Bugs for the Next Century: The Issue of Antibiotic Resistance

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Abstract

***Objective**: To address the issue of emerging antibiotic resistance and examine which organisms will continue to pose problems in the new century. **Methods**: Review of articles pertaining to bacteria recognised for increasing resistance. **Results**: Changing resistance patterns are correlated with patterns of antibiotic use. This results in fewer effective drugs against "old" established bacteria e.g. gram-positives such as* **Streptococcus pneumoniae** *and* **Staphylococcus aureus**. *Resistance in gram-negative bacteria is also steadily increasing. Nosocomial gram-negative bacteria are capable of many different resistance mechanisms, often rendering them multiply-resistant. Antibiotic resistance results in morbidity and mortality from treatment failures and increased health care costs. **Conclusion**: Despite extensive research and enormous resources spent, the pace of drug development has not kept up with the development of resistance . As resistance spreads, involving more and more organisms, there is concern that we may be nearing the end of the antimicrobial era. Measures that can and should be taken to counter this threat of antimicrobial resistance include co-ordinated surveillance, rational antibiotic usage, better compliance with infection control and greater use of vaccines.*

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Introduction

Emerging antibiotic resistance is a global problem. Antibiotic resistance results in morbidity and mortality from treatment failures and increased health care costs. Despite extensive research and enormous resources spent, the pace of drug development has not kept up with the development of resistance. As resistance spreads, involving more and more organisms, there is concern that we may be nearing the end of the antimicrobial era. Unfortunately, the story of antimicrobial resistance closely parallels the usage of antibiotics.

Gram-positive Bacteria

*Streptococcus pneumoniae (*pneumococcus*)* is a common cause of community-acquired infections such as otitis media, bronchitis and pneumonia and a leading cause of illness and death among young children, persons with debilitating medical conditions and the elderly. In 1941, 10,000 units of penicillin 4 times a day was sufficient to treat pneumococcal pneumonia. The doses we use today for pneumonia due to penicillin-sensitive pneumococcus are many hundreds of times that.

In 1967, the first description of penicillin resistance in pneumococcus isolated from an adult with hypo-gammaglobulinaemia was published.[1] This report described what today would be regarded as "intermediate" resistance. This was soon followed by cases that were fully resistant to penicillin as well as resistant to three or more classes of antibiotics.[2,3]

Sixty years after the introduction of penicillin, penicillin-resistant *S. pneumoniae* is being reported with increasing frequency throughout many parts of the world. In addition, many of these strains are also resistant to various other antibiotics such as macrolides, tetracycline, rifampicin, co-trimoxazole and cephalosporins. Some centres in Asia have documented very high prevalence of penicillin resistance (including intermediate and fully resistant) in clinical isolates, with Seoul, Nagasaki, Ho Chi Minh City and Bangkok showing rates of >50%.[4]

Risk factors associated with acquisition of penicillin resistance include young age, day care attendance, prior antibiotic exposure, impaired immunity and prior hospitalisation.

Staphylococcus aureus

In 1941, nearly all strains of *S. aureus* were susceptible to penicillin. Within a few years, Spink and Ferris[5] reported isolation of a *S. aureus* strain that produced penicillinase which inactivated the antibiotic. Today, the majority of *S. aureus* are resistant to penicillin.

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In 1960, all strains of *S. aureus* were susceptible to methicillin. Unfortunately, within a year, methicillin resistance was reported from Europe.[6] Today methicillin resistance, which includes resistance to other beta-lactam antibiotics, is reported from many countries throughout the world. In Singapore, methicillin-resistant *S. aureus* (MRSA) are almost always resistant to aminoglycosides as well [methicillin and aminoglycoside resistant *S. aureus* (MARSA)].

Risk factors for acquisition of MRSA include increased length of hospitalisation, multiple hospitalisations, multiple invasive procedures, wounds, severe underlying disease and broad-spectrum antibiotic use. MRSA has for a long time been associated with hospitalisation and nosocomial infections. However, disturbingly, it is now being reported more and more in cases from the community.[7-9] The recent occurrence of 4 paediatric deaths in a rural community in the USA[10] has increased concern about community-acquired MRSA.

To worsen matters and further complicate therapy for *S. aureus*, we now have to contend with the threat of vancomycin intermediate or resistant strains. The first report of infections caused by *S. aureus* with intermediate levels of resistance to vancomycin (MIC 8 μg/mL) came from Japan[11] and were soon followed by others.[12]

Enterococcus

Enterococcus was previously regarded as a rather feeble pathogen. However, it is now being recognised as a leading cause of nosocomial infections, accounting for 14% of isolates in the intensive care units (ICUs) in hospitals surveyed under the National Nosocomial Infection Surveillance (NNIS).[13] Vancomycin-resistant enterococci were first reported in Europe in 1988.[14] Since then, it has become an important nosocomial pathogen accounting for up to 24% of infections in ICU patients.[15]

Gram-negative Bacilli

Resistance has also been increasing among gram-negative bacilli. β-lactamases inactivate β-lactam antibiotics. Ampicillin resistance in *Escherichia coli* is a useful indicator of resistance arising from antibiotic selection of resistant strains among naturally susceptible species. In surveys performed across Europe, the percentage of strains resistant to ampicillin in 1984[16,17] was 8%, 18% and 13% for northern, central, and southern Europe respectively and rose to 28%, 28% and 46% respectively in 1987/1988.[16,17] Though man's use of β-lactam antibiotics did not create β-lactamases, it has certainly selected organisms with more or "better" enzymes.

