SYMPOSIUM ON PRESSING PROBLEMS IN COMMUNITY MEDICINE

Emerging problems of antibiotic resistance in community medicine

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Abstract

Emergence of antimicrobial resistance in bacteria associated with community acquired infections has made the choice of empirical therapy more difficult and more expensive. The problems due to possible spread of MRSA to the community, emergence of penicillin resistance in S. pneumoniae, ampicillin resistance in H. influenzae, and multiresistance among common enteric pathogens are highlighted. Bacteria have a remarkable ability to develop resistance to many of the newly synthesized antimicrobial agents but the appropriate use of antibiotics will delay and in many cases prevent the emergence of resistance.

Key words: Antibiotic resistance, community medicine, emerging problems

INTRODUCTION

The tremendous success of the pharmaceutical industry in creating new antibiotics has not achieved the desired control of infectious diseases. New organisms challenge us while old ones continue to plague us. The recent outbreaks of Ebola virus infections in Africa, epidemics of cholera in South and Central America and problems associated with drug-resistant strains of Mycobacterium tuberculosis and Plasmodium falciparum have underscored the need to be vigilant. Closer to home, Malaysia’s rapid move towards achieving an industrialized nation status, has resulted in the importation of infectious diseases which previously had been under control. There is a need for us to be aware of these threats which include drug-resistant strains of Plasmodium falciparum and Mycobacterium tuberculosis, tetracycline-resistant Vibrio cholerae, chloramphenicol-resistant Salmonella typhi, and the outbreak of cholera caused by the Bengal strain of V. cholerae (0139). Knowledge of the antimicrobial resistance patterns of the bacteria causing infections in one’s own community as well as global trends is essential for the successful management of infectious diseases.

Genetic basis of antimicrobial resistance

Bacteria become resistant to antibiotics as a result of chromosomal mutations, inductive expression of a latent chromosomal gene or by exchange of genetic material through transformation, transduction, or transfer of plasmids by conjugation. Conjugation with plasmid transfer of DNA is particularly common among the Enterobacteriaceae. Bearing in mind that the mean generation time of Escherichia coli is 20 minutes, the frequency with which spontaneous mutation and conjugative transfer of resistance genes occurs gives us an insight into the possible magnitude of the problem. To compound this bacteria may possess transposons, the so-called jumping genes, that have the ability to enter chromosomes or transmissible plasmids. Intergenusspreading of resistance can occur between Gram-positive species such as staphylococci and enterococci and between Enterobacteriaceae. Gram-positive species can transfer resistance to Gram-negative species, but the reverse is uncommon.

Staphylococci

In 1941, virtually all strains of Staphylococcus aureus were susceptible to penicillin G, but by 1944 S. aureus resistant to penicillin by production of beta-lactamase began to appear and today more than 95% of S. aureus worldwide are resistant to penicillin and ampicillin. The pharmaceutical industry responded to this challenge with the synthesis of methicillin and until the 1980s methicillin-resistant S. aureus was rare; now MRSA has become a problem particularly in long-term care facilities. MRSA are resistant to all beta-lactams because of a
meca gene in the chromosome that codes for the production of a new penicillin-binding protein PBP 2a that has a low affinity for beta-lactam antibiotics. As a result of transposition and site-specific integration in many MRSA, the chromosome mediates resistance not only to beta-lactam antibiotics but also to other antibiotics such as erythromycin, tetracycline, sulphonamides, fusidic acid, and gentamicin and to heavy metals and disinfectants.\(^2\) The emergence of MRSA as a major problem has resulted in the increased use of vancomycin, the only agent that effectively treats these bacteria, but this increased use of vancomycin has created vancomycin resistance in other bacteria such as enterococci. In the mid-1980s, the new fluoroquinolone antimicrobial agents, such as ciprofloxacin, inhibited MRSA at \(<2\text{ \text{ug}}/\text{ml}\)\(^3\) but a study carried out in Atlanta, USA showed that ciprofloxacin resistance in MRSA strains increased from 0% to 79% after 3 months of ciprofloxacin use.\(^4\) Mupirocin, a pseudomonic acid derivative, is a topical agent that is highly effective against MRSA and used to eliminate carriage. It has been available in the United Kingdom for a number of years. MRSA with plasmid-mediated resistance to mupirocin have been found, although selection of resistance is slow and stepwise in fashion.\(^5\) The mechanism of resistance is non-enzymic in nature and high-level resistance was first reported in 1987.\(^6\) These aspects of staphylococcal resistance illustrate the rapid ability of bacteria to become resistant to virtually all antibacterial agents, whether of natural origin, semisynthetic or totally synthetic. In the Western Pacific region, the rates of resistance of S. aureus to penicillin vary from 59 to 97%, while resistance rates to methicillin are from 0 to 55% and that to the fluoroquinolones, 1 to 55%.\(^6\) In a recently published local study of antimicrobial resistance in a community setting in the Klang Valley, 91.3% of S. aureus were resistant to penicillin, 23.4% to tetracycline and 13.3% to erythromycin. None of the isolates were resistant to methicillin.\(^7\)

