

ANTIBIOTIC RESISTANCE - EVERY DOCTOR'S CONCERN

Since the 1940s, antibiotics have been the cornerstone of infectious disease therapy. Their remarkable healing power unwittingly led to over confidence and invited widespread and often inappropriate use. It is therefore no surprise that over the past two decades we have seen the emergence of extremely worrying trends of antibiotic resistance with consequent treatment complications. Everyone is loser when antibiotic resistance emerges: the physician faces limited therapeutic options, pharmaceutical companies logically experience reduced sales, but above all, it is the patient who suffers most. Untreatable serious infections are a very distinct possibility in the immediate future unless every medical practitioner, whether in general or hospital practice, takes this problem seriously and adopts rational prescribing practices.

Rational antibiotic prescribing requires continuous education as resistance trends change quickly and often dramatically. For this reason, the Infection Control Unit is organising the first ever local conference dedicated solely to antibiotic use. We look forward to seeing you in November and hope you enjoy the high-calibre presentations particularly from the foreign speakers who will be brought over especially for the event

Why should I care about antibiotic resistance?

The effect of antibiotic usage impacts not only the individual, but also society. These drugs are the only therapeutic agents that are truly societal drugs, because the treatment of individuals can affect the family, the community and society at large. When treating an individual, we are not just targeting disease-causing organisms. We are also affecting the entire normal bacterial flora which are subsequently shed into the environment.

Is antibiotic resistance inevitable?

Resistance problems emerge when the numbers of resistant bacterial infectious agents reach a high proportion. The development of resistance as a clinical problem is not inevitable. It is the steady use of the antibiotic and the continuous selection that propels the rare resistant mutants to prominence in an environment. A resistance problem has arrived when you see that your patient has a resistant bacterial infection. The chance of finding a multiresistant pneumococcal infection in a child is probably millions of times greater now than it was 10 or 15 years ago. The acquisition of resistance may be a rare event; an integration event may occur only once in 10 million bacteria. But once it has occurred, it can be selected and propagated. The reverse situation, loss of resistance gene(s), is not selectable. Moreover, when the new gene inserts into the chromosome or plasmid, it may cause changes which prevent it from coming out by the same way it went in. Therefore, the forward movement, the creation, development and selection of resistance which determines multidrug resistance, is a persistent problem precisely because its selection is so powerful, whereas its reversal is not. Moreover, loss will not emerge while continued antibiotic selection is present.

How transmissible is antibiotic resistance?

Resistance genes can easily spread. Some years ago, data from various laboratories suggested the increase of resistance genes to and from enterococci and the major gram-positive bacterial species to and from *Escherichia coli* and the gram-negative species. It was also noted that mycobacteria have picked up tetracycline resistance genes originally disseminated among enterococci and staphylococci. The frequency of use of nucleotides in the DNA of the tetracycline resistance gene is so different from the mycobacterial host DNA that results suggest the event occurred within recent history, and emerged in this decade. Not only do bacteria exchange genes, but they also move themselves via people, animals and plants.

Where are antibiotics used and misused?

Antibiotics are used extensively in humans at home, and at hospitals, in animals, and in agriculture. In many countries, antibiotics are commonly given to animals, as a growth promotant. Antibiotics are sprayed on fruit trees. Recently the American Society for Microbiology wrote a letter opposing a petition to the US Environmental Protection Agency to permit spraying gentamicin on apple trees to treat infection. This use of antibiotics delivers wide geographical selection; and residues could enter consumers. It came as a surprise that the application was even being considered. Treatment in any environment results in the selection of resistant bacteria and the continued exchange of transposons, integrons and plasmids. What was once a susceptible flora now becomes a resistant one. And the resistant bacteria can move to associate with other members of the environment - people and animals as well as plants.

What is the societal cost of the misuse of antibiotics?

The economic aspect of antimicrobial resistance may be the more compelling force to restore more prudent use of antibiotics. It was once estimated that for the United States alone, antibiotic resistance costs between \$100 million and \$30 billion annually. Another study concluded that at a minimum, resistant infections were twice as costly, in time and dollars, as a susceptible infection. As health care costs continue to rise, the economics of the problem will necessitate a change in how we use antibiotics.

