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A REVIEW ON ANTIBIOTIC RESISTANCE FOR THEIR APPERENCE AND STRATEGIES AGAINST OTHER MICROORGANISM

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ABSTRACT

Developments in chemotherapy for malignancy and organ transplantation make patients more vulnerable to infection, due to immune-suppression. Antibiotics have had a profound positive impact on the management of infectious diseases, but they have also become an essential component of all aspects of modern healthcare. Microorganisms are transferred readily between individuals, and thus resistance emerging in one patient or the environment can soon affect another. Resistance is more likely when the concentration required to inhibit or kill microorganisms exceeds that achievable in a patient. Antibiotic resistance has significant costs to society in terms of increased mortality, morbidity, use of healthcare resources and time off work.

Keywords: Antibiotic, morbidity, healthcare, microorganisms.

INTRODUCTION

Antibiotic resistance has been described as one of the greatest global threats of the 21st century. Although it was recognized soon after antibiotics were first introduced, the impact was mitigated initially by the development and use of newer agents. For some organisms, particularly Gram negative bacteria such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and some

Enterobacteriaceae (e.g. *Escherichia coli* and *Klebsiella* spp.), there are increasingly extremely limited therapeutic options. No advance in medical or surgical practice would remain successful if patients developing infections could not be treated reliably.(1) These medical advances would be less meaningful if a patient survived the initial therapy, only to succumb to infection later. Potentially, if antibiotic resistance became more widespread and infection became more difficult to treat, patients might choose to live with their disabilities rather than undergo joint replacement surgery.(2)

Antibiotic resistance is truly a One Health issue and needs to be monitored and controlled not only in human medicine, but also in animal husbandry, agriculture and aquaculture.(3) However, this review will concentrate predominantly on antibiotic use in humans. Unlike any other class of drugs used in clinical practice, antibiotics act on a third party, the micro- organism, rather than just the patient. Tackling antibiotic resistance is therefore of great public health importance and must not be underestimated. The term 'antibiotic' is used throughout to mean an agent with activity against microorganisms, rather than the more general term 'antimicrobial'. Also, although antibiotic resistance is important in the treatment of infections due to viruses, fungi and protozoa, this discussion is limited to bacterial infections.(4)

OCCURANCE OF RESISTANCE IN MICROBES

Microorganisms can be either intrinsically resistant to an antibiotic or develop resistance following exposure to that antibiotic (acquired resistance). The terms 'susceptible' and 'resistant' relating to antibiotics are usually used in clinical practice to infer the likely success or failure of treatment. Resistance can develop as a result of mutation or direct transfer of genes encoding a resistance mechanism.(5) Transfer of resistance genes can occur by a variety of mechanisms including conjugation (transfer of genes carried on plasmids, which are also known as mobile genetic elements), transformation (direct transfer of naked DNA) or transduction (transfer of similar DNA by bacteriophage). Genetic material, including antibiotic resistance genes, can spread very effectively between bacteria, even those of unrelated species. The efficiency and rate at which a resistant phenotype spreads within a previously susceptible species are unpredictable.(6)

IMPORTANT OF ANTIBIOTIC RESISTANCE

In many areas, the availability of antibiotics 'over the counter' or via the internet allows the non-prescriber to have free and unrestricted access to these agents. Once resistance has emerged, subsequent dissemination of resistant strains is facilitated by the selection pressure exerted by further antibiotic use, failure to adhere to infection control measures and by poor hygiene (notably in terms of hand hygiene, sanitary conditions and food preparation), which can occur both within and outside healthcare settings.(7)

During the past 25 years, only two new classes of antibiotics have been developed and introduced into clinical practice. These include the oxazolidinones (e.g. linezolid) and lipopeptides (e.g. daptomycin). Many of the other newer antibiotics are modifications of older drugs rather than new classes of agent. This is partly due to failure of new drug discovery, failure to bring potential new agents to market and a restrictive regulatory environment.(8) Both of these new classes of drugs have activity against Gram positive bacteria; new classes of compound with activity against Gram negative bacteria have not been found. The failure rate during development is also higher for antibiotics than for most other drugs, and the returns from antibiotic sales are low compared with other drugs because they are generally only used for short periods of time. In addition, because of concern about resistance, new agents are typically used sparingly and as a last resort.(9) Worldwide, the availability of cheaper generic pro- ducts potentiates this issue.

