistance, that are associated with miss use of antibiotics and minimising the use of reserved antibiotics by implementing the antimicrobial stewardship program

KEYWORDS : Antimicrobial stewardship program, Reserved antibiotics, Antibiotic resistance, Adverse drug reactions, Safe drug administrations

INTRODUCTION:

The healthcare system is an intricate network of high-risk situations, involving multiple professionals, institutions, and reliance on technological support. Given this complexity, the potential for errors and their severe consequences is significant. Therefore, it is crucial to prioritize the prevention and assessment of risks and damages to patients within the healthcare setup, as emphasized by the World Health Organization (WHO) [1].

Medication safety is a central concern, encompassing terms like Adverse Drug Events (ADE), Adverse Reactions (ADR), and Medication Errors (ME). ADE refers to any harm caused by a drug, with ME and ADR being two types of ADEs: "Preventable ADE" and "Non-preventable ADE." Preventable ADE or ME results from errors in drug use, such as contraindicated usage, while Non-preventable ADE or ADR stems from appropriate use at normal doses [2, 3].

MEs can occur at various stages of the medication use process, including prescribing, ordering, storage and labelling, distribution, administration, and monitoring. Incidents with potential harm, even if intercepted before reaching the patient or due to luck, are termed Potential ADEs [4, 5, 6]. ADEs, often caused by medications, lead to negative outcomes like hospital admissions, prolonged stays, increased resource utilization, absenteeism, and decreased patient satisfaction. Incidence rates vary across settings, such as 6.5% in adult inpatients, 27.4% in adult outpatients, and 2.3% in paediatric inpatients [7]. Medication errors, more frequent but not always resulting in adverse events, highlight the importance of understanding their epidemiology [8, 9, 10, 11, 12]. Research in the field aims to reduce harm associated with medications, focusing on the epidemiology of ADEs and medication errors [. A methodology for identifying and classifying medication safety issues has been developed over the past decade, providing a framework for investigating ADEs and medication errors in diverse healthcare settings. Antibiotics are among the most precious and they have finite source, different from the other drugs. Antibiotics are the only drugs that do not directly affects the patients, instead they affect the growth and ecology of the pathogens that invade and also to the commensals flora, but because of rampant use of antibiotics in the past years, its value has been compromised at a large scale and leading to crisis of antimicrobial resistance. An important cause of misuse of antibiotics is lacking knowledge of prescribing antimicrobials in many areas of professionals. So to combat this problem implementation of antimicrobial stewardship is very important in every hospitals. The principle of antimicrobial stewardship is avoiding selection pressure in the patient, both for pathogenic bacteria and normal flora, so that no one should use antibiotics unnecessarily, only the least broad-spectrum antibiotic is being use with right dose, right time and possible shortest duration. To date, most of the education efforts have been targeted among the medical doctors after their training and at the adult public. In the recent years it has been taught among the children also. It is now high time that academician and health and education ministries jointly focus on an adapted undergraduate medical/ professional curriculm so that an integrated approach can be made which focus principles of infectious diseases, clinical microbiology and clinical pharmacology with special emphasis on the principles of prudent prescribing.

TYPES OF ADVERSE REACTIONS:

Adverse Drug Reactions (ADRs) are unwanted or harmful reactions to medications. They can occur due to various factors, including individual differences in response to drugs, drug interactions, dosage errors, or underlying medical conditions. ADRs are typically categorized into different types based on their characteristics and mechanisms. Here are

some common types of adverse drug reactions

Type A (Augmented) or Predictable	High dose of NSAIDs caused gastrointestinal bleeding
Type B (Bizarre) or Unpredictable	Stevens-Johnson syndrome caused by Sulfonamides
Type C (Chronic)	Drug-induced osteoporosis with long-term corticosteroid use
Type D (Delayed)	Carcinogenic effects or drug-induced malignancies caused by anticancer drugs
Type E (End of Use)	Withdrawal symptoms from certain medications like benzodiazepines.
Type F (Failure)	Antibiotic treatment failure due to microbial resistance.
Type G (Genetic)	G6PD deficiency leading to hemolysis with certain drugs.