Is antibiotic use the only factor influencing the increase of antibiotic resistance?

The antibiotic and the resistance determinant are the two major factors related to antibiotic resistance. Their interaction is compounded by the spread of bacteria and resistance genes. If antibiotic usage is limited, many antibiotic resistance determinants will not be selected. In Europe there is a big difference between the resistance frequencies in Northern Europe and the

Mediterranean region. We can ascribe that to antibiotic use, but it could also be due to differences in infection control. There are too few data to explain the difference. Resistance originates as a local problem, so we all need to be vigilant and maintain good infection control measures combined with prudent use of antibiotics to circumvent escalating resistance.

Why do hospitals and nursing homes have high rates of antibiotic resistance?

In a study of nosocomial infections, it was found that infections correlated directly with the amount of direct contact of patients by physicians and nurses. Others have shown that in nursing homes and hospitals more than 50% of the antibiotic-resistant transmission was by cross-contamination. In health care facilities we have high levels of antibiotic use and high levels of person to person contact - both are important contributors to nosocomial infection. As you treat with an antibiotic, the numbers of resistant organisms increase. Spread from hospital personnel to patients is well documented. A closed environment such as the ICU is a breeding ground for resistant strains. There is a second compounding problem. When you stop using the antibiotic, the resistant strains do not decrease readily. They stay there since there is only a small difference in the growth rate between resistant and susceptible strains in the same bacteria. Eventually, however, with time, if you do not administer the antibiotic, the susceptible strains will come back.

What is the association between antibiotic use and the emergence of resistance?

To date, our understanding of the relationship between antibiotic use and the emergence of resistance is based on several lines of evidence. First is the observed, correlated increase in antibiotic use and resistance development, coupled with our basic science understanding of resistance genes and their selection. More direct evidence comes from a study which examined the effect of low doses of antibiotics used as growth promotants in animals. Chickens raised from eggs were fed sub-therapeutic amounts of tetracycline in their feed. Within 24-36 hours the chickens were excreting tetracycline-resistant *E. coli*. As the number of weeks on tetracycline increased, other resistances in addition to that of tetracycline appeared in the *E. coli* strains. This finding paralleled results reported previously in which chronic use of ampicillin for urinary tract infections of British women was associated with a multi-drug resistant fecal flora. More recently, a Danish study correlated the amount of erythromycin used in different hospitals with the frequency of erythromycin resistance among staphylococci. Likewise, a study of mupirocin, a relatively new treatment for *Staphylococcus aureus* colonization of the nose and skin, demonstrated that as the amount of mupirocin use increased, there was a dramatic increase in resistance to mupirocin among methicillin-resistant staphylococci. While evidence is mounting, more research is needed to better understand the relationship between antibiotic use and the emergence of resistance.

Where do the resistant bacteria come from?

Resistant bacteria are acquired from the environment. One obvious source is in food. A study cultured fresh fruits and vegetables looking for resistant bacteria. Among gram-negative lactose-fermenting bacteria, more than half found on many vegetables tested were resistant to multiple antibiotics. As a result of this study and others like it, uncooked fruits and vegetables were removed from the diets of immunocompromised patients or those receiving cancer chemotherapy at the hospital in question. A study of fecal flora among baboons in Amboseli National Park in Kenya compared the kinds of bacteria harboured by animals eating the refuse from the tourist camp with those of animals eating the roots of trees and other vegetation in the wild. Significantly greater numbers of resistant organisms were found among the animals foraging around the camp than among the animals eating a more natural diet. In a study of the effect of diet on drug-resistant intestinal flora, Corpet demonstrated a 1000-fold drop in tetracycline-resistant bacteria in six volunteers when he substituted a normal diet with one which was sterilized. These studies demonstrate that our fecal flora is dictated to a large extent by what we eat.

How can we reverse the drug resistance problem?

