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AN OVERVIEW PHARMACIST'S ROLE IN PREVENTING MEASURES TOWARD ANTIBIOTIC RESISTANCE

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Abstract:
The issue of antimicrobial medication resistance is a significant global concern. Drug discovery plays a crucial role in addressing present treatment gaps and enhancing established therapeutic methods. However, due to the extensive research duration and substantial expenses involved in introducing novel drugs to the market, focusing on the development of new drugs that target drug-resistant microbes with harmful effects may not be the most optimal approach. The literature was systematically evaluatesing databases to identify all relevant research published until the beginning of 2022. In order to uncover novel classes of antibiotics, there is a pressing need for the development of innovative methodologies in rational design and screening-based approaches. The advancement of efficient molecular methodologies for the identification of resistance genes, as well as the exploration of diagnostic biomarkers such as procalcitonin for the purpose of guiding the discontinuation of antibiotic treatment, holds significant value in the effort to mitigate antibiotic usage.

INTRODUCTION:

Antibiotics have emerged as a fundamental component in the management of infectious diseases, playing a pivotal role in the remarkable advancements in world health during the past seven decades. A significant number of individuals presently experience successful recovery from infections that were formerly considered to be potentially fatal. However, it should be noted that antibiotics possess limited availability. The introduction of each new antibiotic has resulted in decreasing efficacy and the development of antibiotic resistance (ABR) within a very short period of time [1].

The emergence of antimicrobial resistance (ABR) can be attributed to the inappropriate utilization of antibiotics across various sectors, including healthcare, animal husbandry, agriculture, and aquaculture. Misuse of antibiotics encompasses various practices, including unnecessary usage, usage without proper medical guidance, self-administration, inconsistent or interrupted dose, and the sharing of antibiotics. Efforts aimed at addressing antimicrobial resistance (ABR) necessitate a comprehensive approach that encompasses the detection, prevention, and management of resistance. These endeavors must be strategically planned, well-coordinated, and consistently maintained [2]. This necessitates the involvement of governments, academia, industry, healthcare providers, and the general public at both national and international levels. This would not only provide assistance to patient treatment but also promote economic growth and enhance national security [3].

Antimicrobial resistance (AMR) is a comprehensive concept that encompasses the resistance exhibited by bacteria and other microorganisms, including parasites (such as malaria-causing organisms), viruses (such as HIV), and fungus (such as candida), to medications used for the treatment of illnesses. The pharmaceutical business faces challenges in pursuing the development of novel treatments due to the prevailing objective of reducing antibiotic usage and the consequent impact on incentives. Consequently, industry objectives frequently shift towards allocating resources to the creation of medications targeting chronic ailments necessitating prolonged consumption. The establishment of a "one health" plan to address regulation, independent monitoring, and policing is of vital importance, even in the presence of newly successful antibiotics. This necessitates worldwide collaboration and commitment [4].

The presence of knowledge gaps, preconceived conceptions, and non-adherence to prescribing recommendations among both patients and prescribers contributes to the emergence and progression of resistance.It is imperative to enhance the dissemination of knowledge on ABR, modify behaviors, formulate guidelines tailored to specific contexts for prescribers, and implement comprehensive regulations across all domains. In order to mitigate the proliferation of antibiotic- resistant diseases, it is imperative for the industry to collaborate with policy-makers and adopt innovative business structures [5].

The World Health Organization (WHO) has identified antibiotic resistance as a significant global security concern, with far-reaching implications for global health, food security, and development. It is considered to be of equal importance to other pressing global issues such as terrorism and climate change. According to the World Bank, the potential economic consequences of the current situation are projected to surpass those of the global financial crisis that occurred in 2008-2009. It is estimated that the impact might result in a reduction of world gross domestic product ranging from 1.1 to 3.8 percent. Unlike the recession, the effects of this situation are expected to be experienced over a longer duration, rather than being limited to the short term. This information is supported by reference [6]. Quantifying the actual expenses incurred due to the inability to employ antibiotics as a regular practice poses a challenging task [7]. The cost estimates have been characterized as rudimentary, as they mostly reflect current conditions rather than future projections, and are primarily applicable to industrialized nations rather than emerging ones [8].

