Chapter 1

Introduction

1.1. Antibiotics and antimicrobials

Most microbiologists distinguish two groups of antimicrobial agents used in the treatment of infectious disease: antibiotics, which are natural substances produced by certain groups of microorganisms, and chemotherapeutic agents, which are chemically synthesized. A hybrid substance is a semi synthetic antibiotic, wherein a molecular version produced by the microbe is subsequently modified by the chemist to achieve desired properties. Furthermore, some antimicrobial compounds, originally discovered as products of microorganisms, can be synthesized entirely by chemical means. In the medical and pharmaceutical worlds, all these antimicrobial agents used in the treatment of disease are referred to as antibiotics, interpreting the word literally (Toder K, 2009).

The modern era of antimicrobial chemotherapy began in 1929, with Fleming’s discovery of the powerful bactericidal substance, penicillin, and Domagk’s discovery in 1935 of synthetic chemicals (sulfonamides) with broad antimicrobial activity (Chauhan A et al., 2011). In the early 1940’s, spurred partially by the need for antibacterial agents in World War II, penicillin was isolated and purified and injected into experimental animals, where it was found not only to cure infections but also to possess incredibly low toxicity for the animals. This fact ushered into being the age of antibiotic chemotherapy, and an intense search for similar antimicrobial agents of low toxicity to animals that might prove useful in the treatment of infectious disease. The rapid isolation of streptomycin, chloramphenicol and tetracycline soon followed, and by the 1950’s, these and several other antibiotics were in clinical usage (Ashwathi PN, 2011; Toder K, 2009).

Antibiotics are medicines that treat infections caused by the approximately one hundred bacterial species that cause illness. They have changed the way we treat many illnesses. Penicillin has been used to treat bacterial infections and prevent death from infectious diseases.
since the 1940s. This is just one of the many antibiotics used to treat bacterial infections. Antibiotics have added about ten years to the life expectancy (Toder K, 2009).

There are two main categories of antibiotics:

- Narrow-spectrum antibiotics only kill a limited number of bacteria. They can target and kill the bacteria that are causing your illness without killing other, good bacteria. Narrow-spectrum antibiotics are usually prescribed when your doctor knows exactly what bacteria are causing your infection.

- Broad-spectrum antibiotics work against many different bacteria, including some bacteria resistant to narrower-spectrum antibiotics. They are prescribed when your doctor does not know exactly what bacteria are causing your infection or when your illness is caused by several different bacteria.

Although antibiotics are generally safe, they may interact with other medication you are taking and may cause a number of side effects. Disruption of the normal balance of bacteria in your body can lead to diarrhea or to a yeast infection. It is also possible to have an allergic reaction, which could be minor or severe.

The increase in antibiotic resistance is another reason not to take antibiotics unless they are necessary. The more we use an antibiotic, the more likely it is that bacteria will adapt to it. This resistance can then be transferred to other bacteria. Some bacteria, such as methicillin-resistant Staphylococcus aureus (MRSA), are resistant to several antibiotics and are often called “superbugs.” It is very difficult to treat these infections (Ashwathi PN, 2011).

Because of their widespread availability and familiarity, generally low cost, and relative safety, antimicrobials are among the most misused of all medicines. Prompt antimicrobial therapy for an infected patient can make the difference between cure and death or long-term disability. Unfortunately, the use and misuse of antimicrobials has driven the relentless expansion of resistant microbes leading to a loss of efficacy of these “miracle drugs” (Ashwathi PN, 2011).
1.2. Antimicrobial resistance

Resistance occurs when an antibiotic is no longer effective at killing or limiting the growth of bacteria. It can occur naturally (innate ability or genetic mutation), or can be acquired through previous exposure to an antibiotic or through contact with another organism that is resistant (transfer of resistance). There are several ways that bacteria can resist the effects of antibiotics. Some bacteria develop the ability to neutralize the antibiotic before it can harm them, others can change the antibiotic attack site so it cannot affect the function of the bacteria, and still others can pump the antibiotic out of the cell or prevent the antibiotic from getting into the cell (Byarugaba DK, 2009; Byarugaba DK, 2004).

Once bacteria are resistant, the infections they cause may not be cured or controlled by antibiotic treatment, or there may be few effective drug choices. In some cases, these illnesses can lead to disability or even death. Antibiotics were once considered the solution to most infectious diseases. Unfortunately, the misuse and overuse of antibiotics, combined with bacteria’s ability to resist treatment, mean that antibiotics are no longer as effective. Antibiotic resistance is now a worldwide public health problem (Aarestrup FM et al., 2001; Bush K et al., 1995).

