Antibiotic Stewardship

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Abstract: The discovery of antibiotics had been one of the most significant events in the history of medicine. Antibiotics had saved countless number of lives and had contributed significantly to the health of mankind. The emergence of resistance is however a major threat to the continued usefulness of antibiotics. There are now strains of bacteria which are resistant to virtually all available antibiotics and these strains are increasingly being encountered in clinical practice. The development of new agents had not kept pace with resistance and it is unlikely that there will be major breakthroughs in the near future. The world needs to conserve and prolong the useful lives of the existing agents. This can only be achieved through good antibiotic stewardship programmes. As antibiotic resistance is a global threat all major stakeholders have to work together to meet this challenge.

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Introduction

Stewardship is the conducting, supervising, or managing of something; especially: the careful and responsible management of something entrusted to one's care.[1] Antibiotic stewardship is the careful and responsible management of our precious resource, the antibiotics. Antibiotic stewardship involves using antibiotics only when absolutely necessary, selecting the most appropriate agent and using the right dosage regimen and route of administration for the optimum duration. Good stewardship will help improve patient treatment outcomes, minimize adverse effects of the agents, reduce cost of health care and most importantly prevent or reduce emergence of resistance.

Resistance to antibiotics

The discovery of antibiotics was one of the most significant event in medical history. After only 20 years in clinical use antibiotics had added a decade to the life expectancy of man.[2] Together with vaccination, clean water and other public health measures mortality from infectious diseases was dramatically reduced to the extent that in the 1950s and 1960s, scientists thought that infectious diseases were no longer a major challenge. In 1967, the Surgeon General of the United States of America, William Stewart was purported to have said that "the time has come to close the book on infectious diseases and declare the war against pestilence won." There is now some dispute as to whether Stewart actually made this infamous pronouncement.[3] Nonetheless such optimism expressed at that time has unfortunately been shown to be unfounded. This has been due to various reasons, among which is the emergence of antibiotic resistance.

Resistance is not a new phenomenon. Sir Alexander Fleming in his Nobel Lecture delivered on the 11th of December 1945, warned that, "It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body".[4] The resistome is defined as the collection of all the antibiotic resistance genes and their precursors both in pathogenic and non-pathogenic bacteria.[5] Recent studies of the soil resistome have revealed the presence of genes encoding for antibiotic resistance to a wide variety of antibiotics including synthetic compounds like quinolones and newer antimicrobials like Synercid and daptomycin. It would appear that the development of antimicrobial resistance had been going on in nature long before antibiotics came into medicinal use. The environment, in particular the soil is regarded as an important reservoir of antibiotic resistance determinants.

In a recent study, a library of 480 strains of soil bacteria was screened against 21 antibiotics. The majority of strains were resistant to 7-8 antibiotics. A wealth of antibiotic inactivating enzymes was uncovered including inactivating enzymes to rifampicin and Synercid. Intrinsic resistance to quinolones was also seen despite

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no known prior exposure of the soil to these synthetic antibiotics or their analogues.[6]

Soil bacteria are not just resistant to antibiotics. Some strains of soil bacteria areas can utilize antibiotics as their sole carbon source. These "antibiotic-eating" bacteria have been found in pristine soil i.e. soil from non-urban areas which have had minimal human contact for the past hundred years.[7] Most of the strains identified in this study were proteobacteria, and more than 40% were *Burkholderia* spp. Pseudomonads were also well represented. Catabolic pathways responsible for antibiotic digestion in nature can therefore provide a rich source of potential resistance determinants.