Advances in medical technology have made S. epidermidis infection of various medical devices and intravenous catheters a major problem both in the hospital and in the community where therapy may be administered at home for patients with malignancy or infection. Most S. epidermidis that cause these infections are resistant to methicillin, aminoglycosides and fluoroquinolones.\(^8\) Although rifampicin and fusidic acid inhibit S. epidermidis, resistance may develop when either agent is used singly or combined with another agent.\(^9\) Coagulase-negative staphylococci are felt to be a reservoir of resistance genes amplified through antibiotic selection that occurs when antibiotics administered to patients achieve low concentrations in skin.\(^9\)

**Streptococcus pneumoniae**

In 1941, 10,000 units of penicillin administered 4 times a day for 4 days cured patients with pneumococcal pneumonia. Today, a patient could receive 24 million units of penicillin and die of pneumococcal meningitis.\(^10\) Pneumococci remain the most important cause of community-acquired pneumonia and a major cause of otitis media, sinusitis, and meningitis both in children and in adults.

The resistance of S. pneumoniae was first noted in South Africa\(^10\) but has recently become a worldwide problem. In Spain 6% of S. pneumoniae were resistant to penicillin in 1979 but increased to 44% in 1989.\(^11\) Such strains are also present in Malaysia and meningitis due to a penicillin-resistant strain has occurred locally.\(^12\) These strains are also resistant to cephalosporin antibiotics such as cefotaxime or ceftriaxone, which have been used to treat meningitis when the infection is caused by relatively resistant strains. The mechanism of penicillin resistance of S. pneumoniae involves the development of altered forms of PBPs that have decreased affinity for beta-lactam antibiotics. Strains with the highest level of resistance show reduction in the affinity of the five high molecular weight PBPs, 1a, 1b, 2a, 2x, and 2b. The BDB and 2x genes of penicillin-resistant pneumococci differ extensively from the genes of susceptible strains and it appears that the altered PBP genes arose by interspecies recombinational events in which segments of the PBP structural genes had been replaced by regions derived from PBP genes of oral streptococcal species that were resistant to penicillins.\(^13\) By travel, such strains can spread, as shown by a study comparing strains isolated from children in a day care center in Cleveland and strains from Spain by electrophoretic analysis of the PBPs and by restriction enzyme analysis of the PBP genes.\(^14\)

In a study carried out in Hungary, 58% of the isolates were resistant to penicillin and almost 70% of the strains were also resistant to tetracycline, erythromycin, trimethoprim/sulphamethoxazole, and 30% were resistant to chloramphenicol.\(^15\) In Sweden 11% of S. pneumoniae had reduced susceptibility
to penicillin and 7% to trimethoprim/sulphamethoxazole and 8% to erythromycin. In Japan, 46.7% of *S. pneumoniae* had reduced susceptibility to penicillin. The resistance of pneumococci to macrolides such as erythromycin averages 20 to 25% in France, 18 to 20% in Japan, and less than 10% in Spain. The resistance is a result of a plasmid-mediated production of an enzyme that methylates a crucial adenine residue in 23S rRNA which is the binding site of erythromycin. The resistance can be induced by erythromycin or bacteria can constitutively produce it. It is possible that the increased use of the new macrolides will cause an increase in macrolide-resistant *S. pneumoniae*. Two out of 22 strains (8%) isolated from the community in the Klang Valley were found to be resistant to penicillin while resistance rates in the Western Pacific region are 0 to 60% for penicillin and other beta-lactams, 1 to 80% for trimethoprim/sulphamethoxazole, 0 to 44% to erythromycin, and 2 to 70% for tetracycline.