Almost all bacteria have developed some form of resistance, making antibiotics less effective at treating serious infections. Someone with an infection that is resistant to a certain medicine can pass that resistant infection to other people, including family members, and co-workers. In this way, a hard-to-treat infectious disease can threaten whole communities. This can be especially dangerous for young children, the elderly, and people with weakened immune systems (e.g. individuals already in the hospital or chronically ill) who are more vulnerable (Butaye P et al., 2003).

In Canada last year, over 3000 individuals died from infections they contracted in a health care institution. Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections.
Resistant microorganisms are able to withstand attack by antimicrobial drugs, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others. The evolution of resistant strains is a natural phenomenon that occurs when microorganisms replicate themselves erroneously or when resistant traits are exchanged between them. New resistance mechanisms emerge and spread globally threatening our ability to treat common infectious diseases, resulting in death and disability of individuals who until recently could continue a normal course of life. Without effective anti-infective treatment, many standard medical treatments will fail or turn into very high risk procedures. Some microorganisms may develop resistance to a single antimicrobial agent (or related class of agent), while others develop resistance to several antimicrobial agents or classes. These organisms are often referred to as multidrug-resistant or MDR strains. In some cases, the microorganisms have become so resistant that no available antibiotics are effective against them (Dessen A *et al.*, 2001; Enne VI *et al.*, 2001).

Antimicrobial drug resistance occurs everywhere in the world and is not limited to industrialized nations. Hospitals and other healthcare settings are battling drug-resistant organisms that spread inside these institutions. Drug-resistant infections also spread in the community at large. Examples include drug-resistant pneumonias, sexually transmitted diseases (STDs), and skin and soft tissue infections (Dessen A *et al.*, 2001).

For several decades antimicrobial resistance (AMR) has been a growing threat to the effective treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. AMR results in reduced efficacy of antibacterial, antiparasitic, antiviral and antifungal drugs, making the treatment of patients difficult, costly, or even impossible. The impact on particularly vulnerable patients is most obvious, resulting in prolonged illness and increased mortality.

People infected with drug-resistant organisms are more likely to have longer and more expensive hospital stays, and may be more likely to die as a result of the infection. When the drug of choice for treating their infection doesn’t work, they require treatment with second- or
third-choice drugs that may be less effective, more toxic, and more expensive. This means that patients with an antimicrobial-resistant infection may suffer more and pay more for treatment.

1.2.1 The phenomenon of resistance

Microorganisms have lived together with humans since the beginning. Nevertheless, infections caused by microorganisms have been a threat to mankind. Over the last century, the discovery of antimicrobial agents, particularly antibacterial agents (hereafter referred to as antibiotics), have altered the relationship between humans and bacteria. Frequent use of antibiotics have reduced the susceptible strains of bacteria, and increased the resistant variants, thereby leading to the phenomenon of antibiotic resistance.

Bacterial resistance has been defined by the Centres for Disease Control and Prevention (CDC) as ‘the result of bacteria changing in ways that reduce or eliminate the effectiveness of drugs, chemicals, or other agents to cure or prevent infections’ (CDC, 2014). Resistant bacteria are able to block the action of antibiotics. Treatment therefore becomes ineffective and infections continue with possibilities of complications and spread. The evolution of resistant strains is thus mainly a natural phenomenon that happens when bacteria are exposed to antibiotics. Resistant traits can be exchanged between bacteria also.

Drug-resistant strains initially appeared in hospitals, where most antibiotics were being used. Soon after introduction of penicillin in 1940’s, penicillin-resistant Staphylococcus aureus emerged in hospitals in London. After the discovery of streptomycin, resistance in Mycobacterium tuberculosis soon emerged (Barber M et al., 1948; Crofton J et al., 1948; Watanabe T et al., 1963). In the 1950s and 1960s, multi-drug resistance was noticed in enteric bacteria such as Escherichia coli. In the 1970s, Haemophilus influenzae emerged with resistance to ampicillin, chloramphenicol and tetracycline. The rising resistance over the years has meant that few antibiotics remain truly effective (De Graaff J et al., 1976; Marshall B et al., 1984; Van Klingelen B et al., 1997).

