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Education

Antimicrobial resistance: Where are we now?

EDUCATION

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ABSTRACT

Summary

This article discusses the global importance and multifactorial nature of the growing antimicrobial resistance (AMR) threat. It outlines how resistance arises at the level of the bacterium; including intrinsic and acquired resistance mechanisms. It also assesses current approaches to tackling AMR, both in the UK and worldwide, such as: drug development, calls for changes to medical, industrial and legislative practices, and antimicrobial-stewardship.

Relevance

With increasing numbers of multidrug resistant organisms causing infections worldwide, medical students must enter the workforce equipped with an understanding of the severity and origins of this situation as well as an appreciation of the steps being taken, and which they themselves can take as future clinicians, to address this challenge.

Take Home Messages

AMR is a multifactorial and continually evolving threat with its origins in the inherent genetic properties of microbes and their evolutionary nature. Consequentially, whilst urgent action is needed to combat an AMR problem exacerbated in recent decades, AMR will always persist. As microbes continually evolve new survival strategies, it is essential to continue to develop new pharmacological agents in conjunction with new practices and policies on institutional, national and international scales to protect global public health from the threat posed by AMR.

INTRODUCTION

Antibiotics were classically defined in 1947 by S. A. Waksman as natural substances that inhibit the growth of, or destroy, bacteria. In the current literature "antibiotic" may refer to any antimicrobial substance (toxic to viruses, fungi, protozoa or bacteria) that has natural, synthetic, or other origins. (1) Since the development of modern antibiotics in the early part of the 20th Century mortality from infectious diseases has declined significantly; illustrated by the 8.2% average annual decrease in infectious disease mortality in the USA from 1938 to 1952. (2) This was seen at the time as revolutionary, however contemporary optimism was to be undermined by the emergence of antimicrobial resistance (AMR). The current challenges and grave potential consequences posed by AMR to healthcare provision mean that it is essential for medical students, as future clinicians, to have an appreciation of the origins, causes and implications of AMR. In addition to addressing these issues, this article will discuss current strategies for tackling AMR both in the UK and around the world.

AMR describes the emergence of pathogen strains which have developed an immunity or resistance to antimicrobial drugs which previously had been lethal to that species. It is a consequence of evolution by natural selection and is exacerbated by the increased selection pressure applied to microbes by overuse of antibiotics. AMR is a rapidly developing problem which poses a significant threat to global health. (3)

AMR is not a new phenomenon. In his Nobel Prize lecture in 1945 Alexander Fleming himself warned of the risks of resistance stating that it was possible to produce resistant bacteria by exposing them to non-lethal concentrations of penicillin. (4) However, the scale and severity of the problem has grown in recent decades.

The bacteria identified as presenting the greatest AMR threat, and the causes of the majority of nosocomial infections worldwide, are collectively termed the "ESKAPE Pathogens" (summarised in Table 1). The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) have reported increases in the incidence of bacteraemia caused by each of the ESKAPE pathogens each year since 2014.(6) The global scale of the risk posed by these organisms, and others such as Mycobacterium tuberculosis, was summarised five years ago in a report by the World Health Organisation (WHO). (5) They reported that carbapenem-resistant Klebsiella pneumoniae is now present in all regions of the world, with carbapenem drugs ineffective in up to 50% of patients in some countries. They also report that in 2014 there were approximately 480 000 cases of multidrug-resistant Tuberculosis. 9.7% of these cases were Extensively Drug-Resistant Tuberculosis caused by M. tuberculosis which is resistant to four different antibiotics and found in 105 countries. In terms of global impact; the O'Neill Report estimates that by 2050, AMR related deaths will reach 10 million per year with an economic impact of up to $100 trillion. (3)

ESKAPE Pathogens				
Species Name	Gram Positive/Negative	Rate of bacteraemia per 100,000 population in England		
		2014	2018	Percentage Increase
Enterococcus faecium	Positive	-	-	
Staphylococcus aureus	Positive	19.4	23.2	19.59%
Klebsiella pneumoniae	Negative	9.1	12.1	32.97%
Acinetobacter spp.	Negative	1.3	1.5	15.38%
Pseudomonas spp.	Negative	6.4	7.6	18.75%
Enterobacter spp.	Negative	9.6	12.7	32.29%

Table 1:
ESKAPE Pathogens and the reported rate of bacteraemia attributed to these species according to the ESPAUR report 2018 to 2019 (6)

HOW DOES RESISTANCE ARISE?

