The development of antibiotics was truly one of the greatest advances in medical science whereby previously untreatable and feared infections became readily curable. However, soon after the first antibiotics were developed, antibiotic resistance was detected – mainly in vitro but also in nature. Currently, efficient treatments of many common infections are complicated by the development of drug resistance in causative bacteria.

There are four major means by which the antibacterial agents destroy the bacteria. They are (1) interference with cell wall synthesis, (2) inhibition of protein synthesis, (3) interference with nucleic acid synthesis and (4) inhibition of a critical metabolic pathway. Some bacteria are inherently resistant to one class of antibiotics but usually susceptible to others. The concern is for acquired resistance where once susceptible bacteria develop resistance to widely used antibacterials.

Bacteria often develop resistance to antibacterials by new mutations. This "vertical evolution" may occur in bacteria by different mechanisms such as (1) Altering the target protein to which the antibacterial agents bound to. This may be by either modifying or eliminating that site so that the antibiotics cannot be bound – this occurs with alterations in the penicillin binding protein in the pneumococcus or...
Staphylococci. (2) Increasing or producing enzymes that inactivate the antimicrobial agent - most commonly with beta-lactamases which inactivate beta-lactam antibiotics. (3) Altering the bacterial outer membrane, thereby decreasing the entry of the antibacterials into the bacterial cell which can occur with a range of bacteria (4) Efflux pumps in the bacteria which expel the antibiotics, most commonly in Pseudomonas and other gram-negative bacterial species.

Bacteria can also acquire drug resistance by gaining genetic material from other resistant bacteria in the environment or horizontal evolution. This may occur by (1) Conjugation: Transfers of plasmids containing resistant genes directly from another bacterium (2) Transduction: Transfers resistance genes from one bacterium to another by bacteriophages. This method is now considered to be uncommon. (3) Transformation: Bacteria acquire and incorporate the DNA segments that were released by other bacteria into the environment.

Multi-drug resistance is clearly a potential public health threat given the emergence of many of these antibiotic resistant strains worldwide. According to the US Centers for Disease Control and Prevention (CDC), more than 70% of the hospital acquired infections in the US are resistant to at least one class of antibiotics. Industry funded studies - MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) and SENTRY Antimicrobial Surveillance program, are involved in monitoring antibiotic resistance worldwide. Their results indicate that the antibiotic resistance pattern of bacteria has increased globally in most study sites. A laboratory based surveillance program involving six acute care hospitals in Singapore to monitor the drug resistance pattern of six pathogens namely Staphylococcus aureus, Escherichia coli, Enterococcus spp., Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter spp. showed that the problem of antibiotic resistance in Singapore is on the increase. Drug resistance spares no continent and is, in fact, becoming a major concern in Asia. Hospitals, and in particular, the intensive care units are proliferation zones for antimicrobial drug resistance. This is due to the increased usage of antibiotics together with the risk of cross infection in severely ill patients. Many risk factors have been identified for the occurrence of drug resistant bacterial infections among these critically ill patients. These include broad spectrum antibiotic usage, presence of invasive devices such as endotracheal tubes, vascular and urinary catheters, prolonged hospital stay, immunosuppression and malnutrition. Failure to adhere to infection control measures by the healthcare staff, contamination of equipment and the environment are also important modes of transmission of these drug resistant organisms. These drug resistant bacteria among these critically ill patients have consistently been shown to increase the length of stay in hospital, thus increasing the financial burden on the patient as well as on society. The increased mortality due to the presence of these drug resistant organisms is controversial as certain studies have shown limited impact of the multi-drug resistant organisms on overall mortality. This may be related to the fact that many of these infections occur in patients who have multiple comorbidities and are already critically ill from other causes. In these patients, infection with multi-drug resistant bacteria might in fact be a marker for increased mortality rather than a cause of the increased mortality per se.