Significance Of Drug Safety:

Preserving public health relies heavily on ensuring the safety of pharmaceuticals. Despite the numerous lives saved and enhanced by pharmaceutical interventions each year, every drug carries inherent risks, spanning from mild side effects to severe adverse reactions [13]. The overarching goal of drug safety initiatives is to recognize and minimize these risks, safeguarding patients and optimizing the overall benefit-to-risk ratio of medications. Upholding drug safety in stills confidence in patients, fosters adherence to treatment plans, and mitigates the burden of drug-related illnesses and fatalities.

Drug Development Process And Safety Evaluation:

Prior to a drug entering the market, it undergoes a stringent development and evaluation process. Preclinical studies, involving laboratory and animal experiments, assess the drug's potential efficacy and safety. Positive results lead to clinical trials, conducted in phases to evaluate safety and efficacy in humans. These trials, involving carefully chosen populations and meticulous monitoring, aim to identify any adverse effects [14]. Regulatory bodies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) scrutinize trial data, making informed decisions on drug approvals based on benefit-to-risk assessments.

Pharmacovigilance: Surveillance Of Drug Safety:

Pharmacovigilance encompasses the science and activities related to detecting, assessing, understanding, and preventing adverse effects or other drug-related problems. It plays a crucial role in post-marketing surveillance, monitoring the safety of approved drugs once they are accessible to the general population. Healthcare professionals, patients, and pharmaceutical companies contribute to pharmacovigilance by reporting adverse drug reactions (ADRs) to regulatory authorities [15]. These reports facilitate ongoing assessment of drug safety profiles, identification of emerging risks, and implementation of appropriate risk mitigation measures, such as labelling changes, dose adjustments, or even drug withdrawals if necessary.

Adverse Drug Reactions And Risk Communication:

Adverse drug reactions (ADRs) are unintended and harmful effects resulting from the normal use of a medication. They can range from mild reactions, like nausea or dizziness, to severe or life-threatening events. Prompt detection and assessment of ADRs are crucial for preventing harm and ensuring drug safety. Regulatory authorities collaborate with healthcare professionals, pharmaceutical companies, and patients to collect and analyse ADR reports. Effective risk communication is vital in disseminating information about potential risks associated with specific drugs to healthcare providers and patients, enabling informed decision-making and minimizing potential harm.

Ensuring Drug Safety In The Digital Age:

In the era of rapid technological advancements and the widespread availability of health information online, the landscape of drug safety is undergoing transformation. Social media platforms and online forums have become channels for patients to share experiences and report potential ADRs. Pharmaceutical companies and regulatory authorities are exploring innovative approaches, such as data mining of social media posts, to complement traditional pharmacovigilance systems. These emerging methods hold the promise of enhancing drug safety surveillance by improving the detection of previously unknown adverse effects.

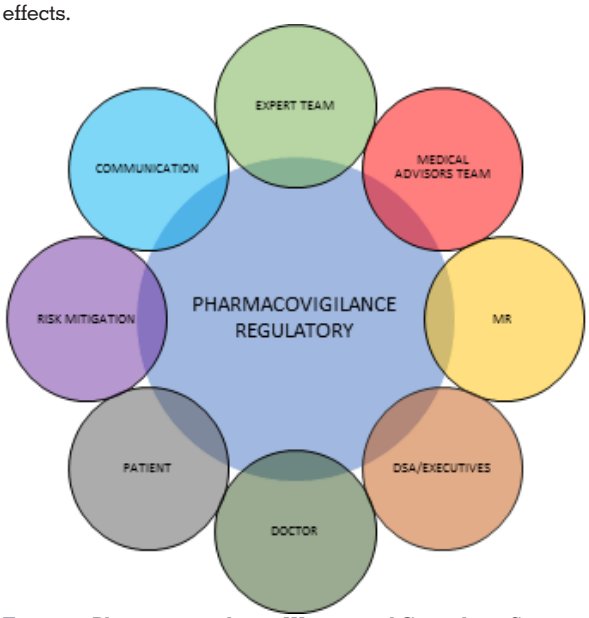

Figure 1: Pharmacovigilance Writing and Consulting Support

AIM OF THE REVIEW

With this background, it is important that by prescribing proper antimicrobial and stewardship strategies can help to minimise the untoward events and also reduce harm associated with medications, focusing on the epidemiology of ADEs and medication errors which would support the rationale of antimicrobial stewardship programme and prevent antimicrobial resistance unintended consequences. The article explain the adverse drugs reactions and its consequences, the need and implications of the antimicrobial stewardship programme, to fight resistance , adverse drug reactions , safe drug delivery and save global health.

Literature Search

Relevant literature as searched using PubMed, Google scholars, Scopus, using different words, e.g., antimicrobial stewardship, Antibiotic resistance, Adverse drug reactions and Drug safety. Original article, short communications, reviews, correspondence were reviewed, and information were collected.

Antimicrobial Stewardship Program (AMSWP)

Antimicrobial stewardship (AMS) is a coherent set of actions which measures, optimizes and improves antimicrobial drug use [16]. The goals of AMS are to change inappropriate prescribing and excessive use of antimicrobial drugs in order to preserve antibiotic effectiveness and limit further spread of resistant microorganisms. AMS actions comprise evaluation of antimicrobial therapy prescriptions, providing feedback to drug prescribers, setting antimicrobial therapy guidelines and educating prescribing physicians [17]. AMS actions improve healthcare, increase patient safety and reduce inpatient therapy costs [18].

PROBLEMS ASSOCIATED WITH ANTIBIOTIC USE

There are various factors that contribute the problems of antibiotic use. Among those, inavailability of data and poor commitment, unassured drugs and irrational use [19]. Another factor is unable to prevent and control infections [20]. Although various preventive approach have been implemented for antibiotic resistance, but antimicrobial stewardship program is taking the upper hand. It will registry on an annual basis to look for the quality of antibiotics use in different hospitals. Some of the important aspects such as, switching the parenteral antibiotics to oral antibiotics, which would minimise the antibiotic resistance. Use of Ciprofloxacin and Ceftazidime in empirical treatment is an another contributing problem. Restricting use of these antibiotics can minimse various adverse reactions and narrow down the antibiotic resistance cases. Another issue is favouring the antibiotics. So clinician should practices rotational antibiotics prescriptions [21]. It has seen that, because of improper empirical antibiotics treatment, resistance increases drastically. For clinician it is not easy to balance the early and aggressive treatment against conservative approach, but switching to narrower spectrum or cut off use of antibiotics when not need would be the best approach for prevention of antimicrobial resistance, and its associated adverse effects [22].

Reserved Antibiotics In Population Pharmacokinetic And Antimicrobial Stewardship Program

It is very much important to esure prudent use of antimicrobials agents so that resistance of antibiotics will cut down, its associated adverse effects are nullified, so the ELMMB formulary of National Health Service United Kingdom has formulated some antimicrobials as ' reserved antimicrobials'[Table 2]. According to the guidelines, the pharmacy will not spply those antimicrobials until prescribed for a specific indication or there is documented evidence from a consultant microbiologist in a notes or a prescription pad. Pharmacist will not dispense unless they get a confirmatory notes from a consultant microbiologist.

Reserved antibiotics are a category of antimicrobial medications that are employed with prudence and have limited accessibility due to their potential for the development of resistance and adverse effects. These investigations have underscored the necessity for antimicrobial stewardship programs to optimize the utilization of reserved antibiotics and avert the emergence of resistance. The prescribing patterns of reserved antibiotics displayed variation across the investigations, with different antibiotics such as Meropenem, Colistin, Piperacillin/Tazobactam, and Linezolid being commonly prescribed [23, 25]. Furthermore, the investigations emphasized the significance of adjusting the dosage based on renal function for certain reserved antibiotics in order to ensure safe and optimal utilization. In addition, a pharmacoeconomic analysis has been conducted to evaluate the cost-effectiveness of reserved antibiotics and provide guidance for drug selection. The escalation in bacterial antimicrobial resistance, particularly in neonatal intensive care units (NICUs), has been attributed to the inappropriate utilization of antibiotics. Research has indicated that the implementation of antibiotic stewardship programs can result in a decrease in antibiotic usage and an improvement in clinical outcomes among very low birth weight infants. Studies focusing on KPC-producing Klebsiella pneumoniae have demonstrated that interventions in antimicrobial stewardship have led to a reduction in antibiotic consumption and rates of carbapenem resistance [24]. Reserved antibiotics pose a significant concern within the realm of pharmacokinetics. Multiple studies have placed their focus on the population pharmacokinetic modelling of specific antibiotics, including Cefazolin, Ampicillin, ciprofloxacin, Polymyxin B, and Levofloxacin. The objective of these studies was to establish population pharmacokinetic models and restricted sampling strategies that can aid in the process of therapeutic drug monitoring. To illustrate, Sat navy et al. conducted a study wherein they developed population pharmacokinetic models for Cefazolin, Ampicillin, and Ciprofloxacin [26].