The phenomenon of antibiotic resistance has the potential to impact individuals of various age groups residing in diverse nations across the globe. According to estimates, a significant number of individuals, primarily residing in low- and middle-income countries (LMICs), succumb annually to treatable infectious diseases, with the projected figure reaching 5.7 million. The potential for saving numerous lives would have been realized had antibiotics been effective and accessible. The aforementioned figure significantly exceeds the global yearly mortality rate of 700,000 attributed to antimicrobial resistance (ABR). The emergence of antibiotic resistance poses a significant challenge to the provision of optimal healthcare, highlighting the persistent disparity in access to antibiotics that disproportionately impacts the world's most impoverished populations. Therefore, it may be argued that maintaining the efficiency of antibiotics while also guaranteeing widespread access to them is an ethical responsibility [9,10].

DISCUSSION:

Since the discovery of resistance to the initial commercial antimicrobial drug, penicillin, in 1948, a significant number of bacterial pathogens have exhibited resistance to one or more antibiotics currently employed in clinical settings [11]. The presence of antibiotic-resistant bacteria has been consistently seen in close proximity to the introduction of new antibiotics in hospital settings [12]. This correlation suggests a strong likelihood that the utilization of antibiotics in any context will definitely lead to the emergence of antibiotic resistance. Regrettably, despite the observed rise in antibiotic resistance, there has been a significant decrease in the production of innovative antimicrobial drugs throughout the last three decades [13]. Hence, in order to avert the resurgence of the pre-antibiotic age, it is imperative to exercise greater prudence in the utilization of current antibiotics.

The Study for Monitoring antibiotic Resistance Trends (SMART) is widely recognized as the leading global surveillance system for monitoring the prevalence and trends of antibiotic resistance among various microorganisms. The analysis of data obtained from the SMART research reveals variations in the prevalence of antimicrobial resistance across different geographic regions. Notably, the Asia-Pacific countries exhibit the greatest levels of antimicrobial resistance, as observed in patients diagnosed with appendicitis [12,13]. The most recent findings from the SMART study indicate that the prevalence of ESBL-positive rates in E. coli, which were obtained from intra-abdominal infections (IAIs) in the Asia- Pacific area, had an almost twofold increase from 2002 to 2010, reaching 40.8% [14,15]. The significant surge of ESBL production subsequent to the early 2000s has posed a substantial challenge in the realm of treating infections caused by Enterobacteriaceae [15]. An additional significant concern within the Enterobacteriaceae family pertains to its resistance towards expanded-spectrum cephalosporins. These antibiotics are commonly employed to effectively treat enterobacterial infections. It has been observed that Enterobacteriaceae strains obtained from patients with intra-abdominal infections (IAIs) in the Asia-Pacific region exhibited a gradual rise in resistance to expanded-spectrum cephalosporins, specifically ftazidime and ceftriaxone, during the period spanning from 2002 to 2010 [14,15].

