REVIEW ARTICLE

A SITUATIONAL ANALYSIS OF ANTIMICROBIAL DRUG RESISTANCE IN AFRICA: ARE WE LOSING THE BATTLE?

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ABSTRACT

BACKGROUND: The first arrival of a sizable shipment of penicillin at the North African Theatre of Operations for USA military use in 1943 was a landmark that turned a new chapter of antibiotic use in Africa. Over the past decade the expansion of resources and the technological advances have meant that much larger quantities of drugs are available in developing countries than ever before. As a result, many more individuals are receiving necessary treatment or therapy than just ten years ago. This very welcome event is accompanied by the terrible irony that increases in drug availability and use can promote drug resistance and render the same life-saving drugs ineffective.

METHODS: The study focused on bacterial pathogens. One hundred and three relevant literatures were identified from the PubMed online database. The coverage included research articles concerning antimicrobial resistance involving subjects of an African country.

RESULTS: Resistant bacteria are on a war path and evidently have acquired an edge over us. Our actions are evidently fuelling the resistance. The indiscriminate use of antibiotics in humans and livestock, wrong and substandard prescriptions by unqualified 'medical personnel' together with poor diagnosis or lack of it are all adding fuel to the already fired train of resistant microbes.

CONCLUSION: To win the war and turn tables as we did with the discovery of penicillin and other antimicrobials in the 1940s, then we must all act now. Antimicrobial stewardship programs-Education, training of laboratory personnel and investment in laboratory infrastructure development are desirable in these situations

KEYWORDS: Antibiotics, Resistance, Bacteria

INTRODUCTION

The discovery of penicillin by Alexander Fleming in 1928 (1) and the subsequent administration of its first dose in clinical practice in 1941 (2, 3, 4, 5, 6) marked a landscape shift in patient care. The success of antimicrobials against disease-causing microbes is among modern medicine's greatest achievements (7). After more than 70 years of widespread use, however, many antimicrobials are not as effective as they used to be. The mass production of penicillin near the end of the Second World War (8) ushered in the era of modern antibiotics, causing a paradigm shift in the way we view pathogenic bacterial infection.

The first arrival of a sizable shipment of penicillin at the North African Theatre of Operations for USA military use in 1943 (9) was a landmark that turned a new chapter of antibiotic use in Africa. Over the past decade the expansion of resources and the technological advances have meant that much larger quantities of drugs are available in developing countries than ever before. As a result, many more individuals are receiving necessary treatment or therapy than just ten years ago. This very welcome event is accompanied by poor practices that promote drug resistance (10). Resistance to common antimicrobials affects diseases that have not received dedicated increases in funding over the past decade. Examples include pathogens such as *Shigella* and *Vibrio cholerae* and *Streptococcus pneumoniae*. These diseases are major causes of childhood death in Sub-Saharan Africa (11).

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Antibiotics are among the most commonly prescribed drugs in hospitals (12). In Africa, About 90.1% individuals seek care outside the home, of these, 94.7% take medicines and 36.2 % receive antibiotics. Of all those who receive antibiotics, 31.7 % do not receive a prescription from a doctor and about 26.4% obtain antibiotics from an informal dispenser (13). Evidently antibiotics are widely and inappropriately used in Africa resulting to antibiotic resistance. This situation impinges on the quality of patient care through its associated mortality, morbidity, and significant economic consequences (14). Since antibiotics are the most commonly prescribed drugs in hospitals and their use is one of the important factors for the development and spread of resistance in the hospitals, an audit of their susceptibility patterns is important in implementation of rational empirical antibiotic strategy.

MATERIALS AND METHODS

The study focused on bacterial pathogens. Relevant literature was identified from the PubMed online database. Each search was performed on only English language articles using terms like 'bacterial resistance', 'antibiotic use', 'antimicrobial resistance' and 'bacterial surveillance' combined with the different countries. Bibliographies of all relevant papers were searched to identify further papers. Only publications listing original data on bacterial resistance in humans were included. The coverage included research articles concerning antimicrobial resistance involving subjects of an African country.

RESULTS

The Global Burden of Antibiotic Resistance: Worldwide, the prevalence of antimicrobial resistance limits the therapeutic options for treatment of infections, and increases the social benefit from disease prevention (15). Antimicrobial resistance contributes to the global specter of a post-antimicrobial era in which some of the most effective tools in the physician's armamentarium including antibiotics, anti-tuberculosis and anti-malarial drugs lose their effectiveness (16-23). Greater consumption of antibiotics appears to correlate with increases in antibiotic resistance (24). This is most clearly observable in data from the European Surveillance of Antimicrobial Consumption (ESAC) study in Europe (25).

Antibiotic Resistance in Southern Africa: A review of the susceptibility profiles of *Neisseria gonorrhoeae* over a 20-year period in the Pretoria region (26) best portrays the desperate situation of antibiotics in South Africa. Findings show that Penicillase-producing *Neisseria gonorrhoeae* strains increased from 4% to 16%, whilst chromosomally mediated penicillin-resistant strains increased dramatically from 0% to 16% from 1984 to 2004. High-level tetracycline-resistant strains (36%) were detected for the first time in 2004. Ciprofloxacin resistance emerged at 7% in the same year. Additionally, Methicillin-resistant (80%) *S. aureus* (MRSA) continues to be a problem for clinicians (27). Up-regulated resistance to many first and second line antibiotics in *K. pneumoniae* and *S pneumoniae* isolates has been documented as well (28, 29).

In Zimbabwe, there is high resistance to Ampicillin (84.5%) and Cotrimoxazole (68.5%) among the Gram negative bacilli (30). Gram positive cocci show resistance to Nalidixic acid (81%) and Cotrimoxazole (69%) with *E. coli* showing as high as 84% resistance to ampicillin and 68% to Cotrimoxazole. Over 90% of isolates are resistant to Trimethoprim/Sulfamethoxazole and 16% are resistant to Tetracycline (31).

In Mozambique and Angola, increasing resistance to Ampicillin, Streptomycin, Spectinomycin, Trimethoprime-Sulfisoxazole, Kanamycin, Chloramphenicol, Tetracycline and Gentamycin has been observed (32-35). In patients with no history of prior tuberculosis treatment, the multidrug resistance rate is 3.4% and resistance to isoniazid and Streptomycin (HS) is 5.2% (33). Drug resistance is significantly more common among those with a history of prior treatment.

Antibiotic Resistance in East Africa: In Kenya, the bacterial infections that contribute most to human disease are often those in which resistance is most evident (36). Antibiotic resistance patterns are reportedly up-regulated in persons living with HIV/AIDS (37). Evidently, prolonged exposure to antibiotics makes these individuals harbor strains that are significantly more resistant to antibiotics.

In other studies, 71% *Staphylococcus aureus* isolates from Kenya have demonstrated multiple drug resistance (38). Elsewhere in Kenya, isolates from areas mainly populated by the Maasai community majority of who practice traditional medicine were characterized (39). Overall antibiotic resistance levels was found to be much lower than those reported from the rest of Kenya, possibly due to the lower levels of exposure and usage of antimicrobials among the Maasai community.

In Uganda, resistance to Ampicillin, Amoxycillin and Chloramphenicol has been documented (40). *Staphylococcus aureus Pseudomonas aeruginosa*, *Proteus mirabilis* are reportedly multidrug resistant. In western Uganda, most isolates are resistant to the most commonly prescribed antimicrobials (41, 42). Resistance in surgical inpatients is significantly higher than outpatients (43).

In Ethiopia, the situation is much dire. Gonococcal strains have been found to be multidrug resistant (44). Elevated resistance among gastrointestinal pathogens (45) as well as increased and multiple resistance rates to Erythromycin (89.4%), Amoxicillin (86.0%) and Tetracycline (72.6%) have been documented in isolates from urine, ear discharge, pus swab from wounds, and eye discharge (46). Isolates from the cerebrospinal fluids (CSF) as well as urinary pathogens have demonstrated multidrug resistance (47, 48).

Vlieghe et al. (2008) systematically reviewed published literature on bacterial resistance in Central African (Cameroon, Chad, Gabon, São Tomé e Príncipe, Congo-Brazzaville, Democratic Republic of the Congo (DRC) (formerly Zaire), the Central African Republic (CAR), Angola and Equatorial Guinea) countries (49, 50). Significant findings included multidrug resistance in *Shigella* and *Salmonella* spp. and the emergence of Meticillin-resistant *Staphylococcus aureus*, high-level Penicillin-resistant *Streptococcus pneumoniae* and extended-spectrum beta-lactamases among Gram-negative pathogens (50). Clearly, Central African region shares the worldwide trend of increasing antimicrobial resistance.

Antibiotic Resistance in West and Northern Africa: In Egypt, studies have reported Penicillin resistant *S. pneumonia* (51-57). One of the initial studies revealed a low percentage of antimicrobial resistance (54). An increase in penicillin resistance was recorded in a later study where, 0.8% resistance was detected (52). Other studies in Egypt reveal an increase in resistance to most clinical isolates (55, 58, and 59). High rates of multidrug resistance in *S. pneumoniae* have been linked to dispensing of antibiotic which are generally available as an over-the-counter medication (53, 56).

Nigerian isolates show high resistance in both Gram-positive and Gram-negative isolates (60, 61). Examination of antimicrobial susceptibility of *Shigella* spp. and *Escherichia coli*, isolates from diarrheal patients in Nigeria (62, 63) indicate that over 70% of the *Shigella* isolates are resistant to two or more drugs. During 1990–2000, resistance to Ampicillin reportedly increased from 70% to 90%, Co-trimoxazole from 77% to 85%, Chloramphenicol from 71% to 77%, Streptomycin from 71% to 79%, and Nalidixic acid from 0% to 11.3%.

Root-cause Analysis of antimicrobial resistance in Africa: The emergence of antimicrobial resistance is primarily due to excessive and often unnecessary use of antibiotics in humans and animals (64-66). But in Africa, the situation is more complex than simple antimicrobial overuse. Increasing antimicrobial resistance in Africa has been exacerbated by multiple factors. For instance, the human resource problem in the health sector in sub-Saharan Africa has reached crisis proportions. A complex set of factors has contributed to this problem, some exogenous, such as the austere fiscal measures introduced by structural adjustment, which often result in cutbacks in the number of health workers. But endogenous factors are also to blame, including misdirected human resource and training policies, weak institutions, and inappropriate structures (67). Conspicuously, there are no adequate laboratory facilities (68-70) and enough trained staff (71-74) to isolate pathogens and perform sensitivity tests so that infectious diseases are treated empirically. This leads to the extensive use of antimicrobial drugs which have favored the emergence of resistant strains.

National laboratory strategic plans that specify the policies that govern laboratories are inadequate. Consequently, information about drug resistance is not properly communicated to those

prescribing antimicrobials and no adequate guidelines regarding the selection of drugs are available (75-80). Additionally, there is no adequate documented local retrospective data on the benches of health care providers to guide good antibiotic stewardship. Compounding this problem is the lack of infection control procedures and wound management in hospitals, resulting in the spread of infectious disease and resistant strains particularly from the environment (81-84).

There are several reports of sub-standard and counterfeit antimalarial drugs circulating in the markets of developing countries (85). About 15% of all drugs in circulation worldwide are believed to be counterfeit, with the figures rising to as high as 50% in some parts of Africa (86). Safety, quality, and efficacy of medicines are the three most important criteria used by governments to regulate pharmaceuticals (87). Quality of drugs is especially important and is one of the earliest to come under governments' scrutiny (88). In developing countries, the development of national drug policies (89, 90) has been necessary to ensure the availability of quality pharmaceutical products. However, there are still many difficulties in effecting quality assurance measures on pharmaceutical products circulating in the market. Poor quality of drugs has been linked to counterfeiting of medicines (91), chemical instability especially in tropical climate (92) and poor quality control during manufacturing (93).

Other unresolved chemotherapeutic dilemmas have arisen as a result of the AIDS epidemic. For example, there is inconclusive evidence to support or refute the use of Trimethoprime-Sulfisoxazole for the prevention of opportunistic infections in AIDS patients (94, 95). This leads to overuse of antimicrobials in these population and thus propagates resistance. Additionally, HIV infection is associated with primary multi-drug resistant-tuberculosis (96-98).

Patient knowledge, attitude and behavior of antibiotic usage can define nature of antibiotic stewardship. Illiteracy among African populations and lack of antibiotic awareness leads individuals to seek antibiotics for ailments that are naturally self-limiting and or at best caused by other factors and not necessarily bacterial pathogens (99, 100). As well, there is abuse of antibiotic usage in cattle (101) in addition to self-medication with antibiotics among the African population (102, 103).

WAY-FORWARD

Antimicrobial stewardship programs have to be developed as a response to these issues. As antimicrobial resistance increases and the development of new antimicrobial agents declines, it is critical that we use antimicrobials that are still effective wisely and judiciously. Antimicrobial stewardship is a systematic approach to optimizing the use of antimicrobials. It is used by healthcare institutions to reduce inappropriate antimicrobial use, improve patient outcomes and reduce adverse consequences of antimicrobial use.

Education is needed to promote acceptance of antimicrobial stewardship programme strategies and influence prescribing behavior. Education should be provided in conjunction with active intervention because passive education alone is only marginally effective for modifying prescribing behavior. Guidelines and clinical practices that are evidence based and take into consideration local microbiology and antimicrobial resistance patterns may improve antimicrobial use. These guidelines and clinical practices should be developed with multidisciplinary input to improve the likelihood of adherence.

The systemic acute lack of qualified laboratory personnel is a major and severe constraint in implementing and scaling up antibiotic stewardship. In most developing countries, there is a clear correlation between the quality of trained staff and proximity to the capital city. National reference laboratories that are situated in the capital city tend to have more qualified staff than do regional or district-level laboratories. The severe lack of trained laboratory experts at the regional and district levels presents an additional layer of challenge in the rapid expansion and decentralization of prevention and care services to district health centers in areas where most of the population resides. To achieve rapid scale-up of services, the training of laboratory personnel is critical at all levels of the laboratory network.

In many African countries, health facilities and laboratories in particular are reportedly faced with significant infrastructural challenges.

Documentary evidence indicates that these facilities have minimal physical infrastructure, with even the physical building being inadequate for the needs of the laboratory. Moreover, laboratories, when they exist, are reportedly often in a degraded state. Significant investment in laboratory infrastructure development is desirable in these situations. This requires a concerted effort by government and external donors, preferably within a strategic plan.

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