Table 2:- List Of Reserved Antimicrobials

1	Amikacin
2	Amphotericin B
3	Aztreonem
4	Ciprofloxacin
5	Ceftazidime
6	Cholramhenicol
7	Flucytosine
8	Linezolid
9	Meropenem
10	Nalidixic acid
11	Pipericllin+tazobactam
12	Tobramycin
13	Ertrapenem

Impact On Environment Of Antibiotic Use

It has been shown that, there is a huge impact on ecosystems, especially on microbial population and their function because of improper disposal and use of antibiotics [27, 28] such as disruption of normal flora and increases the pathogenic bacteria. It will also contribute to the emergence of drug resistance bacteria in the environment which is a greater threat to human world [29, 30, 31, 32]. [3,4,5,6]. So it is utmost important to consider the impact of antibiotic use in the environment and promote proper use of antibiotic practices that prioritize to protect both human and environmental health. Awareness program should be implemented among the public and the healthcare worker regarding the potentials impacts of antibiotics on environment and the importance of proper disposal. This awareness program should also incorporated the role of individual responsibility in reducing the environmental impact of antibiotic use, e.g. reducing unnecessary antibiotic use, avoiding flushing antibiotics down the toilet and unused antibiotics should be returned to the pharmacy for proper disposal. At the same time it is the responsibility of governments and the agencies that regulate the development and implementation to encourage sustainable practices for antibiotic manufacturing and the use in agriculture and other sectors. Parallely animal agriculture also raise concern about the antibiotic resistance and spread of antimicrobial resistance, which ultimately effect the human health. As such it is crucial to balance the demands of agriculture industry with the need to preserve te efficacy of antibiotics and protect public health. It include promoting use of alternatives to antibiotics in agriculture sector, such as probiotics and prebiotics as well as implementing regulations on the discharge of untreated wastewater from pharmaceutical facilities and hospital preimises [32]. With these steps we can contribute to help the preservation of antibiotics for our future generation and at the same time can protect the human and environmental health.

CONCLUSION:

Protecting lives and promoting public health are central goals in ensuring drug safety, a critical aspect of pharmaceutical development and usage. The process involves a holistic approach, encompassing all stages from drug development to post-marketing surveillance. Robust Pharmacovigilance systems and collaborative efforts among regulatory bodies, healthcare professionals, pharmaceutical companies, and patients play a pivotal role in identifying, minimizing, and effectively communicating potential risks associated with medications. As the field continues to evolve, embracing technological advancements and leveraging data will enhance drug safety measures, ultimately contributing to the well-being of individuals worldwide and advancing public

health. Rampant use of reserved antibiotics is a special factor for antibiotic resistance and adverse effects so there is a need of control of reserved antibiotic use. Antimicrobial stewardship program is very much necessary to implement in the hospital for the establishment of drug formularies in hospitals and the involvement of the clinical pharmacist in order to ensure rational antibiotic therapy and quality of patient care by reducing cost of therapy. Rapid laboratory testing, verifying prescriptions for the reserved antibiotics, should be carried out by the cinical pharmacist. Therefore, it is now crucial to focus on an adapted undergraduate medical/professional curriculum that teaches all necessary principles of microbiology, infectious diseases and clinical pharmacology, with emphasis on the principles of prudent prescribing in an adequate format. Appropriate curricula on antimicrobial stewardship are a joint responsibility of the academia and the ministries of Health and Education.

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