Numerous guidelines have been published regarding optimal antibiotic prescribing in the context of infections associated with extended-spectrum beta- lactamase (ESBL) manufacturers [16,17]. Nevertheless, it is imperative that these rules are consistently revised in accordance with the progressions in understanding. An in-depth comprehension of community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-acquired pneumonia (HCAP) can equip physicians with enhanced knowledge for antibiotic selection, thereby aiding in the prevention of antibiotic resistance. The publication of guidelines in 2005 provided a framework for the management of individuals with nosocomial pneumonia, including hospital-acquired pneumonia (HAP), ventilator- associated pneumonia (VAP), and healthcare- associated pneumonia (HCAP) [18]. According to a study that was recently published, adherence to the guidelines has been found to potentially elevate death rates among patients with hospital-acquired pneumonia (HAP) or healthcare-associated pneumonia (HCAP) [19]. Among a cohort of 303 patients who were deemed to be at risk for multidrug- resistant pneumonia, it was observed that 129 patients received treatment in accordance with established guidelines, while the remaining 174 patients were administered non-compliant prescriptions. The 28-day mortality rate was found to be 34% in the compliance group and 20% in the non-compliance group, indicating a significant difference between the two groups. This implies the necessity for revised protocols in the management of nosocomial pneumonia in adult patients. Recent research has been conducted on the optimization of treatment for ventilator-associated pneumonia (VAP) [20]. The administration of cefepime 2 g every 8 h or meropenem 2 g every 8 h, in combination with tobramycin and vancomycin, resulted in a significant decrease in infection-related mortality by 69% (8.5% vs. 21.6%). Additionally, this treatment approach led to a reduction in infection-related length of stay by 55% (11.7 vs. 26.1 days) when compared to the outcomes observed in historical controls who received the traditional low dosing regimen. The observed incidence of superinfections was similarly decreased

(21). This observation highlights the advantages associated with administering high dosages of antibiotics through continuous infusions. According to the literature, it has been observed that the timely initiation of multi-antibiotic therapy in patients with hospital-acquired pneumonia (HAP) can lead to a higher survival rate compared to the use of mono- antibiotic therapy [22]. Several studies have indicated that, when compared to patients with community- acquired pneumonia (CAP), patients with healthcare- associated pneumonia (HCAP) exhibit more severe illness, increased mortality rates for intermediate severity cases, higher rates of comorbidity, poorer functional status, and a greater likelihood of receiving incorrect antibiotic prescriptions [23]. Consequently, it is imperative to administer proper early antibiotic therapy in order to mitigate the mortality rate among patients diagnosed with healthcare-associated pneumonia (HCAP). According to Niederman's recommendation, ertapenem is suggested for the treatment of both severe and non-severe patients with healthcare-associated pneumonia (HCAP) who do not have a risk of Pseudomonas aeruginosa infection. On the other hand, for HCAP patients who are at risk of Pseudomonas aeruginosa, imipenem or meropenem are recommended [24].

Pharmacokinetic (PK) and pharmacodynamic (PD):

Another aspect of antimicrobial resistance pertains to the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics exhibited by various antibiotic formulations. The study conducted by Hoffman et al. (25) examined the impact of an orally administered sustained-release antibiotic formulation on the development of antimicrobial drug resistance in rats. The justification for utilizing oral sustained-release medicines is based on two primary factors: the relatively brief half-life of the majority of antibacterial drugs and the challenges associated with achieving pharmacodynamic targets [26]. Nevertheless, the administration of antibiotics through oral means inadvertently affects the natural microflora residing in the colon, a factor that is frequently disregarded. Typically, sustained-release formulations are linked to a higher proportion of unabsorbed medication in the colon compared to immediate-release formulations. This leads to the unnecessary exposure of colonic microflora to an antimicrobial agent, which may potentially facilitate the colonization of antibiotic- resistant bacteria in this specific anatomical region [26].

The research employed amoxicillin, a β-lactam antibiotic that is frequently prescribed for the management of aerobic Gram-positive bacteria as well as certain aerobic Gram-negative bacteria. β-lactam antibiotics has a relatively brief duration of action and demonstrate a mode of action characterized by time- dependent bactericidal activity. It is of significance to note that the absorption window for β-lactams in rats closely resembles that observed in humans [27]. After the administration of amoxicillin by oral route, the presence of amoxicillin-resistant colonic bacteria was observed in fecal samples, although no such bacteria were found in samples from subjects who received a placebo. This finding indicates that a portion of the antimicrobial agent was not absorbed and reached the colon, hence promoting the development of bacteria that are resistant to amoxicillin. The administration of a β-lactamase was employed to prevent the occurrence of these adverse effects. This enzyme facilitated the degradation of the unabsorbed portion of the substance prior to its passage into the upper intestine. Consequently, the prevention of drug-resistant bacteria was achieved through the neutralization or inactivation of an excessive amount of drug in a therapeutic setting. The findings of this study suggest that it is crucial to thoroughly evaluate the potential for microbial resistance throughout the development and administration of a sustained-release antibacterial formulation [28].

