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REVIEW

Antibiotic resistance in bacteria - an emerging public health problem

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Abstract

The discovery and eventual introduction of anti-microbial agents to clinical medicine was one of the greatest medical triumphs of the twentieth century that revolutionized the treatment of bacterial diseases. However, the gradual emergence of populations of antibiotic-resistant bacteria resulting from use, misuse and outright abuse of antibiotics has today become a major public health problem of global proportions. This review paper examines the origins and molecular epidemiology of resistance genes, global picture of antibacterial resistance, factors that favour its spread, strategies for its control, problems of control and the consequences of failure to contain antibiotic resistance in bacteria.

Introduction

The discovery of antibiotics must surely rank as one of the greatest medical triumphs of the twentieth century. Starting with the introduction into medical practice of the sulphonamides in the 1930s, penicillin and streptomycin in the 1940s, the broad spectrum bacteriostatic antibiotics during the 1950s, followed by bactericidal antibiotics in the 1960s, together with other important synthetic chemicals and highly specific narrow spectrum antibiotics during these years, one might have thought that the stage had been set for revolutionizing the treatment of bacterial diseases[1].Steadily trailing these developments, however, was the gradual emergence of populations of antibiotic-resistant bacteria occasioned by use, misuse and outright abuse of antibiotics by humans such that drug-resistant bacteria has today become a major global public health problem.

The phenomenon of antimicrobial resistance has prompted two WHO meetings in the last four years, the United States Institute of Medicine occasioned a report on emerging infections by antimicrobial resistance[2] and it has also been debated by the British House of Lords[3]. Within the last two years the European Union has conveyed three scientific sessions in addition to several review articles on antimicrobial resistance.[4-6]This review article is an attempt to draw attention to an emerging public health problem that may negatively impact healthcare delivery particularly in developing countries should the situation be allowed to escalate.

Origins and molecular epidemiology of resistance genes

Antibiotic resistance should be defined in terms of clinical outcome rather than by laboratory methods[7] and in the medical *in vivo* setting therefore, a resistant microbe is one which is not killed by an antimicrobial agent after a standard course of treatment[8]. The use of antimicrobials for any infection, real or feared, in any dose over a period of time, forces microbes to adapt or die (selective pressure) and it is the surviving microbes which carry drug resistance genes which may be transferred to other strains within their own genus and species and across them even to other unrelated species[2]. Clinical resistance is therefore a complex phenomenon involving interaction between the type of bacterium, its location in the body, the distribution of the antibiotic in the body and its concentration at the site of infection, and the immune status of the patient[7].

Resistance in bacteria can be intrinsic or acquired. While intrinsic resistance is a naturally occurring trait arising from the biology of the organism e.g. vancomycin resistance in *Escherichia coli*[7], acquired resistance occurs when a bacterium which was previously sensitive to antibiotics develops resistance. This frequently happens by mutation or by acquisition of new DNA[9]. Mutation is now recognised as the commonest mechanism of resistance development in bacteria especially in *Mycobacterium tuberculosis*[10] and it occurs regardless of whether antibiotic is present. Resistance genes produced in the process are replicated and transferred to in-contact individuals via plasmids and transposons resulting in the emergence of multi-drug resistant tuberculosis, which has now been identified in over 100 countries [11].

In addition to mutation, bacteria have developed a diverse array of biochemical and genetic systems for ensuring the evolution and dissemination of antibiotic resistance[7]. These include antibiotic modification such that it does not react with the target site such as occurs in b-lactamases which enzymatically cleave four-membered b-lactam ring, rendering the antibiotic inactive[12].

In some cases, antibiotic resistant bacteria may protect the target of antibiotic action by reducing antibiotic uptake and/or a quick efflux of it, as happens between b-lactam antibiotics and Gram negative bacteria[10]. Furthermore, the target antibiotic action may be altered thus rendering the antibiotic ineffective e.g. the resistance of enterococci to cephalosporins[12].