**Haemophilus influenzae**

Ampicillin had been the major antibiotic used to treat *H. influenzae* meningitis from 1960 to the 1970s. In 1974, a plasmid mediated beta-lactamase was first noted in *H. influenzae*. Since then, resistance to ampicillin has continued to increase. The beta-lactamase called TEM is a plasmid-mediated enzyme. Beta-lactamase production by *Haemophilus* ranges from 5 to 55%, and world-wide resistance of *H. influenzae* type b is approximately 20%. In a Swedish study 10% of *H. influenzae* were beta-lactamase positive while non-beta-lactamase induced resistance to all beta-lactams was first detected in 1988 and accounted for 3% of *H. influenzae* in 1992. In Spain, it has been said that 50% of *H. influenzae* type b are resistant to 5 or more antibiotics, including chloramphenicol and trimethoprim/sulphamethoxazole. The resistance of *Haemophilus* to chloramphenicol and trimethoprim/sulphamethoxazole is a result of plasmid-mediated enzymes. *Haemophilus* resistance to rifampicin has been developed in patients receiving it as chemoprophylaxis to prevent meningococcal or *Haemophilus* meningitis. In Kuala Lumpur it has been reported that 5 of 43 (12%) strains of *H. influenzae* were resistant to ampicillin and 1 strain was resistant to chloramphenicol. In the Western Pacific region resistance rates of *H. influenzae* isolated from respiratory specimens vary from 3 to 41% for ampicillin, 3 to 52% to trimethoprim/sulphamethoxazole and 0 to 26% to tetracycline. This has led to the increased use of beta-lactamase stable penicillins and cephalosporins and the newer macrolides for the treatment of respiratory infections. Emergence of resistance to the newer macrolides will need to be monitored.

**Neisseria and Moraxella**

Most strains of *Neisseria meningitidis*, an important cause of meningitis world-wide, are susceptible to penicillin, but in Spain the concentration of penicillin required to kill meningococci has increased tenfold. *Neisseria* have acquired new PBPs from commensal organisms by gene transfer and plasmids that mediate beta-lactamase production have been found in *N. meningitidis* in Europe and North America. *Moraxella (Brachmella) catarrhalis* causes otitis media and bacterial bronchitis in elderly individuals with chronic lung disease. In the 1970s virtually all isolates were susceptible to ampicillin, but now in excess of 75% produce beta-lactamases that inactivate ampicillin, amoxicillin, and cefaclor, oral antibiotics widely used to treat ear and sinus infections.

Penicillin was the drug of choice to treat gonorrhoea, but over the years the concentration of penicillin needed to achieve cure rose as a result of a chromosomal mutation that reduced the affinity of PBPs for penicillin. In 1976, the plasmid-mediated TEM beta-lactamase of *E. coli* was found in *N. gonorrhoeae* in Africa and Asia. Today in the Philippines and Thailand, in excess of 90% of *N. gonorrhoeae* produce beta-lactamase. In 1986, a plasmid that contains the gene *terM* and mediates tetracycline resistance in enterococci, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Gardnerella vaginalis*, appeared in gonococci. The concentration of beta-lactamase-stable cephalosporins such as ceftriaxone and of fluoroquinolone agents required to kill *N. gonorrhoeae* isolates from Asia have been increasing yearly. In Kuala Lumpur, of 112 strains of *N. gonorrhoeae* studied, 59% were resistant to penicillin, 81% to tetracycline but all were susceptible to ceftriaxone and spectinomycin. PPNG rates in the Western Pacific region vary from 0 to 80% while non-beta-lactamase mediated resistance to penicillin was reported to be from 0 to 62%. Fluoroquinolones have been used increasingly in the treatment of gonococcal infections and emergence of resistance will have to be carefully monitored. In a study in Japan, the quinolone susceptibility of gonococci isolated in the the
period 1981 to 1984 was compared to those isolated in 1992 and the latter strains showed about 8 fold increases in MICs; the MIC_{M IC}(mg/L) for norfloxacin increased from 0.25 to 2.0, ofloxacin 0.125 to 1.0 and for ciprofloxacin, from 0.063 to 0.5.²¹

