Strategies for the Prevention and Containment of Antibiotic Resistance

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Key words:antibiotic resistance, rational drug use, infection control, risk factors, pharmacokinetics, pharmacodynamics

Abstract

Antibiotic resistance may emerge by antibiotic selection pressure but is perpetuated by diverse risk factors and maintained within environments as a result of poor infection control. Population-specific drug pharmacokinetics and pharmacodynamics also play a role. The WHO, US, UK and EU have initiated strategies for the containment of resistance, with surveillance and delineation of the cause(s) cited as essential. Surveillance of antibiotic efficacy should be disease-based, establishing sensitivity profiles of common causative organisms to inform the development of or amendment to standard treatment guidelines and essential drugs lists adopted within the national drug policy. The manner of antimicrobial use (overuse, underuse, inadequate dosing) associated with resistance should be established for appropriate intervention in terms of rational drug use, a reduction in use and dosing regimens based on population-specific pharmacokinetics and pharmacodynamics. Risk factors unique to South African communities (poverty, HIV) and hospitals (duration of hospitalisation, location within the hospital, intensive care unit stay, surgery, wounds, previous and current antimicrobial therapy, mechanical ventilation, urinary catherterisation, nasogastric intubation, central venous and peripheral catheters, previous hospitalisation and transfer from another unit or hospital) must be determined and due vigilance exercised in patients exhibiting classical risk factors for the acquisition of or colonisation with resistant pathogens. Hygiene and sanitation (in communities) and infection control (in hospitals) status must be determined and interventions initiated to prevent the spread of resistance. Pharmacokinetics and pharmacodynamics specific to diverse populations must be devised to optimise antimicrobial therapy. South Africa has unique needs in the antimicrobial resistance arena, needs to be addressed in the context of severe financial, human resources and technological challenges.

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Introduction

Antimicrobial resistance is currently the greatest challenge to the effective treatment of infections globally. Resistance adversely affects both clinical and financial therapeutic outcomes with effects ranging from the failure of an individual patient to respond to therapy and the need for expensive and/or toxic alternative drugs to the social costs of higher morbidity and mortality rates, required and/or longer durations of hospitalisation, increased health care costs and the need for changes in empirical therapy.[1, 2]

Surveillance Study in State Hospitals in Kwazulu-Natal, South Africa

A recent study evaluated the appropriateness of national standard treatment guidelines (STGs) and the essential drugs list (EDL) for infections within the public health care system in Kwazulu-Natal, South Africa in the context of antibiotic resistance. A multi-centre surveillance study was undertaken in 16 hospitals at 3 levels of health care (district, regional, tertiary – a system of referral with services ranging progressively from general medical services in district hospitals to highly specialised care in tertiary hospitals) where each hospital was requested to submit 100 consecutive, non-repetitive isolates. Identification and susceptibility testing were accomplished using the API system (bioMérieux sa, Lyon, France) and NCCLS disc sensitivity method[3] on antibiotic test panels of up to 19 antibiotics for Gram-negative and 11 for Gram-positive organisms. Isolates were grouped according to their natural resistance profiles and percentage sensitivity to each antibiotic was stratified per hospital level. The total sample of 1270 isolates consisted of 24 different species. Sensitivities ranged from 14-100% with a general trend of highest sensitivity in district hospitals followed by regional and tertiary hospitals consistent with the referral system where health conditions become increasingly severe/complex requiring greater antibiotic use and broader spectrum agents at progressive hospital levels. The study concluded that resistance profiles amongst bacteria vary too much to allow a national

antibiotic policy as proposed in the STGs and EDL. Rather, such guidelines should be directed to specific profiles found at different levels of health care. Regular surveillance to adjust such guidelines is essential.

Surveillance

The World Health Organisation (WHO) cites antimicrobial resistance surveillance as a critical tool against resistance citing surveillance data as essential in updating national EDLs, STGs and infection control policies. The WHO further recommends that surveillance in hospitals where intensive antimicrobial use, overcrowded conditions and large patient numbers drive the emergence of multi-resistant pathogens be prioritised and recommends the formation of drugs and therapeutic committees aimed at establishing institution-specific treatment guidelines.[4] Thus the objective of surveillance is to facilitate the containment of antibiotic resistance by informing different strategies such as improved prescribing (rational drug use, a reduction in drug use, the implementation of dosing regimens based on drug pharmacokinetics and pharmacodynamics in different patient populations), the implementation of infection control policies and procedures, the development of or amendments to empirical therapy/STGs and due vigilance in patients exhibiting classical risk factors for the acquisition of or colonisation with antibiotic resistant pathogens.[5]