We must control the environmental densities of two major factors: the antibiotic and the resistance genes. Reduction of either component will lessen the generation of antibiotic resistant bacteria. In this effort, we can evaluate shorter or rotating courses of use. Education of the consumer as well as the prescriber is critically important. We need to find new drugs which can circumvent the resistance mechanisms or which have new targets. We also have to consider how to use the new drugs once we have them. It appears that the most effective approach will be that which restores the susceptible microbial flora. There is a need for a global surveillance system to monitor where the organisms are, where they are being transported, and what new ones appear. These data will greatly assist in our understanding of the spread of resistance. Increased understanding of the science of resistance, the approach to clinical problems, and how we can deal with resistance in line with the ecological considerations, will lead to a return of the susceptible strains, which will help us diminish and curtail the drug resistance problem.

On an individual level, it is vital to wash hands thoroughly between patient visits and not accede to patients' demands for unneeded antibiotics. In addition all practitioners should familiarize themselves with local data on antibiotic resistance data and whenever possible, antibiotics that target only a narrow range of bacteria should be prescribed.

WORKSHOP REPORT

Sensible Antibiotic Prescribing

Over 100 delegates attended the workshop and included a mixture of ~80 hospital doctors – ranging from consultants (mainly physicians) and senior registrars to house officers – as well as ~30 hospital pharmacists. The two groups were organised in the room so that it was possible to identify differences in opinion during the ensuing discussions.

Dr. Michael Borg, workshop co-moderator, introduced the session indicating the paucity of data currently available on antibiotic prescribing in Malta. He stated, however, that from what statistics were available it was clear that the situation needed urgent rectification – antibiotic expenditure data, as well as sample case studies were used as examples. He argued that on a broad basis it was important to:

- ◆ Define & implement institutional guidelines
- ◆ Monitor & provide feedback on resistance
- ◆ Optimize antimicrobial prophylaxis
- ◆ Optimize choice & duration of empiric R_x
- ◆ Improve antibiotic prescribing practices by educational & administrative means

Dr. Barry Cookson then proceeded to chair the second part of the workshop and dealt with possible approaches to achieve these objectives. To encourage interactions, he used the templates he had developed from UK antimicrobial prescribing policies and a simple questionnaire circulated in the morning that had been completed by ~30 attendees. These strategies proved to be a very effective means of exploring attitudes amongst the audience. There was broad consensus on the importance of re-vamping the currently dormant Antibiotic Committee following an agreement of all parties on its way of working. The workings of the Antibiotic Committee & the attendance of its members should be subject to regular review.

Any first initiative would concern antibiotic prophylaxis. This was advisable as there was good scientific evidence to support policy statements and large cost savings might be possible. There would first of all be an audit of prophylaxis used in agreed procedures e.g. colonic surgery, TURP, vascular. This would be followed by drafting an antibiotic prophylaxis policy and circulating this widely for agreement by a set date. If there were issues then these would be resolved by specific meetings (there were several consultant surgeons not present at the meeting). Perhaps a SR interested in the subject could facilitate this process? It would then be possible to estimate savings from the audit. A re-audit would then be undertaken in 6 months to assess improvements in practices and cost-savings. Procedures to improve practice would also need to be agreed: these would depend on the results of the audit but might include automatic stop dates? Results would be widely circulated once agreed by all and aoiding potential problems of deductive disclosure.

Reviews were also indicated for:

- ◆ Antibiotic usage data: the new pharmacist post would greatly assist in this process.
- ◆ Antibiotic resistance data: the committee would explore how improvements in microbiology IT could provide appropriate resistance surveillance data that would inform empirical antimicrobial prescribing.
- ◆ New targets for antibiotic policy: several options were explored

Future initiatives by the Committee would involve assessment of novel issues in antibiotic prescribing such as:

- ◆ Agreed restricted susceptibility reporting policies
- ◆ Different categories of restricted antimicrobials including: 24 - 48 hour consultant signing, ICD/CMM endorsement
- ◆ Stop dates for prophylaxis (this might be used early on e.g. before the second or a third audit)
- ◆ Stop dates for agreed treatments e.g. uncomplicated UTIs and LRTIs. There was a statement from some of the physicians that this was already practiced so an early audit of this might be interesting

KEYNOTE LECTURE

Resistance is futile - or is it?

Dr B.D. Cookson. Director - Laboratory of Hospital Infection, Central Public Health Laboratory, PHLS, UK

The global threat of antimicrobial resistance and potentially untreatable infections is a matter that is being considered seriously by the WHO and many countries throughout the world. I will outline the main resistance challenges and some of the problems in surveillance. MRSA in the UK will be used as an example of using surveillance information from several sources to gauge the impact and inform the prioritisation of control measures.