In a more recent study[8], metagenomic analyses of rigorously authenticated ancient DNA from 30,000-year-old permafrost sediments revealed a highly diverse collection of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics. Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants. These results show that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

The Antibiotic Pipeline

Antibiotic resistance is a major challenge world-wide. It is seen in gram positive as well gram negative organisms; in health-care associated as well as community acquired infections. The Infectious Diseases Society of America had identified 6 organisms as being the most problematic; the so-called ESKAPE organisms namely *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Acinetobacter baumanni*, *Pseudomonas aeruginosa* and *Enterobacter* sp. In their 2008 Report on the pipeline of new antimicrobial agents, the IDSA concluded that the number of new agents in the pipeline is disappointing and there were no pure anti-gram negative agent or agent to counter the emerging carbapenemases. There was decreased involvement of top pharmaceutical companies in the area of anti-microbial drug development and that it is unlikely that there will be any major advance in ability to treat antibiotic-resistant infections.[9]

A similar European report came to the same conclusions. A gap exists between multidrug-resistant bacteria and the development of new antibiotics. Resistance to antibiotics is high among bacteria that cause serious infections in humans. Resistance is increasing among certain Gram-negative bacteria. Very few antibacterial agents with new mechanisms of action are under development to meet the challenge and there is a particular lack of new agents for multidrug-resistant Gram-negative bacteria.[10]

There is overwhelming evidence that the overuse of antibiotics is the main driver of resistance.[11] Resistance is most prevalent in settings where antibiotic use is high eg intensive care units.[12] There is an association between the prevalence of resistance in a country with the amount of antibiotics consumed.[13] Resistant mutants are also selected for during therapy.[14]

Furthermore surveys conducted worldwide point to a high prevalence of inappropriate antibiotic use. Inappropriate use is rampant in both hospital and community practice and occurs in both developed and developing countries. The studies also indicate that there has been no improvement in antibiotic usage over the years.[15]

International initiatives

In 1998, a World Health Assembly resolution (WHA 51.17) urged Member States to develop measures to encourage appropriate and cost-effective use of antimicrobials.[16] In 2010 the Third Global Patient Safety Challenge 2010 adopted "Tackling antimicrobial resistance" as its theme. In 2011 the WHO also adopted the issue of antibiotic resistance as the focus of World Health Day.[17]

The World Health Organization has published a document entitled "Global strategy for Containment

of Antimicrobial Resistance".[18] It describes a comprehensive, multi-faceted strategy which may be adopted by nations to contain antimicrobial resistance. Nonetheless it is the onus of the individual nation to implement the strategy. The important components of the strategy include interventions in the areas of education, resistance surveillance, health care associated infection control, antibiotic use monitoring, diagnostic laboratories, the non-medical use of antibiotics and research.

National initiatives

The containment of antibiotic resistance should be a matter of national policy. An inter-sectoral task force which includes all stake-holders should be established. This task force should be represented by members from government, the health sector, the agricultural sector, the pharmaceutical industry, and the consumers. The government should be involved as resources need to be allocated for the various activities. The task force should also establish specific outcome measures to determine the effectiveness of the interventions undertaken.

The national strategy will require a governance and management framework. In Malaysia, Infection and Antibiotic Control Committees have been established at national, state and hospital levels. The National Committee is chaired by the Director General of Health and comprises all state representatives and selected technical experts. The Committee meets regularly to reviews reports on antibiotic resistance monitoring, nosocomial infection rates, antibiotic utilization rates and other outcome measures. The committee makes policies and recommendations based on the data presented.

An important component of the national strategy would be a national antibiotic resistance surveillance programme. All participating laboratories should employ a standardized method of testing, a predetermined panel of antibiotics to be tested and a uniform method of expressing the data. The WHO Net software programme[19] which is available free of charge would be a suitable software for entering and analyzing the data. A national coordinating centre would have to be established to collect and collate the data from the various hospitals and to produce and disseminate regular reports. In addition to the national surveillance programme, there can also be established monitoring programmes for specific alert organisms. These organisms are those that pose significant challenges in resistance and may include MRSA, ESBL producing organisms, pan-resistant *Acinetobacter* and carbapenamase producers e.g. NDM1-producing bacteria. Such information should not only be disseminated nationally but also shared internationally as resistant organisms can spread widely throughout the world.[20] Some of the data collected e.g. MRSA incidence rate can also serve as outcome measures to determine effectiveness of interventions.