The class of medications referred to as fluoroquinolones serves as a prime illustration of how pharmacokinetic (PK) and pharmacodynamic (PD) qualities can exert an influence on treatment results. According to a study, fluoroquinolones rank second in terms of frequency of prescription in US hospitals, with cefazolin being the most regularly prescribed antibiotic [29]. Stamey et al. (30) were among the pioneers in establishing the direct correlation between inadequate antibiotic dose and the development of microbial drug resistance. The researchers observed a correlation between the concentration of nalidixic acid and the number of resistant strains in their study involving 100 strains of Enterobacteriaceae. Subsequent investigations have yielded analogous findings with numerous

different fluoroquinolones. A valuable reference point in the determination of the most effective dosage regimen with minimum development of antibiotic resistance for a certain class of antibiotics is the mutation prevention concentration (MCP) [31]. The minimum inhibitory concentration (MIC) refers to the concentration of a medicine that is necessary to inhibit the emergence of any single-step mutations within a bacterial cell population of at least 10^32. The study conducted by Dong et al. (33) examined the impact of delivering different amounts of fluoroquinolones on the formation of bacterial colonies. With an increase in antibiotic concentration, there was a significant drop in colony number, facilitating the calculation of the minimum inhibitory concentration (MIC). It is postulated that bacteria who exhibit survival following an initial substantial decline have likely undergone a mutation in the first stage. Following an initial fall, a period of stability, or plateau, ensued, which was then followed by a second notable decline in the population of surviving colonies. This observation suggests the presence of a minimum point of inflection, or a critical turning point, in the data. Bacteria that exhibited survival in the presence of the MPC presumably possessed an additional mutation in a subsequent phase. This study establishes the foundation for the notion of the 'mutant selection window', which refers to the range of antibiotic concentrations situated between the minimum inhibitory concentration (MIC) and mutant prevention concentration (MPC). This window represents the conditions under which selective antibiotic growth can take place, leading to the selection of resistance mutants [34]. The mutant selection window has been established for numerous fluoroquinolones and other antibiotics. Prudent utilization of this data throughout the process of prescribing has the potential to enhance the efficacy of fluoroquinolones while simultaneously reducing the occurrence of resistant strains [34].

The study conducted by Madras-Kelly et al. (year) examined the effectiveness of an intervention aimed at reducing nosocomial MRSA infection rates by the promotion of decreased fluoroquinolone utilization [35]. The intervention implemented a visual cue in the form of a flagged message, which would be shown on an automated order-entry screen if fluoroquinolones were chosen as the prescribed antibiotic. The communication encompassed the advice provided by the Society for Healthcare Epidemiology of America (SHEA) about the prevention of nosocomial transmission of multidrug-resistant strains of S. aureus and Enterococcus species. Additionally, the message included recommendations for the restriction of broad- spectrum antibiotics, with a specific focus on fluoroquinolones [35].

Antibiotic overuse:

In the United States, the medical profession predominantly prioritizes the care and treatment of individual patients, rather than emphasizing the overall health and well-being of the broader population. As an illustration, a medical practitioner commonly administers a certain treatment regimen for an infection, irrespective of its association with elevated levels of resistance [36]. Consequently, there is a frequent occurrence of incorrect prescription of antibiotics. There has been a rise in the utilization of broad-spectrum antibiotics, regardless of the specific infection or reason for treatment, despite the growing emphasis on reducing antibiotic prescriptions for common ailments [36,37].