The final mechanism by which bacteria may protect themselves from antibiotic action is the production of an alternative target (usually an enzyme) that is resistant to inhibition by the antibiotic while the organisms continue to produce the original sensitive target. This allows bacteria to survive in the face of selection as the alternative enzyme bypasses the effect of the antibiotic. The best-known example is the alternative penicillin building protein (PBP2a) which is produced in addition to the normal penicillin building proteins by methicillin resistant *Staphyloccoccus aureus* (MRSA). It is however not uncommon to find a bacterium exhibiting more than one of these mechanisms[7].

Global picture of antibacterial resistance

Resistance to antimicrobials is a global problem with geographical variation. Acquired bacterial resistance is common in isolates from apparently healthy but carrier individuals and from

patients with community-acquired infections in both developed[4] and developing countries particularly where the demand for antibiotics is driven by high incidence of infectious disease[12]. Several pathogens[6,13,14] are increasingly developing resistance, particularly to first-line inexpensive broad-spectrum antibiotics (Table 1), while the introduction of new drugs (e.g. fluoroquinolones) has been relatively quickly followed by the emergence and dissemination of resistant strain[15]. As resistance develops, outbreaks occur which may result in high mortality. Acute respiratory tract infections, for example, cause 3.5 million deaths in children each year[16] and the most important pathogens associated with pneumonia particularly in pre-school children are *Haemophilus influenzae* and *Streptococcus pneumoniae*. Penicillin resistant pneumococci were first reported in Australia and Papua New Guinea in the 1960s[17] and are now worldwide in distribution. In a study of carriage of pneumococci in Malawian children, 22% and 23% of clinical and carriage pneumococci isolates were found to be penicillin resistant[18].

Typhoid is also endemic in the developing world where an estimated 16 million cases occur each year resulting in some 700,000 deaths[19]. Unfortunately multidrug resistant *Salmonella typhi* emerged in 1987 and has spread throughout the Indian subcontinent, south east Asia, and sub-saharan Africa[20]. Furthermore, in two separate studies on non-typhoidal salmonellae (NTS) bacteraemia in Malawian children, in vitro resistance to the commonly available antibiotics was 76% and 79% (ampicillin), 72% (co-trimoxazole), 71% (trimethoprim – sulfamethoxazole) and 55% (gentamicin) while an increasing resistance (20%) to chlorampenicol was also observed. [21,22]

Isolates from burn patients have not been spared from the consequences of the development of antibiotic resistance, in fact; immuno-compromised burn patients, who receive multiple antibiotics are essentially incubators for antibiotic resistant strains which can manifest rapidly[23]. For example, susceptible Enterobacter notoriously generates resistance to third generation cephalosporins even within a single course of treatment[24]. In a recent study[25] of the bacteriology of burns in the Burns Unit at the QECH, Blantyre, a general broadspectrum resistance (≤ 100%) to panels of antibiotics used was observed in 20% of all bacterial isolates.

Even more alarming has been the emergence of multidrug resistant tuberculosis, spreading rapidly and threatening to spiral out of control[11]. The HIV/AIDS pandemic, acting as a catalyst, has increased the impact of tuberculosis and may have led to a gradual increase in resistance to antituberculosis drugs. In Russia, Estonia and other hotspots, spanning over 100 countries scattered round the world, the multidrug resistant tuberculosis (MDR-TB) is reaching unprecedented heights[11]. While TB and MDR-TB have traditionally been viewed as a scourge of the poor, a study commissioned by philanthropist George Soros Open Society Institute has traced the spread of MDR-TB not to the peri-urban slums of the third world but to Western Europe and North America[9]. Unless checkmated, MDR-TB poses the greatest threat to public health in the new millennium.[26]