Intrinsic Resistance

Some bacteria have intrinsic resistance to antibiotic drugs. This includes bacteria which lack the molecular targets of a specific antibiotic, and those with innate efflux mechanisms or cell walls which are highly impermeable. (7) Bacteria have varied and complex outer membranes composed of phospholipids and lipopolysaccharides meaning that they have varying susceptibility to cell wall acting antibiotics such as beta-lactams. Additionally, widely varied cell wall permeability found within gram-negative bacteria makes the discovery of effective antibiotics particularly challenging. (8)

Acquired Resistace

Unlike intrinsic resistance, acquired resistance mechanisms are not inherent properties of a given bacterial species – they are assimilated through random genetic mutation, from other bacteria or from the environment. (9)

Horizontal gene transfer (HGT) is one of the most prevalent strategies for conferring or acquiring AMR in bacteria. HGT involves the exchange of mobile genetic elements, containing 'resistance genes', between bacteria. Extra-chromosomal plasmids and conjugative transposons - which integrate into the genome of the recipient bacterium, can be transferred by conjugation or transformation. (10) AMR genes can also be acquired via bacteriophages through transduction, or through intra-genomic rearrangement, for example, involving insertion sequences. (11) Acquired AMR may also arise spontaneously through genetic mutation. For example, micro-organisms such as Helicobacter pylori have acquired resistance to Fluoroquinolones and Clarithromycin through mutation. (12, 13)

Acquired AMR mechanisms fall into three groupings:
- Prevention of the antibiotic accessing the target molecule within the bacterium
- Changes to this target molecule
- Direct modification or destruction of the antibiotic.

Bacteria may prevent antibiotics reaching their molecular targets by either decreasing permeability or by increasing efflux of the antibiotic. Decreased permeability may be achieved through the down regulation of transmembrane channels known as porins. Decreased porin expression has been shown to contribute to AMR in several species of Acinetobacter, Enterobacteraciaeae and Pseudomonas. (9) Increasing the efflux of an antibiotic can be achieved through the expression of efflux pumps. Efflux pumps are transmembrane structures which actively remove both endogenous and exogenous substances from the bacteria cytosol which are present across a wide variety of species. The use of these pumps to specifically remove antibiotics has been documented as a cause of AMR in many bacterial species including important human pathogens such as Legionella spp. and Brucella spp. (14)

Changes to the targets of antimicrobial agents by mutation, modification or protection of the target can all confer AMR. An example is resistance to Linezolid, an antibiotic which targets 23S ribosomal RNA subunits (rRNA). Most bacteria possess multiple copies of this gene and even single base-pair mutations have been shown to produce 23S rRNA which is impervious to Linezolid action, for example in Staphylococcus species. (15) Another way in which bacteria may protect their ribosomal components from antibiotic action is through methylation. The erm genes encode an enzyme which methylates both 23S and 50S rRNA subunits, impairing the ability of antibiotics such as macrolides to bind to these molecules. (16)

The third group of acquired AMR mechanisms is the direct modification or destruction of antibiotic drugs. The expression of enzymes for hydrolytic inactivation of antibiotics is a strategy employed by numerous bacterial species, for example, lactamase enzymes expressed by a variety of bacteria including Enterobacteriaceae. (17) Additionally, bacteria may modify antibiotics by adding chemical moieties such as nucleotides or phosphate groups to them thus reducing their ability to bind to their targets. Due to their chemical structure aminoglycoside antibiotics are particularly vulnerable to enzymatic modification by bacteria. (9)