The mechanisms by which antibiotic resistance occur in bacteria are varied. They include antibiotic detoxification, target protection and substitution, and block of intracellular antibiotic accumulation. Two broad points need to be considered in the resistance phenomenon.
Firstly, the antibiotic which inhibits the susceptible and selects the resistant bacteria, and secondly, the genetic resistance determinant in bacteria selected by the antibiotic. Antibiotic resistance occurs when these two converge in the host leading to disease complications. Under continuous antibiotic selection, resistance genes spread to other hosts and environment. They are transferred among various taxonomic and ecological groups such as plasmids, integrons, bacteriophages, or transposonss. Plasmids can serve as a scaffold. On this, arrays of antibiotic resistance genes can be assembled by transposition and site specific recombination mechanisms such as integron gene cassettes. These genes are usually directed at a single family or antibiotic type. However, multiple genes carrying single drug resistance traits can be present in the same organism. Plasmids and transposons usually mediate high-level resistance. Low-level resistance in bacteria can be transformed to high level resistance through sequential mutations in chromosomes (Bennett PM et al., 2008; Schneiders T et al., 2003).

If usage of a particular antibiotic is widespread, susceptible strains will be at a disadvantage as compared to resistant strains. This imbalance can generate a larger pool of resistance in the environment. If the antibiotic is not widely used, the impact is often felt more at an individual level with less serious consequences. The selected resistant strains will be suppressed by the drug-susceptible bacteria (Alekshun MN et al., 1997). However, each individual is potentially a generator of resistant bacteria that moves into the environment.

Increasing the density of antibiotic usage can increase resistance selection. This ‘selection density’ is based on the total antibiotic used in a geographic setting with a specific population. Selective pressure also reflects the number of individuals who are promoting resistant bacteria in a particular setting and the residual number of susceptible but surviving bacteria. Selection density and pressure makes antibiotics a unique group. Individual use affects resistance and therefore community use. They are therefore truly societal medicines (Alekshun MN et al., 1997).
1.2.2 The global resistance situation

Antibiotic resistance has reached a crisis level in the world and especially so with the emergence of multidrug resistance (MDR). Community and hospital MDR strains of *Staphylococcus aureus*, *Enterococcus faecium*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Salmonella enteritidis*, *Shigella flexneri*, *Acinetobacter baumanii* and *Pseudomonas aeruginosa* are widely prevalent (Magiorakos AP et al., 2012; de Kraker M et al., 2007).

Among Gram-positive bacteria, *S. aureus* has been associated prominently with resistance. 40–60% of nosocomial *S. aureus* strains in USA were methicillin-resistant (MRSA). A steadily increasing proportion of MRSA is becoming resistant to vancomycin and even to newly developed medicines such as dalbopristin/quinopristin and linezolid. Among the Gram-negative bacteria and especially in hospitals, *P. aeruginosa* and *A. baumanii* have been a problem due to MDR. Extended spectrum beta-lactamases (ESBL) have been another grave problem, especially in the last decade. ESBL in Enterobacteriaceae such as *Enterobacter* and *Klebsiella*, have destroyed the later generations of penicillin and cephalosporins (Weinstein RA et al., 2001; Fridkin SK, 2001; Meka VG et al., 2004; Bradford PA, 2001).

Hospital patients have been the major casualty of resistance. However, the community has not escaped resistance. MRSA strains differing from hospital strains have emerged in communities with resistance to beta-lactam antibiotics (Vandenesch F et al., 2003). Strains of *E. coli* have become resistant to fluoroquinolones with the emergence of ESBL (Zervos MJ et al., 2003). In Southeast Asia and China, 70% of *E. coli* are resistant to fluoroquinolones. Pneumococcal resistance to penicillin, macrolides and tetracyclines are common in many areas. This has affected the treatment of pneumonia and otitis media. Similarly, strains of *eisieria gonorrhoeae* have become resistant to penicillins, tetracyclines and fluoroquinolones (Wang H et al., 2001; Schrag SJ et al., 2004; Tanaka M et al., 2000).
In recent years, antibiotic resistance has been in the news with reported cases in 2010 of New Delhi metallo-beta-lactamase-1 (NDM-1) producing Enterobacteriaceae. This phenomenon has been reported from continents across the world. Another carbapenemase, OXA-48 has reared its head in countries in Africa and Europe (Kumarasamy KK et al., 2010; Struelens MJ et al., 2010; Mulvey MR et al., 2011; Chihara S et al., 2011; Moquet O et al., 2011; Carrer A et al., 2010).

1.2.3. The antibiotic resistance situation in India

Antibiotic resistance is also a problem in LMIC such as India. Researchers working in the area of antibiotic resistance have been recommending appropriate use of antibiotics for a long time. These attempts largely remained in the background until the NDM article appeared (Kumarasamy KK et al., 2010) and became frontline news in the media. Overall, antimicrobial resistance in both gram positive and gram negative bacteria appears to have become widespread.