Factors that favour the spread of antimicrobial resistance

General overuse of antibiotics

Most antibiotic use is in two areas, that is, in humans in the community and in animals for growth promotion and prophylaxis. It has been found out that 20 – 50% antibiotics used in human and 40 – 80% in animals[2] are unnecessary and highly questionable. In Denmark for example, while 24kg of active vancomycin was used for human therapy in 1994, 24000kg of active avoparcin (vancomycin equivalence in veterinary practice) was used as feed additives for animals[27]. In Austria, between 1992 and 1996 an annual average of 582kg of vancomycin was imported for medical purposes and 62,242kg of avoparcin for animal husbandry[28]. As expected vancomycin resistant Enterococcus faecium (VRE) of animal origin has been detected in humans[29] through consumption of contaminated meat[29,30,31] thus making the treatment of these infections, difficult. When avoparcin was banned in Denmark (1995), Germany (1996) and the whole of European Union countries (1997), the net effect was a dramatic reduction in the incidence of VRE in humans[32] suggesting that antimicrobial resistance can be controlled through prudent use of antibiotics.[33]

Misuse of antibiotics by physicians

Misuse of antibiotics by physicians is commonplace and worldwide[34] especially in the intensive care unit (ICU) in hospitals which are fast becoming a breeding ground for the development and spread of antimicrobial resistance due to exposure of heavy antibiotic use in a high density patient population[35]. When patients are discharged to continue medication at home, it further facilitates antibiotic resistance spread to other in-contact humans.

The unnecessary prescription of antibiotics seen in industrialized nations[34,36,37] although for different reasons has also been documented in many developing countries.[38,39] While the overuse of antibiotics in developed countries[33] among other reasons is patient-driven, in developing countries where laboratory diagnostic facilities are scarce, this has led to the introduction of empiric, pragmatic and problem oriented management strategies for the administration of antimicrobials which inevitably results in over treatment[19] thus placing antibiotic-resistant bacteria at a competitive advantage. Either way there is need for physicians to prudently use/prescribe antibiotics to stem the tide of drug resistance in bacteria.

Misuse by unskilled practitioners and general public

This is a major problem in developing countries where qualified and well-trained health personnel are scarce and ill-trained or self-trained quacks parade themselves as medical personnel in rural areas[40]. While many of them are semi-literates, do not preserve their drugs appropriately, are unaware of the deleterious effects of antibiotic misuse and care less about inappropriate prescription, they seem to have an antibiotic for every human ailment[4]. For example, pharmacy technicians in Thailand prescribe rifampicin for urethritis and tetracycline for young children[41] while their counterparts in Nigeria and elsewhere prescribe antibiotics for headache, dyspnoea and to prevent sexually transmitted diseases among prostitutes[42,43]. In these and other developing countries, self medication is common and antibiotics are readily available across the counter in pharmaceutical stores, market stalls, by the roadside, and from hawkers. This practice usually leads to antibiotic underuse (sub-optimal dosages) that invariably increases selective pressure and antimicrobial resistance.

Poor quality antibiotics

Antibiotics degraded by exposure to temperatures higher than 25°C by hawkers[44], harsh adverse conditions during shipment to the tropics[45] or when laid out on the hot pavement, expired drugs which receive new labels, sometimes dumped without labels or donated rather than destroyed are common in developing countries[46,47] all of which promote development and spread of antimicrobial resistance when used.

Furthermore, counterfeit antibiotics with much reduced or no active ingredients at all[48-50] have been identified in Nigeria, Indonesia, Brazil, Thailand, Bangladesh, Malaysia and francophone African countries. In a potency study of various drugs[51] available in Bangladesh, for example,8 of the 10 brands of ampicillin were substandard. There have also been reports of traditional healers mixing antibiotics with their concoctions to increase potency[52].

Increase in International travel

Enormous increase in international travel in recent years means that individuals may be exposed to resistant microbes in one country and carry them to other countries, where resistance can then spread. A typical example is the resistant strains of *Neisseria gonorrhoea* which originated in the Philippines and Asia and have now spread throughout the world[8].

Strategies for decreasing antimicrobial resistance

Antimicrobial resistance being a natural response of microbes to exposure to antimicrobial agents, an effective control strategy has to be one of containment, aimed at reducing the rate of emergence and spread of resistance[8]. These objectives can be achieved in all of four ways.