Extended spectrum beta-lactamases (ESBLs) first became a problem in France where their incidence amongst *Klebsiellae* rose from under 1% in 1985 to 10-11% by 1988-1989.[18] They are now found worldwide. They have not only caused significant problems in *Klebsiella* but also in *Enterobacter*, *Citrobacter* and *Serratia*. The presence of ESBLs renders almost all beta-lactam antibiotics ineffective, requiring the use of carbapenems, quinolones or aminoglycosides.

Pseudomonas and *Acinetobacter* species are other gram-negative bacilli which have shown increasing resistance pattern over the years. Resistance to beta-lactam antibiotics is increasing, and there have also been outbreaks of *Acinetobacter* resistant to all antibiotics including imipenem.[19,20] Resistance to carbapenems in *Pseudomonas* species has also been reported in various studies.[21,22]

As with gram-positive bacteria, resistance in gram-negatives has been attributed to increased usage of antibiotics. The increased use of broad-spectrum third generation cephalosporins and stay in ICUs are risk factors for colonisation and subsequent infection with resistant gram-negatives.

Tuberculosis

History of Tuberculosis

Tuberculosis is an ancient disease. Archaeologic evidence of spinal tuberculosis has been found in neolithic, pre-Columbian and early Egyptian remains. Moving on to the later centuries, the over-crowded conditions of industrial revolution contributed to its spread, such that tuberculosis was responsible for a quarter of adult deaths in Europe in the 17th and 18th centuries.

In 1884, Robert Koch, published "The Etiology of Tuberculosis" in which he established:

- the presence of tubercle bacillus in tubercular lesions of various organs
- the cultivation of organisms in pure culture
- production of tuberculosis by inoculation in guinea pigs

More than a hundred years later, tuberculosis continues to cause significant morbidity and mortality worldwide.

A report from the World Health Organisation[23] in 1997 gave an estimate of 7.96 million new cases in 1997, while existing cases of the disease numbered 16.2 million with the number of people infected estimated at 1.86 billion. The number of people who died from the disease was estimated to be 1.87 million.

Besides the sheer number of cases, the other worrisome fact is that of increasing drug resistance. In the same WHO report, primary resistance to any drug ranged from 2% (Czech Republic) to 40% (Dominican Republic). Primary resistance to isoniazid ranged from 1.5% to 32% while primary resistance to rifampicin ranged from 0% to 6.9%. Primary multi-drug resistant tuberculosis (MDR-TB) rates

ranged from 1.4% to 14.4% while rates of acquired resistance to any drug ranged from 5.3% to 100%.

The factors that have contributed to the rise of tuberculosis and increase in resistance are well known. There has been breakdown in public health services especially in countries of the ex-Soviet Union. Mass migration, either due to natural disasters or wars, has resulted in large displaced populations at risk for infectious diseases of all kinds. Unfortunately, the countries endemic for tuberculosis are also experiencing an increase in HIV cases, and cases of co-infection of the two diseases number in the millions. Lastly, complacency in the last few decades about the seriousness of infectious diseases and antimicrobial resistance has led to underfunding and understaffing. This has led some public health authorities to regard *Mycobacterium tuberculosis* as "the real millennium bug".

The Future

New Antimicrobials

Development of new antimicrobials slowed down in the 1980s and 1990s as pharmaceutical companies turned their attention to other fields of research and development. It has been almost 20 years since a new class of antimicrobials was discovered, but in the last few years, streptogramins and oxazolidinones have been introduced. However, new drugs for resistant gram-negative bacteria are urgently needed.

Rational Use of Current Antimicrobials

In institutions, rational antimicrobial usage may take the form of antibiotic guidelines, as well as audits of usage. Various strategies such as cycling antimicrobials especially in the ICUs, or combination therapies have been suggested to retard development of resistance. At the community level, primary health care physicians should be given antimicrobial recommendations based on current resistance patterns. In the developing world, many antimicrobials are available over the counter without prescriptions and this contributes to a scenario of worsening resistance. Increased awareness and education will be required to reverse these trends and these may only be forthcoming with improved economic and political settings.

Centralised Surveillance

We can also improve on our treatment of various infectious diseases if we have more accurate information on infective aetiologies and resistance patterns. Some authorities recommend centralised surveillance of resistance patterns and antibiotic recommendations. Perhaps we can learn from the experience of Denmark, a country not much larger than Singapore in terms of population.[24] There is formal collaboration between clinical microbiologists, hospital pharmacists, doctors in hospital and private practice and national centres. In addition to centralised surveillance, medical audit projects are carried out and the medical association issues antibiotic recommendations annually. The very low use of antimicrobials is associated with a low rate of antimicrobial resistance.

Preventive Methods—Vaccines, Infection Control

We will need to look at other ways of preventing infections, rather than relying on new antimicrobials to treat diseases. The role of vaccines for more bacterial and viral diseases will be expanded. Greater importance will need to be placed on infection control to limit the spread of infectious organisms, especially for multi-resistant organisms.

Conclusion

Although there are new antimicrobials on the horizon, bacteria have shown that they are capable of rapidly developing resistance to everything that has been discovered. We have to be judicious in using all antimicrobials to preserve their usefulness and retain some options for the future. As we enter the next millennium, the problems of infectious diseases and antibiotic resistance loom ever larger. The "old" bugs will continue to cause significant morbidity and mortality and public health challenges.

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