Among the different groups of resistant bacteria, it has been observed that resistant gram negative organisms are increasing and today the majority of infections especially in ICUs in Asia are caused by multi-drug resistant gram negative bacteria. This trend is also being observed all around the world and is a potentially dangerous threat. These organisms are associated with pneumonia, blood stream infections, urinary infections and surgical site infections. Data from the US National Healthcare Safety Network (NHSN) has shown that 30% of overall hospital acquired infections are due to gram negative bacilli largely associated with pneumonia and urinary tract infections. The annual report of the European Antimicrobial Resistance Surveillance (EARS) network has stated that the resistant Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa have been steadily showing an increase. Studies from Singapore have also shown that there is diminishing susceptibility to antibiotics among the gram negative bacteria. The important
gram negative bacteria in health care settings that are difficult to treat because of resistance are Acinetobacter baumannii, Pseudomonas aeruginosa, ESBL producing Klebsiella pneumoniae and Escherichia coli. Antibiotic susceptibility patterns in the ICU of a hospital in Indonesia showed the predominant pathogens were Pseudomonas aeruginosa (26.5%) followed by Klebsiella pneumoniae (15.3%)\(^5\). In Thailand, among device associated infection from the medical and surgical ICUs showed that among the resistant gram negative organisms, Acinetobacter baumannii was the commonest followed by Klebsiella pneumoniae, Pseudomonas aeruginosa and Escherichia coli\(^16\). The International Nosocomial Infection Control Consortium findings pertaining to device associated infections in ICU of seven Indian cities showed that 27.3% of hospital acquired infections were caused by multi-drug resistant Pseudomonas spp followed by multi-drug resistant Acinetobacter baumannii\(^17\). Many studies from other parts of Asia have also shown that these drug resistant Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae and Escherichia coli were the organisms that were most frequently isolated from the cultures of the critically ill patients\(^18,19,20,21\). The Study for Monitoring Antimicrobial Resistance Trends (SMART) investigating the antimicrobial profile of intra-abdominal infections due to Gram negative bacilli in Asia has showed that there are a few of Extended-spectrum beta-lactamase (ESBL) producing K. pneumoniae that were resistant to carbapenems especially from the isolates from ICU signaling the emergence of extremely difficult to treat infections\(^22\). More recently, the emergence of NDM-1 and KPC beta-lactamases\(^23,24,25\) has raised the specter that these resistant gram-negative infections can even become untreatable or pan-drug resistant with only recourse to much older and more toxic antibiotics such as the polymyxins including colistin.

Studies have been carried out on these critically ill patients to determine the major risk factors predicting the occurrence of these resistant gram negative rods (RGNR) in the Asian context. In general, risk factors identified in Asian hospitals tend to be similar to those found in the west\(^26,27,28,29\).

ICU admissions, higher severity of illness, increasing age, and surgery have been documented as independent risk factors by many studies\(^30,31,32,33,34\). The presence of invasive devices such as the endotracheal tubes, central venous catheters and urinary catheters are also important factors for the acquisition of the RGNR infection\(^35,36\). Almost all of the studies have pointed out that previous use of broad spectrum antibiotics carries a higher risk of resistance among the gram negative bacilli\(^27,28\). These studies suggest that empirical antibiotics should be used judiciously so as to reduce occurrence of multi-drug resistant gram negative organisms.

The impact of these RGNR can be evaluated from both clinical and financial aspects. From a clinical point of view, the outcomes that are most important are the attributable mortality and the length of stay at the hospital or the ICU. The clinical outcome of mortality that is attributed to the multi-drug resistant gram negative organisms’ remains controversial. Certain studies have showed that the resistance of the gram-negative bacilli such as Escherichia coli, Acinetobacter spp are a cause for increased mortality\(^39,40\) whereas it has been highlighted by others that the resistant gram negative bacterial infections are not associated with increased hospital mortality\(^41,42\). Patients with RGNR infections have been found to have longer hospital stays or ICU stays, although their overall mortality outcome was similar to those without resistant bacterial infections\(^43,44\). It is felt by many that initial appropriate antibiotic therapy is the reason for better outcomes amongst these groups of Resistant Gram-Negative Rods (RGNR) patients rather than the effects of drug resistance per se. On the other hand, it has also been shown that even short durations of broad spectrum antibiotics can lead to the development of antimicrobial resistance\(^45\), thus calling into question a strategy of de-escalation from empiric broad spectrum initial antibiotic therapy.