Good infection control is crucial to the containment of antibiotic resistance.[21] Patients infected by resistant organisms need to be identified early and measures taken to prevent the spread of these resistant organisms to other patients. Every country needs to put in place a policy pertaining to infection control. Education and training in infection control should be an integral part of all health-related programmes as infection control is an important patient safety issue. There should be nosocomial infection surveillance programmes complemented by audits of infection control practices like hand disinfection.

The monitoring of antibiotic use is another important strategy. In many countries national antibiotic utilization studies are conducted regularly. It has been shown that countries that have high antibiotic consumption rates also have high levels of resistance.[13] To improve prescribing practices, national antibiotic use guidelines and national formularies may be established. The professional societies can also issue evidence-based clinical practice guidelines for the more commonly encountered infections.

The education of the public through the mass media will help create awareness of the serious challenges posed by antibiotic resistance.[22] Legislation to control prescriptions, dispensing and sales of antibiotics for medicinal use should be introduced. Similar legislation to control antibiotic use in agriculture and for other medicinal purposes is also required.[23] A major stakeholder is the pharmaceutical industry and it is important that the health profession work with industry to ensure ethical marketing and promotional activities.

Institutional initiatives

At the level of the institution stewardship programmes are also very important. There are good published guidelines on establishing institutional stewardship programmes but the institution may have to tailor the programme to meet its own specific requirements.[24,25] There are four main areas in an institutional programme: (i) Education and Feedback (ii) Strategies to improve prescribing (iii) Dealing with forces that influence prescribing (iv) Audit and quality improvement activities.

Education and Feedback is probably the most important element in an institutional programme. The primary aim is to optimize prescriber behavior and a variety of educational strategies may be employed. A targeted rather than a universal strategy is preferred. The institution should identify the most acute problems, define desired outcomes which should be measured, plan and implement the intervention and give feedback to prescriber. Immediate concurrent feedback which is individualized has been shown to be effective in reducing antibiotic consumption without compromising on clinical outcomes and resulting in considerable cost-savings.[26]

Many hospitals also issue institutional antibiotic usage guidelines. The development of these guidelines must involve all major stakeholders to achieve a sense of ownership of the guidelines. The guidelines have to be evidence based, updated regularly, tailored to the local situation taking into account local patterns of infections and resistance. Emphasis should be given on major areas of deficiencies. Guidelines should also consider local constraints in supporting facilities, the availability of antibiotics and financial matters.

Good microbiology facilities are essential for the stewardship programme. Results generated by the laboratory should be accurate, reliable and timely. Antibiotic resistance surveillance should be performed regularly and the results disseminated to those who need to know in a timely fashion. Laboratories should practice restricted susceptibility reporting, provide some interpretation of culture reports to assist clinicians in distinguishing between pathogens and colonisers. There should be a close working relationship between the laboratory and the clinicians. The specialist antibiotic pharmacist can contribute to the stewardship programme by introducing strategies to improve prescribing.[27] They include modified antibiotic prescribing forms and automatic antibiotic stop orders. The antibiotic pharmacist should also undertake the monitoring of antibiotic use and feedback the information to clinicians. The antibiotic pharmacist should participate in ward rounds and assist the clinicians in making decisions on antibiotic use. Other pharmacy strategies would include restriction of antibiotics and making formulary changes.

The institution should have a policy on its interactions with the pharmaceutical industry. There should be some form of regulation of promotional activities in hospitals. Doctors should also learn how to cope with patient demands for antibiotics and appreciate the need to counsel patients on the negative consequences of unnecessary antibiotic use.

There should be regular audit and quality improvement activities in the institution. It is important to explain to the staff the purpose of quality activity; namely to improve practices and not a fault finding exercise. Monitoring of compliance with the stewardship programme is essential. Measuring outcomes to assess the effectiveness of interventions is necessary to complete the quality cycle.

Conclusion

The emergence of resistance is threatening the usefulness of antibiotics and there is an urgent need to conserve this precious resource. Antibiotic stewardship is crucial to contain resistance. A concerted effort employing a multifaceted strategy is essential at international, national and institutional levels is required and we need to work together to meet this challenge.

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