ADDRESSING ANTIMICROBIAL RESISTANCE

One of the most prominent publications detailing strategies for combatting the rise in AMR is the O'Neill report commissioned by the UK Government in 2014 to investigate the threat posed by AMR and recommend international actions to address the problem. (3) The report's recommendations include strategies to reduce the need for antimicrobials by reducing infectious disease spread. Such strategies involve: increasing global public awareness, improving hygiene including access to clean water and sanitation and increased vaccination. Preventing infection will clearly reduce use of antimicrobials, reducing the rate of AMR development and preserving the utility of existing antimicrobial agents. (18) The UK is now is the middle of a five-year action plan (2019 to 2024) which builds upon This plan echoes many of the recommendations in the O'Neill report; its "three key ways" of tackling AMR are reduced antimicrobial exposure, optimised use and investment in innovation.

Antimicrobial Stewardship

In addition to reducing the overall need for antibiotics, the concept of antimicrobial-stewardship aims to optimise antibiotic prescribing through directing their use to only evidence based, appropriate indications. Some aspects of antimicrobial-stewardship have attracted controversy in recent years. Many studies have reported the benefits of these practices for slowing AMR development and improving patient outcomes. (20) However, some publications have suggested that actions such as delaying the start of antimicrobial treatment and early treatment de-escalation may have negative impacts on patient outcomes. Fitzpatrick et al. (21) discuss the "tension" between antimicrobial-stewardship and sepsis prevention. This may force clinicians and policy makers into difficult decisions between administering antibiotics for the potential benefit of the patient or withholding antibiotics for the potential benefit of the wider population. Furthermore, mathematical modelling by Obolski and colleagues suggests that restricting the use of antimicrobials may actually lead to increased emergence of multidrug resistant pathogens. (22). This may be due to, or exacerbated by, reduced antimicrobial prescribing leading to an increase in 'sub-lethal' exposure of bacterial populations to antibiotics and thus yielding more effective selection and exacerbating the AMR problem.

Rapid Diagnostics

Rapid diagnostics to reduce unnecessary antimicrobial use and target the use of narrow spectrum drugs, is a further proposal of the O'Neill Report, (3) and one which is already being appraised for use in clinical settings, with a range of positive and negative findings. Researchers have predicted the useful life of current last line antibiotics for Neisseria gonorrhoeae could be extended by point-of-care susceptibility testing – i.e. taking a patient sample, culturing the organism then testing its susceptibility to various antibiotics before deciding which one to prescribe , potentially postponing the situation where gonorrhoea becomes untreatable with current antibiotics. (23) On the other hand, in 2018 the National Institute for Health and Care Excellence (NICE) investigated point-of-care testing for Streptococcus A infection in patients presenting with sore throats. Their resultant briefing describes 11 tests, and states that there is "limited evidence" that such testing would change current antibiotic prescribing practices. (24) In November 2019 this research was incorporated into their Diagnostics Guidance in which they do not recommend this kind of rapid diagnostic testing for people aged over 5 years with sore throat symptoms. (25) The reasons are that Group A Streptococcus is not the only bacterial cause of sore throat symptoms, and that these symptoms are often self-limiting and thus rapid diagnostic testing of this nature does not represent pragmatic, cost-effective practice. Therefore, these NICE recommendations represent a more nuanced assessment of not just test accuracy and validity but also how testing fits into the broader clinical picture – a factor which is an important consideration for all novel testing practices.