As these RGNR infections increase the hospital stay for a patient, they usually result in an increase in the total costs for the patient and loss of bed days to the hospital. A retrospective matched cohort study from Taiwan showed that patients with multi-drug resistant Acinetobacter bacteremia experienced two times more hospital costs as compared with the controls. In addition, they also showed that the costs for antibiotic therapy were higher among the cases\(^46\).

There are mixed reviews of utilizing routine surveillance cultures which detect asymptomatic carriers to select empirical antibiotics and control cross infection in ICU patients. A study by Hayon et al\(^47\) obtained surveillance cultures to effectively treat even before the onset of Ventilator Associated Pneumonia (VAP) found that only 33% of surveillance cultures matched the actual organisms causing VAP which required microbiologic processing of protected specimen brush (PSB) or bronchoalveolar lavage (BAL) samples. In another study by Bouza et al\(^48\), similar results were obtained where only one third of the patients with a VAP had the same microorganism causing pneumonia as the surveillance culture. Routine and strict surveillance may be necessary to identify the high risk patients colonized with resistant organisms who might then go on to develop clinical infections or act as sources for cross transmission. On the other hand, routine surveillance if not properly handled can lead to inappropriate treatment. Organisms which are simply colonizers may end up getting treated and this paradoxically increases the risk of even more resistance being selected out.

Invasive devices are a major risk factor for resistant gram negative bacterial infections; steps should be put in place to either reduce the use of these devices or to use novel coated devices or other technological solutions. Studies have shown that impregnated devices reduce adherence of bacteria to the devices potentially reducing the incidence of RGNR infections\(^49,50\). Unfortunately, clinical trials have failed to show consistent improvements in infection rates or mortality although there have been some promising results – in particular with silver coated endotracheal tubes\(^51\) or with coated central venous catheters\(^52,53\). One problem with these devices is the need to maintain antibacterial activity over time while not releasing potentially toxic products into the host.

New antibacterial agents are not being introduced in pace with the growth of
multi drug resistant organisms. Many novel antibiotics are targeted at gram-positive organisms which are more common in Europe and North America. There are no new agents in the pipeline for resistant gram-negatives as the current reimbursement structure for medications does not encourage innovation in antibiotics. Antibiotics are used for short term critically ill patients as compared to drugs for hypertension or hyperlipidemia or even HIV which are used lifelong.

The Infectious Diseases Society of America’s (IDSA) antimicrobial availability task force has identified six pathogens, the so-called ESKAPE organisms (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) as problematic organisms and is encouraging new antimicrobial research to combat them. IDSA has called for combined efforts from industry, academia, the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, the US Department of Defense, and the new Biomedical Advanced Research and Development Authority at the Department of Health and Human Services to combat this issue. The IDSA has launched the attractively named “Bad bugs no drugs” campaign to lobby for increased funding for antibiotic development.

Antimicrobial resistance is a major worldwide problem. Untreatable infections threaten the gains of healthcare in the last century. Advances in chemotherapy as well as the use of new monoclonal therapies have improved outcomes in many areas of healthcare but many of these are accompanied by increased risk of infection. In the recent past, these infections were easily treated but the same unfortunately cannot be said today. A concerted effort by industry and academia is needed to find solutions to this pressing problem.

References


About the Authors

Dr Paul Anantharajah Tambyah is currently the Associate Professor of Medicine and the Senior Consultant Infectious Diseases Physician at the Yong Loo Lin School of Medicine, National University of Singapore. He is also the President of the Society of Infectious Disease (Singapore). His past appointments have included Assistant Dean of the School of Medicine, Founding Head of the Division of Infectious Diseases. He was also the international councilor of the Society for Healthcare Epidemiology in America until December 2009 and is currently a council member of the Western Pacific Society for Chemotherapy. His research interests are in nosocomial infections in particular device associated infections and emerging infectious diseases.

Dr Anupama Vasudevan is currently pursuing her doctorate at Yong Loo Lin School of Medicine, National University of Singapore. She is also a clinical researcher with presentations in multiple International conferences, one of which won the top prize at the International Conference of the Infection Control Association of Singapore. She is technologically savvy and has pioneered the use of statistical tools and novel software in infection control surveillance. She holds her Masters in Public Health from NUS, added to her Bachelors in Dental Surgery from MGR Medical University, India.