Among the Gram positive bacteria, MRSA appears to be widely prevalent. In a study looking at 12 intensive care units (ICU) in seven Indian cities, 88% of S. aureus strains were MRSA among 476 hospital-acquired infections. This problem is not isolated to ICUs or inpatients. A study done in paediatric outpatients in central India found that the prevalence of nasal carriage of S. aureus was 6.3% of which 16.3% were MRSA. In a study on north Indian children, Group-A beta-hemolytic streptococci from throat swabs showed up to 25% resistance to macrolides, tetracycline and cotrimoxazole (Mehta A et al., 2007; Pathak A et al., 2010; Jain A et al., 2008).

The problem of resistance among Gram negative bacteria appears equally problematic. The multicentric study in ICUs found that of the hospital acquired infections caused by Pseudomonas spp., 65% was resistant to ceftazidime, 43% to piperacillin-tazobactam, 29% resistant to ciprofloxacin, and 42% to imipenem (Mehta A et al., 2007). In a study on 265 Acinetobacter spp. isolates, 80% resistance to later generation cephalosporins, quinolones and aminoglycosides was noted (Gaur A et al., 2008). A study of K. pneumoniae isolates from samples of urine and pus found that 25% were ESBL producers (Shahid M et al., 2008). A
study done in Vellore, south India found that 42% of commensal E. coli had resistance with higher resistance rates in infecting strains (Mathai E et al., 2008).

Overall the situation appears to be grim. The consequences could be catastrophic to India where high population, urbanization, inadequate health infrastructure and rising costs make a potentially explosive situation.

1.2.4 The consequences of antibiotic resistance

The pan-global use of antibiotics has favoured the growth of resistant strains. Confinement to a specific environment is improbable due to movement of vehicles such as people, animals, water and wind (Finley RL et al., 2013). Resistant bacteria developing in vegetables, fruits, animals and water sources have used the food chain and environment to gain access to humans. This problem has been compounded when commensal bacteria transfer their resistance genes to pathogenic bacteria in the same environment. This has led to the creation of ‘superbugs’ that are multidrug resistant. These superbugs have been responsible for serious infectious diseases for which most antibiotics are ineffective. This in essence is the consequence to humans (Magiorakos AP et al., 2012; de Kraker M et al., 2007).

There are a number of other potential implications. Due to reduced effectiveness of antibiotics, patients may remain infectious longer, thereby increasing the spread of resistant bacteria. If the infections are caused by resistant bacteria, there will be a failure of standard treatment. This may result in prolongation of infection, possible complications and a greater risk of mortality. Besides individuals, this may have implications for national policies and health programmes. Other implications are in particular groups of patients. Immunocompromised patients, those in transplantation programmes and cancer chemotherapy are at risk of infections. The effectiveness of antibiotics in such patients is crucial to the success of overall treatment (Vandenesch F et al., 2003).

Cost implications at individual and aggregate levels are also important to consider. Infections caused by resistant bacteria are often resistant to first line of therapy. This leads to a loss of valuable time and complications. The second line of therapy maybe costlier and the
treatment of complications may add to the financial burden. This economic burden will extend to the family, and depending on the source of support, to hospital and government budgets.

There are larger epidemiological and political concerns. Antibiotic resistance can hamper control of infectious diseases. This could lead to serious outbreaks of infections, especially in crowded populations and areas where hygiene is poor. Multilateral trade pacts and tourism have led to a situation where people and food products travel widely between countries. The risk of quick transfer of superbugs through these vehicles is important to consider. The lack of new antibiotics on the horizon and the lethargy of pharmaceutical companies in researching and developing newer classes may complicate this already perilous scenario (Butler MS et al., 2013).

1.2.5. Rational use of antimicrobials

The appropriate use of antimicrobials by healthcare providers such as doctors, pharmacists, and nurses, is essential in optimizing care. A rational approach would include: identifying the patient’s problems and focusing on an appropriate indication; choosing safe, effective and affordable treatment; selecting appropriate medicines, dose and duration for that indication; improving the patient’s understanding of disease and medication through adequate communication; evaluation of treatment response. The patient’s tolerability and adverse effect profile should also be taken into consideration and monitored. Unfortunately, many of these criteria are not met in practice due to differing reasons and circumstances. This then becomes inappropriate use. The systems, structures and factors influencing medicine use are complex and vary from country to country. Medicines may be produced locally or imported, thus bringing into play price, availability and quality issues. Counterfeits and substandard medicines are other problems to be considered. Medicine use occurs at multiple levels of healthcare facilities such as hospitals, clinics, private practitioners, pharmacy shops or even over the counter (OTC). In India, there are many alternate systems of medicine whose practitioners may prescribe allopathic medicines and also untrained practitioners who may prescribe without enough knowledge. The end user is another key stakeholder. In many countries such as India, there could be a wide spectrum of knowledge, beliefs and attitudes among the public. Appropriate
prescribing therefore becomes rather complex, but paradoxically, its need becomes crucial for optimal health and treatment.