Innovation and Development

Both the O'Neill Report and The UK Government's 5-year plan also advocate incentives for research and development of novel antimicrobials. (3,19) Suggestions include a Global AMR Innovation Fund of over $2 billion, market entry rewards and improved industry incentives. Such suggestions are designed to counteract a well-documented slump in the number of new antibiotics that have come to market in recent decades. Since the 1980's drug companies have increasingly shunned antimicrobial research in favour of more lucrative treatments for chronic and non-communicable diseases. (26) A further disincentive for novel antimicrobial research and design is reservation of novel drugs for second and third-line usage. Whilst this exemplifies good antimicrobial stewardship, it curtails the opportunity for pharmaceutical companies to generate profit and recoup development costs. For example, ceftaroline was added to the "Reserve Group" of antibiotics for "last resort" use in The WHO's List of Essential Medicines within 7 years of licencing by the Federal Drug Administration. (27,28) Many commentators have cited the lack of new antimicrobials as an exacerbating factor for the global AMR crisis. (29)

O'Neill's recommendations in this arena are supported by other publications calling for global changes to drug development, (3) licensing and funding policies in order to remove obstacles and incentivise large pharmaceutical companies to re-engage with antimicrobial research and development. (30) Legislative changes in the last decade give rise to hope that institutions and governments are taking note and enacting some of the demanded changes; however, there is limited evidence of the effectiveness of these measures and thus a need for greater international coordination. (31)

There are a multitude of ways to quantify and predict the future impact and costs of AMR including patient impact, impact on healthcare providers, the wider economic burden, and the perspective that any given study or prediction chooses to take can significantly alter their findings. (32) This variability is part of the reason that current health-economic models are unable to accurately incorporate the wider societal costs of increasing AMR.

Optimism can be drawn from several promising avenues of research into new drugs to treat resistant microbes. One such area is antibiotic adjuvants, also referred to as antibiotic resistance breakers (ARBs). ARBs are substances which increase or prolong the effectiveness of existing antimicrobial drugs by inhibiting bacterial resistance strategies. (33) lactamase enzyme inhibitors are among the oldest ARBs. Several decades of research have brought many candidate drugs into clinical trials although few have succeeded to clinical utility. Those which have made it to market include drugs which have improved the effectiveness of lactam antibiotics against resistant bacteria. (34)

In addition to preserving and improving existing drugs, novel classes of antibiotics are being discovered and investigated. Teixobactin is perhaps the most salient of the novel antibiotics currently in development. Teixobactin was discovered using an exciting new technology known as iChip, a device which can both capture traditionally unculturable environmental bacteria and collect the potential antibiotic compounds produced by these bacteria. (35) Teixobactin kills Gram-positive bacteria by binding to lipid molecules and inhibiting cell wall synthesis. Teixobactin and its analogues currently look promising in preclinical trials, for example proving to be effective treatments for methicillin-resistant S. aureus in murine models. (35) Additionally, review of the literature by Wright et al. found that cefiderocol, for example, is a promising novel antibiotic for the treatment of Gram-negative infections such as Pseudomonas aeurginosa. (36) However, these compounds have a long way to go through the clinical trials process before potentially reaching clinical utility.

It is also worth noting that almost all antibiotics are either natural microbial products or synthetic derivatives of microbial products. These phenotypic molecules, expressed in the context of evolution and natural selection, are complex and thus difficult to modify, replicate or synthesise on industrial scale. (37) Another implication is that these molecules exist due to an evolutionary race between microbes and thus antibiotic resistance long predates the clinical use of antimicrobial drugs. As a result, the potential for resistance to emerge to any novel compound exists long before that drug reaches clinical utility. (38)

CONCLUSION

Antimicrobial drugs have been one of the major medical achievements of recent centuries. However, the emergence of AMR and its increase in both prevalence and clinical significance in recent decades threatens to return us to an era of increased morbidity and mortality from infectious diseases. The mechanisms underpinning AMR are complicated, multifactorial and continually developing. Furthermore, the evolutionary nature of AMR means that resistance is likely to pose a challenge to all future antimicrobial drugs.

Increasing recognition among the medical and scientific communities matched by political will and increasing awareness and action by governments and global institutions, such as the WHO, have brought us action plans and strategies to combat the AMR crisis. Whether these plans can be implemented successfully and in an appropriately prompt manner remains to be seen.

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