Scenarios:

Our “nightmare” is perhaps that there may soon be no effective therapy for infections caused by antimicrobial resistant organisms and that these would occur at such frequency that we would in effect have returned to the pre-antimicrobial era. We have already almost run out of antibiotics for certain infections and physicians are having to face another nightmare scenario: doing their patients harm with toxic antibiotics rather than their dying from infection. Is this scenario inevitable: is it futile to resist? Another scenario is we might be faced with a “Nirvana”; a heavenly state where organisms are again susceptible to antimicrobials. Nirvana is defined as “a state of blessedness when the soul is united with divine infinity and all personality is extinguished.” This definition could also imply a certain complacency and we will return to this possibility shortly.

Microbial Strategies:

One of the few benefits of the emergence of antimicrobial resistance is that more resources have been devoted to research genetic aspects and biochemical basis. We are increasingly amazed by the ingenuity with which they have amassed an armoury of mechanisms to avoid destruction by many different groups of antimicrobial agents. They often “improvise” calling upon existing mechanisms within their own or other microbial species or even develop new ones by mutation. Microbes exist in their countless billions and are capable of multiplying at rates several orders of magnitude greater than our own; their potential to explore mutational events when stressed is awesome. Resistance is often described before antimicrobials are used clinically and occurs even where these agents are totally, or partly, synthesised. Their reservoir of resistance genes extends across veterinary and human therapeutic boundaries. Our adversaries adopt a variety of such strategies in a way that has similarities to guerrilla warfare. Early on, it was thought (or perhaps hoped) that antibiotic resistance would compromise microbial pathogenicity. However, this generalisation appears to be untrue. Microbes might, of course, evolve to become less virulent but we cannot rely on any such prediction. Enterococci, once considered the cockroach of bacteria, are capable of causing infections especially in immuno-suppressed patients and transfer of resistances to “genuine” pathogens such as *S. aureus* is well documented in-vitro and in-vivo.

Mankind's Strategies:

It is unlikely that Ehrlich's magic bullet (the microbes nightmare) will ever be realised; neither is it likely to be our favoured strategy, unless such therapy can be prevented from affecting our own commensal flora. Perhaps our being in a Nirvana-like state contributed to our delusions in this Century that we had won the battle against the microbes, ignoring the evidence that resistance would become a significant problem? We prescribed antimicrobials in a haphazard or at best a poorly co-ordinated manner and in some countries even made them available over-the-counter. We have abused the amazing therapeutic arsenal made available to the health care community and under-estimated opponents with far more tricks up their sleeves (or rather inside or on their surfaces).

It has at last dawned on “us” that the academic and pharmaceutical communities do not have any new classes of antimicrobials that will be available in the near future and that if and when they do arrive, there is the real threat we will again misuse them as we did their predecessors. However, microbes do have an Achilles heal, by and large they are pragmatic and a little lazy, merely responding as necessary to the prevailing environmental pressures.

Our two major weapons in the control of antimicrobial resistance are antibiotic prescribing control, to reduce the advantages to organisms of becoming resistant, and effective infection control practices, to stop these organisms spreading. We must write evidence-based guidelines, design, review and audit standards and policies for infection control and antimicrobial prescribing. These processes should have “top-down” and “bottom up” input. The EU has recently shown its commitment to this by funding several projects in this field. These strategies must encompass the human and veterinary/agricultural therapeutic “communities”. A global strategic approach must be developed taking into consideration each country's particular “drivers” for resistance development. In addition, we must also encourage a healthy debate with patients and their advocates as to what needs to be done to reduce the problem.

Conclusion:

Mankind must fight against the microbes and its own failings. We will not win the battle by relying on our ingenuity to develop new antimicrobials. If we explore as a matter of some urgency how best to address these failings our descendants will perhaps see us as having made the first steps to a "Nirvana" of sorts. How we establish and maintain correct reflexive infection and prescribing control practices to emerge victorious from the battle against antimicrobial resistant microbes and ourselves is uncertain. This needs as much investment as has been put into other areas of research into this vitally important matter.