While the multi-centre study quoted above clearly established the prevalence of high levels of resistance in certain hospitals, the data was not correlated with clinical outcome, nor did it inform the potential strategies mentioned above, partly because a multiplicity of factors impacts on antibiotic resistance in hospital settings. Resistance may emerge as a result of selection pressure but is perpetuated as a result of several diverse risk factors and maintained within an environment as a result of poor infection control policies and procedures. Antibiotic pharmacokinetics and pharmacodynamics also play a role in the emergence of resistance and strategies for prevention and containment should be based on the primary cause of resistance in specific healthcare settings/institutions as detailed below:

Antibiotic Selection Pressure

There are numerous reports in the literature citing antibiotic resistance as an inevitable consequence of selective pressures imposed by the widespread use and sometimes misuse of antibiotics. When a bacterial population is exposed to an antibiotic, susceptible organisms are eradicated, while resistant ones persist, passing on their resistant genes to offspring by replication or to other species through horizontal gene transfer (conjugation, transformation and transduction) via genetic elements such as plasmids, transposons and integrons.[6] Several epidemiological studies have shown that the type and frequency of resistance mechanisms varies in environments. Such differences are related to qualitative and quantitative differences in antibiotic use and, conversely, the evolution of different resistance mechanisms may influence future use of antibiotics in the hospital and community.[7] Within the South African context, the inequitable distribution of health resources (both past and present) has manifested in the inequitable accessibility to, and, availability of drugs, including antibiotics. Thus the widespread use of available antibiotics has resulted in specific antibiotic resistance mechanisms in specific health care settings.

If resistance is attributed to selection pressure as a result of excessive antibiotic use within specific healthcare settings, judicious antibiotic use must be the strategy employed. Resistance may be minimised by controlling antibiotic use by means of policies formulated from the evaluation of susceptibility patterns of organisms prevalent in different institutions or areas within institutions.[8] Antibiotic policies are thus surveillance based and have an impact on the rational use of antibiotics.

Rational use also encompasses restricting the use of particular agents, especially those to which resistance emerges rapidly and specifically defining indications for use[9], including the definition of optimum dosage to maximise cures and minimise selection of resistance genes, the optimum duration of antibiotic treatment for specific infections, the costs versus benefits of withholding antibiotics in cases of non-life-threatening infections, and, the value of cycling a regimen in an effort to prevent the emergence of resistance in an institution.[10] Choosing an antibiotic with a narrow spectrum when a pathogen is known and the limiting of oral and topical therapy with drugs that may have to be used parenterally must be considered.[11]

The development of or amendment to STGs, the development of treatment algorithms also forms part of this strategy.

The South African National Department of Health implemented STGs and an EDL for common health problems (including all infections) encountered at primary care and hospital level. STGs and the EDL are critical aspects of the health policy devised in the process of health care transformation in post-apartheid South Africa; addressing major health problems, initiating equity in health care delivery (availability and accessibility of essential drugs to all citizens), and, providing for rational prescribing and dispensing.[12]

Pharmacokinetic and pharmaco-dynamic data, drug interactions, adverse effects, routes of administration, concentrations at anatomical sites and cost are considered in the development of STGs and the EDL. However, the vacillating nature of antimicrobial susceptibility often nullifies such factors in the development of STGs for infections.[13] Further, two of the most important factors influencing the

inclusion of an antibiotic in an EDL are microbial aetiology of the disease and the incidence of antibiotic resistance.[13] The latter did not play a role in the development of the South African STGs. The South African STGs and EDL for infections were compiled by "expert committees", without the benefit of surveillance studies. A single multi-centre study, restricted to blood and cerebro-spinal fluid isolates was published in 2000, a year after the implementation of STGs.[14] It is thus imperative to implement a surveillance strategy informing amendments to present STGs within a public healthcare system increasingly fraught with infections partly as a result of a high incidence and prevalence of HIV/AIDS. It is just as imperative to ensure judicious antibiotic use to effect a decrease in resistant bacteria and prolong antibiotic efficacy.

Risk Factors

Different risk factors have been associated with the acquisition of or colonisation with antibiotic resistance pathogens in communities and hospitals. Poverty indicators such as inadequate hygiene and sanitation, limited access to energy, clean water and healthcare are classical risk factors in comunities while factors such as duration of hospitalisation, location within the hospital, intensive care unit stay, surgery, wounds (surgical or traumatic), previous antibiotic treatment, current antibiotic therapy, mechanical ventilation, urinary catherterisation, nasogastric intubation, central venous and peripheral catheters, previous hospitalisation and transfer from another unit or hospital. Other variables commonly investigated include co-morbidity, age and sex.[15-18]

Risk factors are evaluated in an epidemiological context with a comparative control group. If particular risk factors are statistically significantly associated with the acquisition of resistant organisms, the strategy of greater vigilance must be adopted with patients at risk.

Infection Control

The acquisition of resistant organisms from exogenous sources in the hospital such as other patients, as a result of poor handwashing by healthcare personnel or contaminated equipment points to the dissemination (and not the emergence) of resistance and is reflective of inadequate infection control.[19] This scenario may be confirmed by strain typing of the same bacterial species from similar environments and necessitates the development of strategies to prevent dissemination, focussed on infection control rather than prescribing or use.

Clinical Outcome, Pharmacokinetics and Pharmacodynamics

The relationship between invitro antibiotic resistance surveillance and clinical efficacy or failure is as yet undefined although increasingly associated with less than optimal clinical response.[20] Bacteria categorised sensitive invitro may not be eradicated by virtue of inadequate antibiotic concentrations at the infection site as observed with penicillin treatment of *S. pneumoniae*[21] while antibiotics excreted via the kidney result in high antibiotic concentrations in the urine capable of eradicating bacteria categorised resistant by invitro laboratory tests.[22] Pharmacokinetics and pharmaco-dynamics thus play a crucial role in the efficacious treatment of infections caused by antibiotic resistant pathogens.

Antibiotic concentrations equal to or in excess of the MIC at the site of infection for an adequate length of time is essential for successful treatment of infections, eradicating the bacteria and minimising the selection of resistance.[23] This is contingent on pharmacokinetic parameters such as absorption, distribution and elimination of the drug which influence serum concentrations and pharmacodynamic parameters determining the antimicrobial effect by achieving bactericidal concentrations at the infection site.[24] Good pharmacokinetics and a low MIC are essential for optimal therapeutic efficacy.[25]

A related concept is one of 'calculated chemotherapy' for different sites of infection as opposed to empiric therapy. Calculated chemotherapy is formulated by clinicians, microbiologists and pharmacists and considers five aspects: prevalence of pathogens at site of infection, susceptibility patterns of pathogens, pharmacokinetic aspects (including dosing), condition of the patient, and, cost. Using this data it is possible to create very different therapeutic regimens tailored to the special requirements and dictated by the local epidemiological situation, site of infection and individual patient characteristics. Calculated chemotherapy avoids the impact of a single regimen on the selection of resistance. Cultures must however, be continually and carefully monitored during the time that guidelines are in use in order to detect all possible resistance mechanisms and to give early warning of the emergence of resistant strains. When this occurs, it is time to change guidelines.[26] The feasibility and applicability of 'calculated chemotherapy' within the South African public health system needs to be evaluated.

Thus an improved knowledge of the pharmacokinetics and pharmaco-dynamics of antibiotics defining the correct dose and dose interval is a new focus in the treatment of infections enabling the prescriber to choose an antibiotic least likely to cause resistance.[1]

International Initiatives

Several countries have implemented national strategies for the prevention and containment of resistance, viz. The US's "Public Heath Action Plan to Combat Antimicrobial Resistance" (, the UK's "Resistance to Antibiotics" by the House of Lords Select Committee on Science and Technology and the EU's "Copenhagen Recommendations Report on the EU Conference on the

Microbial Threat". In South Africa, the Medicines Control Council initiated Antimicrobial Resistance Congress, with the theme "Antimicrobial Resistance-Facing the Reality" and mission "appropriate antimicrobial policies for public health", concluded with several recommendations to address the problem in South Africa.

Critical to all these initiatives is surveillance undertaken in manner informing the strategies discussed above.

Conclusion

High levels of resistance are prevalent within public sector hospitals in South Africa. It is imperative to investigate causes and implement strategies for prevention and control in a healthcare system and South African community ill-equipped to deal with the financial, therapeutic and social implications of resistance.

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