ANTIBIOTIC RESISTANCE MAY BE USED FOR HEALTHCARE

Antibiotic resistance does not only develop in the hospital environment. As healthcare systems have evolved, there has been a blurring of boundaries between traditional healthcare facilities and the community, such that nursing and residential homes are now important reservoirs for resistant organisms in addition to out- patient settings such as dialysis and oncology day units.(10) Modern travel networks have also made it easier for people and the resistant organisms they carry to spread rapidly across and between continents. Increasing resistance can result from proliferation of the resistant bacterium itself or by transfer of resistance genes from one bacterial species to another. However, the relative importance of these varies with organism and resistant mechanism. Environmental studies have shown that sewage samples and drinking water contained a variety of different organisms harbouring NDM-1 (e.g. *Shigella boydii* and *Vibrio cholerae*) suggesting transfer of mobile resistance elements between species. Conversely, the spread of *Klebsiella*

pneumonia carbapenemases (KPC) in the USA, Israel and Greece was associated with spread of a single clone of the organism.(11) It was the emergence of these ESBL-producing Enterobacteriaceae that led to increased reliance on carbapenems for effective treatment of infections due to these, and hence an increase in selection pressure for resistance.(12)

Ability to control transmission of resistant in organisms

These initiatives have included infection control programmes to control transmission of resistant organisms, antibiotic steward ship programmes and vaccination programmes. Another success story is the introduction of 13-valent conjugate *S. pneumoniae* vaccine. Increasing uptake of the vaccine reduced the number of bacteraemias due to *S. pneumoniae*, which included antibiotic resistant strains. In the UK, the rates of resistance to cephalosporins and ciprofloxacin in *E. coli* and *Klebsiella* spp. bloodstream infection have fallen since 2008. This may b e due to restricted use of these antibiotics as part of antibiotic stewardship initiatives to combat *Clostridium difficile* infection.(13) This may have simply moved the selection pressure for the development of resistance from the cephalosporins and fluoroquinolones to these antibiotics instead. Antibiotic resistance in *Neisseria gonorrhoeae* has increased over the years leading to abandonment of traditional treatment regimens using penicillin, followed by those using ciprofloxacin and other fluoroquinolones.(14)

Now, regimens using azithromycin and cefixime are under threat, such that a combination of ceftriaxone and azithromycin is currently recommended for treatment. The major emerging resistance issue in many countries is among Gram negative bacteria, particularly Enterobacteriaceae, *P. aeruginosa* and *A. baumannii*. Between 2004 and 2008, *E. coli* bacteraemias increased by 33% in England; the species now accounts for >30% of bacteraemias in those aged over 75 years. Tuberculosis is another example of a disease caused by an organism that has gradually developed resistance over time.(15) Multidrug-resistant (MDR) tuberculosis (i.e. *Mycobacterium tuberculosis* resistant to at least rifampicin plus isoniazid) emerged in the 1990s, whilst extensively drug resistant subsequently emerged. Both of these are associated with increased mortality and morbidity, despite prolonged treatment with multiple drug combination regimens. Antibiotic resistance is an international concern. Firstly, there are strategies aimed at protecting the existing antibiotics and preventing the emergence and spread of further resistance. Then, there are strategies aimed at reinvigorating drug development and bringing new antibiotics to market.(16) Alternatives to current antibiotic therapy also need to be

assessed, either through the development of new drug classes or through the use of vaccines or other therapeutic strategies.

WHO also targets the veterinary and food sectors by publishing booklets on antibiotics for a food safety perspective, running national and sub-regional workshops and creating an advisory group on integrated surveillance. The World Health Assembly may be a forum through which international collaboration can be facilitated.(17)

Most countries have strategies that are based on governance, surveillance, infection prevention and control, regulation, international engagement, communication and research. Effective antibiotic stewardship is required globally, together with better diagnostic tests to identify or rule out infection quickly. Several international groups and societies have been established to tackle antibiotic resistance.(18) One of the most prominent is Action on Antibiotic Resistance (ReAct), an independent international organization funded by the Swedish International Development Cooperation Agency.

It suggested increased funding to support antibiotic research and development and promoted the establishment of a BSAC Chair of Public Engagement in order to increase the public and political awareness of antibiotic resistance and promote dialogue. Initiatives with similar aims have been established in the USA under the auspices of the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA).(19)

In India, Until this, the authors of the declaration claimed that there were no functioning national antibiotic policies and no national policy to contain anti- microbial resistance in India. There were no restrictions in purchasing antibiotics and no standardized infection control practices. The first meeting laid out a roadmap for tackling antibiotic resistance.(20) It managed to create awareness among policymakers and the highest authorities on the need of effective antibiotic policies in India.(21)

In Asia, the Asian Network for Surveillance of Resistant Pathogens (ANSORP) acts as a centre for research collaboration of infectious diseases and antibiotic resistance. More than 100 hospitals in 14 countries participate. The Australian Antimicrobial Resistance Prevention and Containment Steering Group have set out strategies and mandated Standard 3 of the National Safety and Quality Health Service (NSQHS) Standards 'Preventing and Controlling Healthcare Associated Infection' in all Australian hospitals.(22)