(i) Decrease in selective pressures

Two areas, agriculture and medicine supply the greatest selective pressure and it is apparent that to control the generation and spread of resistant microorganisms, there is need to decrease selective pressures that promote and perpetuate the existence of resistant mutants over the sensitive strains[24]. A concerted international effort is required to reduce antimicrobial usage outside human medicine[53,54] and concomitantly improve the rational use of antimicrobials in medicine[34] while the misuse of antibiotics by health care professionals, unskilled practitioners and patients can be alleviated by auditing antibiotic use, limiting antibiotic choice, developing prescription guidelines and emphasizing continuing medical and public education[4]. It is also desirable to ban the sale of drugs across the counter but this may be difficult to enforce in developing countries because of grossly inadequate health facilities.

(ii) Adoption of good infection control

Once an antibiotic resistant pathogen is present on one patient, it has to be carried, conveyed, or in some way transported to other patients in order for the pathogen to spread. The uninformed or careless health care worker is often the vector promoting the dissemination. Therefore, handwashing, simple contact control, disinfection of environmental surfaces and when appropriate, isolation or quarantining of patients are essential for the control of multi-drug resistant pathogens[24].

(iii) Increase in research activities

In spite of the many advances in microbiology, biochemistry and drug discovery and development in recent years, the world is not keeping pace with the ability of bacteria to adapt to and resist antibacterials. It is believed that the rise in bacterial resistance is partly because there have been no new classes of antibiotics since the 1960s.[55] For example antibiotics discovery and development had been exponential since the 1940s, but no new clinically useful structures were discovered after 1961, and almost all the drugs that have been launched since the 1960s are modifications of existing antibiotics which bacteria, over the years, have "learnt" to resist. This meant that bacteria that have 'leant' to resist one member of a chemical drug class did not have to learn much more to overcome its later modifications.[55] There is therefore need to intensify research activities in the area of antibacterials to take the pressure off the existing ones and in the process reduce antibiotic resistance in bacteria.

(iv) Surveillance of antimicrobial resistance

For any antimicrobial strategy to succeed, it has to be backed up by an efficient surveillance system to detect, monitor and document the emergence of any antimicrobial resistance in the locality, at national and international levels[56,57]. Once the relationship between use and resistance have been established, surveillance data can then serve as "information for action" for initiative to decrease unnecessary prescribing and prolong the usefulness of existing antibiotics[58].

International cooperation on resistance surveillance is therefore essential to determine the extent to which different national prescribing practices translate into different resistance rates. The World Health Organisation is already establishing surveillance networks to address the issue. It requires the cooperation of both developed and developing countries to achieve the desired impact.

Problem of control

The implementation of most strategies against antimicrobial resistance is hampered by lack of funds especially in developing countries where statistics from the World Bank has shown that an average of $41.00 per person was spent on health in 1990 in developing countries, whereas $1500.00 per person was spent in the developed world[4]. The consequence of such gross under funding in developing countries is the chronic and perpetual inadequacy of drug supply with continued pressure on health facilities. Even where funds are available, lack of political will to tackle health problems head on and wrong priorities often stand in the way of the effective implementation of strategies to control drug resistance in developing countries.

To further compound the situation, perennial armed conflicts in sub-Saharan Africa and Asia often lead to a break down in health services and sanitation leading to a rapid dissemination of resistant pathogen[59,60]. For example, during outbreaks of cholera and bacillary dysentery among Rwandan refugees, resistance to multiple first-line antibiotics in clinical isolates of *Vibrio cholera* and *Shigella dysenteriae* contributed to high mortality[60].

Even in developing countries not at war, political corruption and gross mis-management of funds have created large populations living in abject poverty, thus, persons with communicable disease who are unable to pay for health facilities may infect others[4]. This is because poverty always inevitably interferes with patient compliance leading to the emergence of antibiotic resistance during short-term therapy of acute infections and long-term therapy of chronic infections e.g. tuberculosis[61].