Inappropriate use of medicines could have various consequences, for the individual, the society, health systems and even the economy. A compromise in the quality or choice of medicines, dose or duration may lead to increased morbidity and mortality. In a scenario where stock is limited or medicines budget constrained, unnecessary use could lead to reduced availability of vital medicines and possibly increased costs. Inappropriate medication with little communication between patient and health provider may increase the risk of adverse effects. In the case of antibiotics, it’s not just adverse effects, but the emergence of antibiotic resistance (WHO, 2012; S KI et al., 2008; Boyd S et al., 2006).

1.3. **Surgical site infections**

Surgical site infections are the second most common type of adverse events occurring in hospitalized patients. A surgical wound infection occurs when micro-organisms from the skin or the environment enter the incision that the surgeon makes through the skin in order to carry out the operation. These infections can develop at any time from two to three days after surgery until the wound has healed (usually two to three weeks after the operation).

Infections are more likely to occur after surgery on parts of the body that harbor lots of germs, such as the gut. Surgical site infections have been shown to increase mortality, readmission rate, length of stay, and cost for patients who incur them. An estimated 40 to 60 percent of these infections are actually preventable. 38% of all nosocomial infections in surgical patients are surgical site infections. 4 to 16% of all nosocomial infections are SSIs. 2 to 5% of operated patients will develop SSI. SSI increases the patient’s length of stay in the hospital by an average of 7.5 days.
Wound site infections are a major source of postoperative illness, accounting for approximately a quarter of all nosocomial infections. National studies have defined the patients at highest risk for infection in general and in many specific operative procedures. These infections number approximately 500,000 per year, among an estimated 27 million surgical procedures and account for approximately one quarter of the estimated 2 million nosocomial infections in the United States each year. Infections result in longer hospitalization and higher costs.

1.4 Post operative wound infections in gastric surgeries

Surgical site infections and wound and tissue dehiscence are well-known postoperative complications in gastrointestinal surgery (Cubertafond P et al., 1992; Ruiz-Lopez P et al., 2002). Postoperative wound infection occurs in the part of the body where the surgery took place. Most patients who have surgery do not develop an infection. However, infections develop in about 1 to 3 out of every 100 patients who have surgery. Some of the common symptoms of a surgical site infection are fever, haematoma, seroma, separation of wound edges and purulent discharge from the wound.

Appropriate post-operative surgical wound care is essential in preventing potential complications, such as surgical-site infections (SSIs), wound dehiscence and haematomas. General practitioners play a major part in managing patients’ postoperative wounds in the community and it is important to appreciate the principles of post-operative wound management to minimise the incidence of wound complications (Yao K et al., 2013). The surgeon must individualize care of each wound, but the sterile dressing placed in the operating room is generally left intact for 24 h unless signs of infection (eg, increasing pain, erythema, drainage) develop. After 24 h, the site should be checked twice/day, if possible, for signs of infection. If they occur, wound exploration and drainage of abscesses, systemic antibiotics, or both may be required (Robert G. J, 2013).
1.5 Motivation for the present study

Postoperative wound infections are still a significant cause of mortality in the world. Antibiotics have been a major factor in successfully treating these infections. Access to effective antibiotics can no longer be taken for granted, due to the emergence of bacterial resistance throughout the world, including India. The problem is complex. Very few novel antibiotics are on the horizon. There has been a major shift in the focus of research and development to non-communicable diseases. A new antibiotic if developed would not solve the problem. It would be important to reverse the ecological imbalance between susceptible and resistant bacteria. If susceptible microbiota were to be restored, there could be a chance to contain antibiotic resistance. For this there needs to be appropriate use of antibiotics (Gales Ac et al., 2001; Hoa NQ et al., 2010; Kandle Sk et al., 2003; Jain D et al., 2005).

Number of factors may influence use of antibiotics such as knowledge and expectations of patients and healthcare providers, economic factors, the health system and processes, as well as the impact of policies and regulatory environments. Many gaps remain in the efforts to contain antimicrobial resistance. Improving knowledge in these areas could help in planning appropriate interventions. For this purpose, studies were planned to monitor the patterns of antibiotic use in an Indian rural teaching hospital, ascertain the perceptions and factors influencing antibiotic use among stakeholders in the community, assess the cost burden and health consequences of antibiotic resistance and determine the impact of existing strategies such as policy guidelines on antibiotic use and patterns over a period of time. This thesis with its constituent papers has therefore been compiled with this overall rationale.