The first UK strategy against antimicrobial resistance was published over a decade ago and

aimed to improve antibiotic prescribing practice and increase funding for drug discovery programmes and research. Some have argued that its impact was limited. In 2013, the Department of Health in England launched a new Five Year Antibiotic Resistance Strategy (2015–2018).(23) It was published as part of a One Health programme, which aimed to address antibiotic resistance in humans, animals, agriculture and the wider environment. Its main objectives were to improve the knowledge and understanding of antibiotic resistance, to conserve and steward the effectiveness of current antibiotics and stimulate the development of new agents, diagnostics and novel therapies.(24)

Optimizing antibiotic prescribing has been targeted in both community and hospital settings. Antibiotic stewardship programmes aim to ensure the effective treatment of patients with infection whilst minimizing collateral damage from antimicrobial use. They do this by optimizing antimicrobial selection, dosing, the route and duration of therapy to maximize clinical cure or prevention of infection while limiting unintended consequences (e.g. emergence of resistance, adverse drug events and costs).(25) Education, audit, guidelines and policies, IV to oral conversion and appropriate de-escalation are all potential elements. These interventions to reduce excessive antibiotic prescribing in hospital in patients can reduce antimicrobial resistance, hospital-acquired infections and can improve clinical outcomes.(26)

Antibiotic cycling or rotating (i.e. the scheduled alternation of various classes of antibiotics) has also been studied, although its benefit is still debated. The goal of antibiotic cycling or rotation is a sustainable decline or stabilization in antimicrobial resistance through successive, prospective alterations in antibiotic selection pressures that prevent the selection of specific resistance mechanisms.(27)

They include '*Target Antibiotics Responsibly, Guidance and Educational Tool* ' (TARGET), available on the Royal College of General Practitioners website. Another is the '*Stemming the Tide of Antibiotic Resistance*' (STAR), an educational programme that includes resources for clinicians to share during public consultation.(28) In 2007, the Health Protection Agency established a multiagency collaboration to improve antimicrobial prescribing in primary care. From this, epidemiological data collections and primary care-directed guidelines were produced (e.g. antibiotic and diagnostic guidance on urinary tract infection). The 'Start smart then focus' programme is an antibiotic stewardship initiative from the UK directed at secondary care.(29)

New techniques have been developed to aid the diagnosis of infection and/or resistance earlier than conventional culture and sensitivity testing. Biomarkers such as C reactive protein (CRP) or procalcitonin can potentially reduce unnecessary antibiotic use.(30) Molecular methods such as polymerase chain reaction (PCR) have allowed earlier detection of MRSA strains and also rifampicin resistance in *M. tuberculosis*.

Multiplex gene detection PCR assays and next- generation sequencing are other methods that are being utilized to achieve earlier detection of antibiotic resistance. Identification of cultured bacteria through mass spectrometry (e.g. by Matrix-Assisted Laser Desorption Ionization Time of Flight (MALDI-ToF) has reduced the time to identification of organisms compared with conventional biochemical means. Automated susceptibility testing also has the potential to deliver results more quickly. (30)

A) Reinvigorating drug development pathways and bringing new antibiotics into market. The need for new antibiotics was illustrated in the TUN report. Among the aspects that need addressing is the failure of new drug discovery (described above). In addition, increasing levels of bureaucracy and lack of clarity within regulatory frameworks and variation in the clinical trials process in different countries hinder the development of new agents. Several antimicrobials have failed to reach the market at this final hurdle.(31) Lack of international harmonization, continual changes to processes and ineffective pathways for dialogue between organizations, industry and regulators are all significant deterrents to the research and development of new antibiotics.

A number of novel approaches to reinvigorate antibiotic development have been proposed. Public–private partnerships could be set up to mitigate the up-front costs of drug discovery. Pathogen-targeted approaches could be developed to optimize efficacy against a single pathogen/resistance mechanism. In Europe, the 'New Drugs 4 Bad Bugs' initiative is a series of programmes that were set up by the Innovative Medicines Initiative (IMI) in the EU and was designed to directly address some of the scientific challenges associated with antibacterial drug discovery and development. This provided a pay-out at the end of the development process with 5 years of guaranteed market exclusivity and priority review for antibiotics that target certain qualifying pathogens.(32) But the initial findings have been published and include a proposal to set up a global antimicrobial resistance innovation fund to boost the number of early research ideas, ensuring that existing drugs are used appropriately,

improving the use of diagnostics wherever they can make a difference, attracting and retaining a high calibre skills base and modernizing the surveillance of drug resistance globally.

Conclusion

The relentless rise in antibiotic resistance is a major public health concern, which will need to be acted upon now. We might not be able to stop antibiotic resistance or, in many cases, reverse the trend to ever- increasing resistance, but we certainly need to contain the speed to which this is happening. No single action or initiative by a single country would be able to achieve this. It requires participation and support from all levels; political, medical, veterinary, agricultural, environmental, academic, industry and the general public. It is clear that there is political engagement with this issue and many different bodies are considering potential options to tackle it.

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