Consequences of failure to control antibacterial resistance

Already, infections caused by resistant microbes fail to respond to treatment resulting in prolonged illness, increased morbidity and greater risk of death. When infections become resistant to first-line antimicrobials, treatment has to be switched to "second line" agents which are usually more expensive, less readily available to the majority of the population, thereby making many infections effectively untreatable.

A case in point is tuberculosis, one of the most wide-spread infections and one of the leading causes of death among adults in the world[62]. The annual global incidence was predicted to increase to 10.2 million by the year 2000 with 3.5 million

people dying annually of tuberculosis and with deadly strains of drug resistant tuberculosis already detected in over 100 countries, and still spreading, the epidemic has taken a chilling new direction and it appears set to become, among others, a public-health catastrophe of the new millennium.

Impact of HIV epidemic

HIV infection is strongly associated with severe invasive bacterial disease in Malawian adults and children[63-65] – see articles in this journal. The HIV epidemic is likely to have a considerable impact on the emergence of antibiotic resistance, although the exact extent of that impact is not yet clear. HIV-infected adults and children are likely to receive more courses of antibiotics and require more frequent hospitalizations, both risk factors for development of antibiotic resistance, than HIV-uninfected individuals. They are also susceptible to recurrence of disease following appropriate antibiotic therapy[66]. There are also data emerging suggesting that HIV-infected individuals have higher and more prolonged carriage rates of common bacterial pathogens than HIV-uninfected individuals. These factors may explain the increased risk of infection with resistant organisms among HIV-infected children and adults[67,68].

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Table 1. Some pathogens with steadily increasing prevalence of acquired antibiotic resistance

Pathogens	Drugs	Country	Ref
Vobrio cholerae	cotrimexoxazole, nalidixic acid, ampicillin	Guinea - Bissau (1987 - 95) India (1993 - 1995)	4 4
	ampicillin, kana mycin, streptomycin, sulphonamides, tetracycline	Simalia (1985 - 86)	19
Shigella flexneri	ampicillin. tetracycline, sulphonamides, (alone or with trimethoprim)	Bangladesh (1993 -1990)	4
S. dysenteriae	nalidixic acid	Brazil (1983 - 93) Rwanda (1983 - 1993) Thailand (1981 - 1995)	4 4 15
	ampicillin, cotrimexoxazole, nalidixic acid, mecillinam	Bangladesh (1995 - 96)	19
Streptococcus pneumoniae	penicillin, chloramphenicol, cephalosporins	Spain, Mexico, South Africa South Korea, Portugal, Croatia France, USA, Belgium	19
	penecillin	Malawi (1995 - 1997)	18, 22
Neisseria menigitidis	penecillin, chloramphenicol	Sub-saharan Africa Malawi (11986 - 1992) Spain (1985 - 1996) UK (1995) Belgium (1998)	19 14
N. gonorrhoea	penecillins, tetracycline, sulphonamides fluoroquinolones	Phillipines, Thailand, USA	14
S. pyogenes	macrolides, erythromycin	Australia, japan, Finland, Uk Italy, Spain	14
Salmonella typhi	ampicillin, chloramphenicol, cotrimexoxazole	Bangladesh (1989 - 1993)	13, 20
Salmonella (non-typhoidal)	cotrimexoxazole	Thailand (1981 - 1995) UK (1991 - 1994 USA	15
	ampicillin, contrimexoxazole gentamycin	Malawi (1996 - 1998)	21, 22
Enterotoxigenic E.coli	cotrimexoxazole fluoroquinolones	Thailand (1987 - 1995) Spain	15
Campylobacter sp.	fluoroquinolones	Thailand (1987 - 1995 Nehterlands	15
Yersinia pestis	streptomycin, chloramphenicol, tetracycline, gentamycin, spectinomycin, kanamycin, sulphonamides	Madagascar	19
Staphylococcus aureus	methicillin, penecillin	Kenya, Sri Lanka, Tunisia, Severa other Countries	19
Mycobacterium tuberculosis	isoniazid, streptomycin, rifampicin.	over 100 countries	11