The Swedish Strategic Program for the Regional Utilization of Antimicrobial Agents and Surveillance of Resistance (STRAMA) was created in 1994 with the objective of safeguarding the efficacy of antimicrobial agents within Sweden. The utilization of antibiotics in Sweden exhibited a notable rise throughout the 1980s and the initial years of the 1990s. After the identification of multidrug-resistant pneumococcal species in young infants during the early 1990s, significant efforts were undertaken by medical professionals to mitigate the transmission of these pathogenic microorganisms. Originally, the endeavor focused solely on pneumococcal species; however, it has recently expanded to include a wide range of microorganisms [36].

The publication by Molstad et al in 2008 provided a comprehensive overview of the initial decade of STRAMA's activities. The primary aim of STRAMA is to effectively mitigate the proliferation of antibiotic resistance on a nationwide scale. From 1995 to 2004, there was a notable decline in total

antibiotic consumption, as measured by day doses per 1000 inhabitants per day (DDD). Specifically, there was a 15% reduction in total antibiotic use, with the DDD decreasing from 17.3 to 14.6. Moreover, outpatient antibiotic use had an even greater fall of 20%, as the DDD dropped from 15.7 to 12.6 during the same period. The study found that there was a 23% decrease in the number of prescriptions, from 536 to 410 per 1000 inhabitants per year. The largest decrease was observed in the usage of macrolides, which declined by 65%. The findings from STRAMA demonstrate that a collaborative approach among healthcare professionals can effectively reduce general antibiotic usage and mitigate the spread of antibiotic resistance [38].

The primary emphasis of a significant portion of the scholarly investigation pertaining to antibiotic management revolves around the issues of excessive and improper utilization. However, Gross et al have lately shed light on the significance of abstaining from the use of antibiotics altogether, particularly in the context of treating bacteriuria that is linked with urinary tract infection (UTI) [38]. A positive urine culture can potentially suggest the presence of a significant medical illness, such as pyelonephritis or cystitis, as well as benign or asymptomatic bacteriuria (ASB) [39].

According to the guidelines established by the Infectious Disease Society of America in 2005, it has been determined that there is no anticipated advantage in conducting screenings or administering antibiotic treatment for asymptomatic bacteriuria (ASB) in specific patient populations. These populations include premenopausal women who are not pregnant, individuals with diabetes, older individuals residing in community or long-term care facilities, as well as patients with spinal cord injury or those with indwelling bladder catheters. It is advisable to do screening and administer treatment when the patient is pregnant or before undergoing surgical procedures that involve the urinary system. Significantly, the guidelines emphasize that attempts to eliminate germs can frequently prove ineffective and may inadvertently contribute to the proliferation of more resilient strains, including extended-spectrum β-lactamase-resistant bacteria, vancomycin-resistant enterococci, and other similar pathogens. Therefore, it is recommended to discourage the utilization of antibiotics for the treatment of asymptomatic bacteriuria (ASB) in order to mitigate the indiscriminate application of antimicrobial agents and the emergence of drug- resistant bacterial strains [4].

CONCLUSION:

The multidisciplinary core group, comprising professionals from many fields such as medicine, pharmacy, microbiology, epidemiology, and infectious disease, possesses the capacity to disseminate knowledge to diverse segments of the population. In the context of healthcare facilities, it is advisable for prescribers to administer antibiotics in accordance with established recommendations and Antimicrobial Stewardship Programs (ASPs). This practice entails a comprehensive evaluation of multiple factors, including pharmacokinetics/pharmacodynamics (PK/PD) and minimum inhibitory concentration/minimum bactericidal concentration (MIC/MPC) of antibiotics, diagnostic test outcomes, antimicrobial susceptibility testing (AST) results, clinical response, and impact on the microbiota. Comprehensive disinfection protocols within hospitals and adherence to personal hygiene practices among healthcare personnel, particularly hand cleanliness, are crucial in mitigating the occurrence of nosocomial infections. The formulation of the guideline for farmers should be expedited. It is recommended that farmers refrain from employing medically significant antibiotics, such as carbapenems and vancomycin. Instead, they should contemplate the utilization of alternative measures such as vaccinations, bacteriocins, antimicrobial peptides, and bacteriophages, which can serve as substitutes for antibiotics.

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