**Enteric pathogens**

That plasmids encode for resistance was first recognised in Japan in 1959. *Shigella* now possess plasmids that mediate resistance to ampicillin, chloramphenicol, tetracycline, aminoglycosides, and trimethoprim/sulphamethoxazole. Strains of *S. flexneri* and *S. sonnei* isolated in the Western Pacific region have resistance rates varying from 0 to 100% to ampicillin, 0 to 80% to chloramphenicol, 11 to 100% to trimethoprim/sulphamethoxazole and 0 to 7% to the fluoroquinolones.⁶ Antibiotics have been found to be useful in the treatment of shigellosis, especially infections due to *S. dysenteriae* type 1 and *S. flexneri*. Therapy with an effective antimicrobial shortens duration of diarrhoea and clinical symptoms, and shortens the duration of faecal excretion of *shigella*, and can be lifesaving in some instances. Antimicrobials that have been found to be clinically useful include the sulphonamides, tetracyclines, chloramphenicol, ampicillin, trimethoprim/sulphamethoxazole, ceftriaxone and the fluoroquinolones.

Nontyphoidal *Salmonella* are resistant to multiple antibiotics with resistance rates of 4 to 44% to ampicillin, 0 to 40% to chloramphenicol, 0 to 37% to cotrimoxazole and 0 to 11% to fluoroquinolones reported in this region.⁵ The extensive use of antibiotics in animal feed may explain the high antibiotic resistance of *Salmonella* species. *Salmonella* have recently been found in Europe and Asia that produce modified beta-lactamases that are related to the TEM enzyme and mediate resistance to extended spectrum cephalosporins. Currently only fluoroquinolones can be used to treat some of these *Salmonella* infections.⁶ Failure to eliminate *Salmonella*, prolongation of *Salmonella* carriage and emergence of resistance after treatment have been described with several antibiotics. These factors along with doubtful clinical efficacy are strong arguments against antibiotic treatment of uncomplicated salmonellosis.

Chloramphenicol-resistant strains of *Salmonella typhi* first appeared in Mexico in 1972. Sporadic outbreaks with such strains have been observed from time to time particularly in Southeast Asia and the Indian subcontinent. Over the past few years, there has been an increasing number of multidrug-resistant *S. typhi* with simultaneous resistance to chloramphenicol, cotrimoxazole and ampicillin. Such strains have been particularly observed in the Indian subcontinent. These strains appear to be susceptible to the fluoroquinolones and ceftriaxone.⁹

Antibiotics decrease the length of illness and decrease intestinal shedding of *Vibrio cholerae*, helping to reduce the spread of cholera. Cholera is currently a major problem in South and Central America, where isolates may be resistant to tetracycline, sulphonamides, chloramphenicol, and trimethoprim/sulphamethoxazole.⁹ That means that inexpensive antibiotics that would decrease the spread of cholera by decreasing the organism burden are no longer available in some parts of the world.⁹

*Campylobacter jejuni* is an important cause of diarrhoea in both industrialized and developing countries. Recently, *Campylobacter* has become resistant to tetracycline as a result of acquiring the *tetM* gene from *enterococci*.⁷ It is now established that *Campylobacter* can acquire resistance during quinolone treatment and it has been proposed that the use of quinolones in farming, especially poultry, and in veterinary practice may contribute to the increasing resistance of campylobacters to fluoroquinolones. The lack of correlation between high in-vitro susceptibility and clinical and bacteriological outcome in salmonella and campylobacter enteritis is well established and the role of antibiotics in the treatment of campylobacteriosis is similar to that of nontyphoidal salmonellosis.

**Conclusion**

In 1992 there were more than 50 penicillins, 70 cephalosporins, 12 tetracyclines, 8 aminoglycosides, 1 monobactam, 3 carbapenems, 9 macrolides, 2 new streptogramins, and 3 dihydrofolate reductase inhibitors.⁸ Despite all these antibiotics a person could die in a hospital in any part of the world as a result of a resistant bacterial infection. The need for new antibiotics will continue because bacteria have a remarkable ability to overcome each new agent synthesized. Appropriate use of antibiotics will delay and in many cases prevent the emergence of resistance. The responsibility of reducing resistance lies with the physician who prescribes antimicrobial
agents and the pharmaceutical industry not to promote inappropriate use of antibiotics for humans or for animals.  

REFERENCES: