School of Pharmacy

Evaluation of pharmacist interventions on drug and dosage prescribing in pediatric settings

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Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made.

Signature

Date

Abstract

Objectives: To evaluate the influence of pharmacist interventions on drug and dosage prescribing in pediatric settings.

Method: Demographic, clinical, and prescribing data and parents' measurement data were evaluated by pre- and post studies including time series studies and control groups. The data was evaluated against Australian Therapeutic Guidelines. Educational intervention strategies were designed and administered and a post-intervention evaluation was conducted. Group comparisons were made using χ^2 and Student's t-test statistics. Time series analysis involved multiple linear regression analysis.

Results: The major study involved antibiotics and analgesic drugs and dosages in appendectomy in children. Significant improvements occurred in the selection and dosages of prophylactic antibiotics ($p<0.001$) and in subsequent ward antibiotic treatments ($p<0.001$) also showed marked conformity with the guidelines. Other pediatric studies involved liquid medication dosing and prescribing accuracy for paracetamol in a developing country where a simple intervention produced very marked improvements ($p<0.001$). An intervention in severe community-acquired pneumonia showed an improvement in the prescription of appropriate drugs ($p<0.001$) and appropriate dosages of paracetamol ($p<0.001$) according to the guidelines. In drug utilisation evaluation of ceftriaxone, flucloxacillin and Liquigesic Co®, there was a significant improvement in the dosage prescribing of ceftriaxone and flucloxacillin and no change in Liquigesic Co® following the intervention. Of the total, 38/218 (17%) of the patients received appropriate post-operative antibiotic dosages, 286/368 (78%) of the analgesic prescriptions and 31/218 (14%) of the patients on postoperative antibiotic choice and dosage that were identified as appropriate in tonsillectomy.

Conclusion: This study has identified deficiencies related to the prescribing of antibiotics and analgesics in children. There was a varied level of improvement in the drug dosage prescribing of pediatricians following the pharmacist educational intervention. Locally developed guidelines are more likely to be accepted and followed than those developed nationally without local input.

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Chapter one

General Introduction

1.1 History of antibiotic resistance

The astonishing effects of antibiotics, the occurrence of resistance, and the considerable resources spent on antibiotics globally are convincing reasons for concern about ensuring adequate and proper use of these powerful agents. Antibiotics are the largest of any therapeutic group of drugs, often accounting for 15%-30% of total drug expenditure. Antibiotics represent agents with the most potential impact on mortality, along with vaccines, oral rehydration solutions, and contraceptives[1].

Antibiotics are given to humans for treatment and prophylaxis of infectious diseases, 80-90% of antimicrobial drugs are used in outpatients and the remainder in hospitals. Antibiotics appear to be used not only in excess but also inappropriately and this accounts for 20-50% of all antibiotic use [2, 3]. The Center for Disease Control and Prevention in the USA has estimated that some 50 million of the 150 million prescriptions for antibiotics written for outpatients every year are unnecessary[4].

In the United States, expenditure for prescription drugs were $33 billion in 1987, approximately 75% of which were in the outpatient setting. Such substantial expenditure may be acceptable if medical outcomes or quality of life significantly improve. The consequence of antibiotic overuse and misuse include increased risk of adverse side effects, higher cost and higher rate of antimicrobial resistance of community pathogens. What distinguishes antimicrobial agents from other drugs is that each antimicrobial agent used may have a potential significant effect on the world microbial ecology. Antibiotics affect both pathogens and the normal flora. In theory any antibiotic can select resistant strains as long as the local concentration of the drug exceeds the minimal inhibitory concentration (MIC) for the susceptible bacterial population but is below the MIC for the resistant clone. To what extent disturbances occur depends on the spectrum of the agent,

dose, and route of administration, pharmacokinetic and pharmacodynamic properties, and in vivo inactivation of the agent[2].

Incomplete absorption of orally administered drugs may influence the intestinal microflora, and secretion of an antimicrobial agent by the eccrine glands may interfere with the normal flora at different habitats. As a consequence, antibiotic-resistant microorganisms may increase in numbers, and they also might serve as reservoirs for resistance genes. Since resistance is genetically linked, one antibiotic may select for resistance to one or more structurally unrelated antibiotics. Some antimicrobial agents are more selective for resistance than others. Besides selective antibiotic pressure, transferable resistance is the major determinant of resistance development[2].

Antibiotic usage and resistance rates vary from one country to another[5-7]. Countries with the highest per capita antibiotic consumption have the highest resistance rates. Countries with high total outpatient antibiotics sales have a higher prevalence of *Haemophilus influenzae* β-lactamase positive strains, than those with low total usage. It is not only the amount of antibiotics used that selects for resistance, but also the number of individuals receiving the drug, and the population density[2]. Giving 1000 doses of an antibiotic to one individual will have considerably less ecological effect on resistance emergence than giving those same 1000 doses to 1000 individuals[8]. A study by Levy [9] suggests that a combination of antibiotic use and population density correlates more strongly with the prevalence of antibiotic resistance in a population than antibiotic use alone.

Since the discovery of the sulphonamides and penicillin in the 1920s and 1930s, physicians around the globe have had a growing armamentarium of antimicrobial agents with which to fight infectious diseases that threaten the health of the human race. Although antibiotics have saved millions of lives, their extensive and often indiscriminate

use has created its own set of problems. Ever-increasing antibiotic resistance among bacteria presents a continuing challenge for physicians[10].

Antibiotic resistance first became challenging shortly after penicillin gained extensive use in the 1940s[11]. Even though β-lactamase was described as early as 1940, its significance emerged only after penicillin was introduced as a treatment for severe staphylococcal infections[12]. Within a decade, most hospital acquired *Staphylococcus aureus* isolates produced β-lactamase and were resistant to penicillin[13]. Nowadays, more than 95% of *Staphylococcus aureus* isolates globally are resistant to penicillin, ampicillin, and the anti-Pseudomonas penicillins[14]. An initial response to this resistance, was the development of methicillin, a semisynthetic penicillin. By the late 1980's, methicillin-resistant *Staphylococcus aureus* had become prevalent in many hospitals and are difficult to treat[10, 15].

Antibiotic resistance amongst hospital-acquired gram-negative bacteria has been a long-standing and well-recognised problem; resistance has been seen in multiple genera, including *Escherichia, Enterobacter, Klebsiella, Proteus, Salmonella, and Serratia*[15]. The majority of these strains are resistant to all β-lactam antibiotics except cephamycins and carbapenems[10, 16].

During the 90's, vancomycin-resistant enterococci have emerged as a problematic cause of nosocomial infection. Until recently, vancomycin was a dependable drug for the treatment of infections caused by multidrug-resistant enterococci, but in the mid-80s, vancomycin resistance began to emerge. The National Nosocomial Infection Survey of the Centre for Disease Control and Prevention reported in 1996, that between nosocomial isolates of enterococci, vancomycin resistance had increased more than 20-fold from 1989 to 1995[17]. Of even greater concern is the chance that enterococci can serve as a pool for the transfer of resistance genes to other organisms[10, 18].

Community-acquired pathogens were slower to build up significant levels of resistance. In the early 1960s, transferable resistance was first described in Shigella species[19]. This resistance restricts the number of dependable antimicrobial agents accessible for the treatment of individual patients and poses a considerable community health problem[15]. An endemic of enteritis caused by *Shigella dysenteriae* that was resistant to all oral antimicrobial agents available in that country occurred, in Burundi in 1990[10, 20].

Neisseria gonorrhoeae is an additional community-acquired pathogen that has undergone significant changes in antibiotic resistance. For a number of years, penicillin was the drug of choice to treat gonorrheae, but in 1976, the plasmid-mediated β-lactamase of *Escherichia coli* was found in *Neisseria gonorrhoeae* isolates in Africa and Asia[21]. Currently, in excess of 90% of *Neisseria gonorrhoeae* isolates in the Philippines and Thailand produce β-lactamase[10, 22].

Streptococcus pneumoniae is very important in pediatrics. The development of antibiotic resistance was first reported in animal models in 1940s [23] and subjectively reported among patients in the 1970s[24], penicillin resistant pneumococci are rapidly rising in prevalence in the United States and are a most important problem globally[10].

1.2 Resistance development due to excessive antimicrobial use

A study by Baquero et al. was one of the first to report a correlation between antibiotic use and bacterial resistance in the community[25]. They found that both individual antibiotic use and total antimicrobial consumption in the community were strongly associated with nasopharyngeal carriage of penicillin-resistant pneumococci in children[2].

Resistance to pneumococcal antibiotics is increasing worldwide. The nasopharyngeal bacterial population is an important reservoir of infection, carriage and spread of pathogenic bacteria including antibiotic-resistant clones. Several randomised prospective studies have shown an association between the use of β-lactam antibiotics and the carriage of penicillin-resistant organisms[2, 26, 27].

A critical threshold of approximately 200-prescriptions/1000 inhabitants/year has been suggested to trigger the dispersion of erythromycin resistance[28]. In Slovenia the number of prescriptions/1000 inhabitants/year is <150, and resistance of *Streptococcus pneumoniae* is below 10%. The twofold increase in macrolide consumption noted in a 6-year period was associated with a nearly linear increase in macrolide resistance, first in *Streptococcus pyogens* then in upper respiratory *Streptococcus pneumoniae* isolates and lastly in invasive strains in *Streptococcus pneumoniae*[2, 29].

Baquero examined the development of macrolide resistance in *Streptococcus pneumoniae* during the late 1980s and early 1990s, and found that the increasing resistance was due to wider use of the newer long-acting macrolides[2, 30].

Antimicrobial resistance rates are higher in paediatric populations in day-care centres and among isolates from the middle ear, nasopharynx or respiratory tract[31-33]. The higher resistance rate is possibly associated with a higher frequency of antibiotic treatment in children than in adults, and extensive child-to-child transmission in some settings, such as day-care centres and nursery schools[2].

Using antibiotics with poor activity or administering them at an inappropriate dosing level, dosing frequency, or for a prolonged duration increases the opportunity for

selection of resistant strains[2]. Guillemot et al.[34] found that children treated with low daily doses of an oral β-lactam had an increased risk of penicillin resistant *streptococcus pneumoniae* carriage compared with children who had recommended doses[2].

A study by Nasrin et al.[27] showed higher penicillin resistance of *Streptococcus pneumoniae* in children who had taken β-lactam antibiotic for more than 14 days compared with a group taking no antibiotics or taking them for less than 7 days in the 6 months before nasal swabbing. Cohen et al.[35] demonstrated an increase in the MIC of *Streptococcus pyogenes* in 8 of 79 children with streptococcal tonsillopharyngitis treated with a low dose of azithromycin, with a bacteriological failure on day 14. The strains of *Streptococcus pyogenes*, which were susceptible to azithromycin before the treatment, might have gained resistance due to low antibiotic doses[2].

During a 7-year period, in a French hospital, the change of both the more prevalent bacterial species and their susceptibility patterns to antibiotics was due to an increase in the consumption of third-generation cephalosporins and aminoglycosides[36]. The increased use of these agents in the hospital was notable by a marked increase in seriously ill patients without an increase in admissions. There was a significant correlation between increase in antibiotic use and decrease in susceptibility. The most remarkable event was the significant relationship between third generation cephalosporin use and the increasing numbers of *Acinetobacter calcoaceticus*, *Pseudomonas aeruginosa* and *Serratia marcescens* isolates[37].

In the Netherlands the correlation between antibiotic consumption and antibiotic resistance rates was studied in 976 human isolates of coagulase negative Staphylococci[38]. A significant correlation was found between percentage of methicillin resistance and the prescription of flucloxacillin for prophylactic, and cephalosporins for therapeutic purposes[37].

A study in a Danish University hospital on the susceptibilities to antimicrobial agents of coagulase negative Staphylococci isolates from blood cultures, cerebrospinal fluids and peritoneal effluents found a great diversity in antibiotic resistance between the wards[39]. When comparing the consumption of antibiotics with antibiotic susceptibilities among coagulase negative Staphylococci, a significant association of multiple antibiotic resistance was seen with broad spectrum β-lactams such as third generation cephalosporins and carbapenems, quinolones such as ciprofloxacin and total antibiotic consumption on a ward[37].

Johansen et al [40] studied the correlation between aminoglycoside consumption patterns and the occurrence of aminoglycoside-resistant bacteria from 12 countries and found that there was a wide variation in the national aminoglycoside consumption patterns. They found a striking correlation of gentamicin resistance and national gentamicin consumption. In addition, there was a clear association between bacterial resistance inside and outside the hospital and the total amount of aminoglycoside, particularly gentamicin, consumption in hospitals. In a study by Courcol et al. [36]there was a significant correlation found between the increase in aminoglycoside use and decrease in susceptibility of *A.calcoaceticus* for gentamicin, tobramycin and amikacin[37].

The development of new classes of antibiotic agents has slowed significantly. During the past four decades, following the introduction of penicillin, over 20 structural classes of antimicrobial agents were discovered through natural product screens[12]. On the contrary, since the early 80s, few vital new agents have been marketed based upon using this method. Accordingly, the cost of developing and bringing new antibiotics to market is enormous[41]. It has led to concerns that antibiotics may not be available to treat multiresistant organisms as they emerge, due to cost and difficulty in producing new classes of antibiotic agents. The appearance of resistance in *Streptococcus pneumoniae*,

an organism accountable for general pediatric infections such as sinusitis, otitis media, and pneumonia and the leading cause of bacterial meningitis in children, has noticeably heightened alertness about antibiotic resistance. We have already begun to see the appearance of organisms, such as *enterococci* and *Staphylococcus aureus* that are resistant to, or have the possibility to be resistant to, all existing antibiotics[10].

The extent of bacteria resistant to general antimicrobial agents, predominantly multidrug-resistant pneumococci, has lead to a new interest in antimicrobial prescribing patterns and the endorsement of cautious antimicrobial use. The five major indications for outpatient antimicrobial prescribing are all upper respiratory infections, and children are given an inconsistent number of these prescriptions[42]. Many of the prescriptions are needless, being given for viral infections such as the common cold[43]. Reducing improper prescribing has been advocated as one way to guard patients against future resistant infections[44, 45].

1.3 Reversing the rise of resistance by reducing the antimicrobial use

In 1970s, the first intervention to decrease bacterial resistance in the community occurred in Japan where decreased erythromycin consumption led to a decreased level of erythromycin-resistant *Streptococcus pyogenes*. In Japan, macrolides accounted for 22% of the antibiotics used and 62% of *Streptococcus pyogenes* isolates were resistant to erythromycin in 1974. By 1988, macrolides accounted for only 8% of antibiotic use and the *Streptococcus pyogenes* isolates resistant to erythromycin fell to 2%[46].

In Finland, a recommendation was made to decrease the use of macrolides in infections caused by Group A Streptococci due to an increase of the macrolide resistance in *Streptococcus pyogenes*[46]. This recommendation reduced to half the usage of macrolides from 2.44 DDD/1000 inhabitants/day to 1.38 in 1992 and 1.44 DDD/1000

inhabitants/day in 1996 respectively. The resistance of *Streptococcus pyogenes* to macrolides decreased from 19% to 9%[37]. Similarly in Iceland during the period 1993-1997, the prevalence of penicillin-nonsusceptible pneumococcal carriage in children attending day-care centres reduced from 20 to 13%[47, 48].

In South Africa, invasive Gram-negative isolates from blood and cerebrospinal fluid were monitored for 1 year before and after the first-line aminoglycoside in a paediatric department was changed from gentamicin to amikacin[49, 50]. In the neonatal unit, an outbreak of amikacin resistant, gentamicin susceptible *Serratia spp*. occurred and abated spontaneously. In the year after the change in aminoglycoside usage, the resistance to amikacin of noscomial Gram-negative infections increased from 7.6 to 27.7% ($p<0.001$) and the resistance to gentamicin decreased from 71.2 to 60.2% ($p=0.07$). The observed effect might have been related to the more intensive usage of aminoglycosides in the neonatal unit[37].

1.4 Australian antibiotic resistance patterns

In 1967, the first clinically important isolate of a penicillin-resistant pneumococcus was reported from Australia[50]. Though, penicillin resistance was not the most important medical problem in this country, it caused major problems elsewhere, mostly in Papua New Guinea and South Africa. In the late 70s and the 80s, rates of resistance increased in Western countries, mainly in Spain. A study from United States found 25% of persistent *Streptococcus pneumoniae* isolates were penicillin-resistant. Resistance rates are generally higher in children, and the circulation of resistance varies within countries and inhabitant groups[51-55]. In 1989, a nation-wide study in Australia of over 1800 isolates of *Streptococcus pneumoniae*, found that only 1% were penicillin resistant[56], a lower rate than in most other Western countries. Though, in aboriginal communities had comparatively high rates of resistance occurred[55, 57].

Staphylococcus aureus is one of the most frequent causes of nosocomial infection in Australia and also globally. It is accountable for postoperative wound infection, intravascular line-associated sepsis, infection of prosthetic devices and a variety of other general problems. Multiple resistant *Staphylococcus aureus* (MRSA) has been well-known among the strains of *Staphylococcus aureus* coupled with hospital acquired infection in Australia, mainly on the eastern seaboard, occurring mainly in teaching hospitals and institutions providing composite tertiary-level care. Efforts to avoid cross-infection with MRSA in Australian hospitals have been mostly unsatisfactory, apart from reports of intermittent accomplishment in single units where rigorous intervention and supervision had been instituted. As a result, antibiotic treatment is the basis of management, and vigilance of changes in resistance patterns is a necessary element of recommendations for therapy[58].

1.5 Factors contributing to overuse of antibiotics

Achieving more thoughtful prescribing of antibiotics requires (a) perception of the factors that encourage overuse and the barriers to modify and (b) the execution of efficient strategies for altering conduct[59].

Results of a decisive study in the United States identified four major factors encourage the overuse of antibiotics: lack of appropriate education, prior experience, patients' expectations, and economics. Lack of education applies to both prescribers and patients. Surveys of primary care physicians show that several have imprecise knowledge about the necessity for antibiotics in patients, and many family physicians do not follow specialist recommendations for diagnosis and management of a particular disease[59, 60].

Lack of knowledge amongst patients and past experience contribute to increased demand for antibiotics[59]. Whether genuine or professed, patients' expectations for antibiotics have an effect on physicians' prescribing behaviour[61]. Years of prescribing or receiving antibiotics for viral respiratory infections have formed a sequence of supply and demand, reinforcing behaviours that are harmful in an era of rising antibiotic resistance. Breaking this cycle requires educating the public that past practices are no longer appropriate and persuade doctors that a patient's fulfilment is based more on communication than on prescription[59, 62].

Diagnostic ambiguity can also contribute to inappropriate antibiotic use. Intermittent diagnostic uncertainty is unavoidable. There is the possibility that a clinician will prescribe an antibiotic "just in case" an infection is bacterial. Suitable clinical assessment combined with good communication and mutual decision making, may reduce the risk of patients' discontent, or other undesirable outcome[59, 63].

Improper use of antibiotics has resulted in enormous wastage of hospital resources, and to overcome this problem a variety of strategies have been adopted. Whether concentrating at antibiotics or other drugs, provisional regulations such as prescribing from a formulary and/or automatic stop policies have often worked[64-66], but may not be suitable in all hospitals as doctors generally perceive obligatory controls as impinging on clinical independence. Educational strategies including the use of guidelines, handbooks, and seminars have also been widely reported[67-70]. On the other hand, the efficacy of such accomplishments have not been publicized constantly and when documented, their impact on prescribing behaviour is often minimal and momentary[68, 70-72]. Methods that are efficient frequently integrate other facilitative manoeuvres like feedback concurrent review and concurrent reminders/directives incorporated into the drug ordering system[73-75].

Education is generally resorted to as a means of changing prescribing practices, but when used single-handedly is not fully successful[72, 76-78]. Intervention programmes that are successful habitually integrate added enabling/reinforcing elements[70, 72]. The use of feedback as a means of enhancing prescribing behaviour has previously been reported but its effectiveness has not been constantly acknowledged[78-80].

1.6 Drug Utilisation Evaluation in Children

Several studies have evaluated antibiotic usage evaluation in children[81-84] and in appendicitis in children[85-87]. None of the studies have considered antibiotic dosage prescribing and the impact of pharmacist educational intervention in appendicitis in children in Australia or elsewhere. Both of these are important in respect to the quality use of medicines.

In a study by Lesar et al[88] the most common types of medication prescribing errors detected among the 696 dosing errors, were overdoses 291 (41.8%) and underdoses 115 (16.5%); prescribing medications to which the patient was allergic 90 (12.9%); and errors involving the prescribing of inappropriate dosage forms 81 (11.6%). The most common medications involved were antimicrobials 276 (17.5%), gastrointestinal agents 122 (7.3%), and non-narcotic analgesics and antipyretics 46 (6.6%). Many of these were clinically significant 557 (80%), fatal 43 (6.2%) and 96 (13.8%) were rated as serious. Hence an evaluation of dosages should be included in all pediatric interventions.

Other factors usually associated with errors included presence of a history of allergy to prescribed medication class 84 (12.1%), incorrect dosage calculations 77 (11.1%), atypical and critical dosage frequency 75 (10.8%), need to specify special dose forms for brand names, 43 (6.2%) and generic names 36 (5.2%), and the presence of duplicative therapy 36 (5.2%)[88].

The use of dosage calculations 17 of 96 (17.7%) serious errors and decimal point placement, allergy history, and unusual or atypical dose frequency 11 of 96 total serious errors were the most common related factors for errors rated as potentially serious[88].

Other workers includes Potts & Phelan[89], Koren & Haslam[90] and Baldwin[91] have demonstrated significant deficiency in the ability of prescribers to correctly calculate drug dosages. Steps to reduce the likelihood of such errors reaching the patient include requiring a double check of all calculations by another individual, increasing the use of standardised drug preparations and dosing, and using dosing tables. The integration of pharmacists on medical teams and patient care units provides an effective method of promoting appropriate medication use[92].

Folli et al[93] identified physician ordering errors, using a pharmacy-based review in two pediatric hospitals. They found that pediatric patients younger than two years and pediatric intensive care unit patients were particularly susceptible to errors, most of them were dosing errors[92].

Of 10788 medication orders written for 1020 patients, 616 (5.7%) orders involved an error at anyone of drug ordering, transcribing, dispensing, administering, or monitoring. There were 5 (0.8%) preventable adverse drug events, 115 (18.6%) potential adverse drug events, and 486 (80.5%) errors with relatively little potential for harm. A total of 320 (31%) patients experienced a medication error; 118 (12%) patients experienced two or more errors. The majority of errors occurred at the ordering stage (77.8%), followed by administering (12.8%) and transcribing (5.8%). The most frequent type of medication errors were dosing errors (28.4%)[92].

In a prospective multicentre study on medication errors in two pediatric teaching hospitals, it was found that errors occurred at a rate of 5.7 errors per 100 orders, with most of these errors occurring at the ordering stage (79%). Many of them involved incorrect dosing (34%)[94]. Importantly, although this overall error rate was similar to that found in a previous study by Bates et al[95] on adult inpatients using similar methods, errors with the potential to cause harm were three times more likely to occur in pediatric inpatients compared with adults.

Medication errors and adverse drug events are serious problems in pediatrics. The relatively higher rates of potentially harmful errors in hospitalised children compared with adults probably occurs primarily because dosing is more complex in pediatrics and underscore the need for safer systems in this setting. However, until recently, the incidence of pediatric medication errors has received relatively little scrutiny compared with adults, and even less has been done to assess their preventability[92].

1.7 Drug Audit

It has been recognized long ago that there is a need for drug audit to assess and improve the quality of medical care[96, 97]. According to the World Health Organization (WHO) drugs are not frequently used to their full potential, nor according to usually accepted criteria[98]. Differences in drug consumption patterns between similar populations in developed countries and the mortality and/or morbidity following inappropriate use of drug/s, adverse reactions, and antimicrobial resistance have often been attributed to physicians. Physicians regulate drug consumption, so their prescribing habits are important when considering the inappropriateness of drug use[99].

Pharmacists today frequently provide an important service of drug usage review/evaluation (DUR/DUE). The outcomes of these assessments often lead to improvements in cost-effective prescribing and, better utilisation of limited resources. This service is in high demand as organisations are searching for methods of reducing their costs. A typical drug evaluation process generally entails an in-depth analysis of an agreed specific therapeutic group. The method of analysis generally involves a pharmacist screening the literature and clinical data, developing and gaining agreement on practice guidelines in conjunction with other related departments, and evaluates the collected data against it. The results of the review will be presented to the prescribers and methods to modify prescribing behaviour sought and then evaluated[100].

1.8 Strategies to modify prescribing behaviour

Strategies to alter prescribing behaviour have been developed around the world two decades ago. These methods include[101-103]:

- persuasive and educational programs including peer review meetings, drug bulletins, lectures[104], guidelines[105, 106], and feedback of prescribing trends based on drug audits;
- professional advice of specialists such as microbiologists, pharmacologists and pharmacists;
- restrictive methods such as required approval by a clinical specialist prior to use, formularies[107], and automatic 'stop' orders.

Four studies conducted in the early 80's have suggested that educational measures can increase the optimal prescribing of drugs. Soumerai and Avorn (1983)[108] reported that optimal prescribing of target drugs was increased when physicians were "detailed' by clinical pharmacists. Ray et al (1985)[109] and Schaffner et al (1983)[110] found that clinical pharmacists who visited physicians to give drug information had a modest effect

on increasing the optimal prescribing of target drugs after a single visit, however multiple intervention strategies are more effective than a single strategy[111].

1.9 Hospital Quality Assurance Activities

Drug utilisation review (DUR) is a quality assurance (QA) approach for the facility per se, and it involves the setting of criteria and standards, an assessment phase using a set of screening criteria and a follow-up correctional phase with the prescriber. It comprises of all aspects of drug treatment from the time a patient presents to a prescriber, to the final outcome of the therapy[112].

The goals of drug usage review were explained by Knapp et al (1975)[113] as the encouragement of optimal drug use and the provision of high quality drug therapy as cost-effectively as possible[114].

1.10 Objectives of quality assurance activities

The objectives of this activity are to achieve quality drug use and patient care by ensuring appropriate, safe and cost-effective drug therapy. The outcomes of drug use are improved by[115]:

- determining drug usage and prescribing patterns;
- developing criteria and standards which explain optimal drug use;
- promoting rational therapy through education and by the provision of drug information and advice;
- carrying out regular drug use audits to evaluate the appropriateness of drug use, and characterize inappropriateness;
- minimizing the risk of adverse drug events caused by inappropriate drug use

- promoting economical drug use by reducing drug wastage, and unnecessary drug and drug related expenditure;
- providing feedback of DUE results to prescribers, managers and other relevant groups.

1.11 Selecting drugs and drug-use processes for evaluation

Drug or drug-use processes should be selected for evaluation for one or more of the following reasons[116]:

- ♠ The drug is known or suspected to interact with another drug, food, or to cause adverse reactions in a way that presents a significant health risk.
- ♠ The drug is used in the treatment of patients who are at high risk for adverse reactions.
- ♠ The drug-use process affects a large number of patients or the drug, which is frequently prescribed.
- ♠ The drug or drug-use process is a critical component of care for a specific disease, condition, or procedure.
- ♠ The drug is potentially toxic or causes adverse reactions at usual doses.
- ♠ The drug is very effective when used in a specific way.
- ♠ The drug is under consideration for formulary retention, addition, or deletion.
- ♠ The drug or drug-use process is one for which suboptimal use would have a negative effect on patient outcomes or system costs.
- ♠ The medication is expensive

Data sources commonly available within the hospitals are patient demographics, clinical and administrative data. The demographic data available such as age, sex, disease, average length of stay etc; clinical data such as patient charts, admission records, adverse drug reaction reports, microbiology/infection control data etc and finally administrative

data such as drug purchasing, drug utilisation, equipment purchasing, utilisation and cost per adjusted hospital bed day data etc[116].

Table 1. 1 Benefits of DUE programs

Benefits of DUE programs[117]	
Area of practice	**Perceived benefits**
Hospital and government administrators	Cost savings Potential to justify expenditure/identify efficiencies Embraces the concept of Total Quality Management In some countries, hospitals require a formal DUE program in place to achieve accreditation
Hospital pharmacists	Extends opportunities for pharmaceutical care Provides a leadership role within a multidisciplinary team Contributes to cost justification of clinical pharmacy services
Other health professionals	Increase potential to prevent adverse drug reactions or iatrogenic disease Recognizes the 'added value' applied by pharmacists to the drug use process Education
Patients	Improved quality of care

1.12 Intervention strategies

Two decades ago studies were undertaken to assess strategies that could improve the therapeutic use of drugs in society. Much of this work has been aimed towards assessing educational and directive strategies. In early 1980's, the psychological aspects of modifying behaviour were explored[99]. Strategies to influence prescribing and improve drug use may take a number of forms[99, 115, 118, 119]:

♣ (Re-) educative strategies are those where a relatively unbiased presentation of fact is intended to provide an impetus for change.

♣ Persuasive strategies which attempt to bring a change partially through reasoning, urging and inducement.

♣ Facilitative strategies recruit the services of others to assist in changing the behaviour of an individual or group.

♣ Power strategies involve the use of coercion of one type or an other to obtain compliance with a desired action.

♣ Combined strategies, which use two or more of the above simultaneously.

1.12.1 Re-educative strategies

A re-educative strategy "is one whereby the relatively unbiased presentation of fact is intended to provide a rational justification for action. It assumes that humans are rational beings capable of discerning fact and adjusting their behaviour accordingly when facts are presented to them. The prefix 're' in re-educative is used because this strategy may involve the unlearning or unfreezing of something prior to the learning of the new attitude or behaviour"[118].

The following should be considered when employing re-educative strategies[99]:

♥ Re-educative strategies often take time to work and may require additional resources to sustain the desired effect, so time should not be a pressing factor

♥ They are useful in creating an initial awareness of a problem

♥ Active opposition, factual ambiguity and an inability to assess the information presented reduce the effectiveness of re-education.

♥ They can be effective in linking causes with symptoms and offering solutions

♥ When used alone, re-education is not capable of affecting large-scale change in the short term particularly if motivation to change is low.

♥ They can be used after change is affected to reduce dissonance, which, if unchecked, could gradually reverse the change.

♥ If the degree of resistance is high, re-educative programs should begin well in advance of the change.

♥ They are essential when radical change is contemplated and high uncertainty exists.

Re-educative strategies can be used to influence prescribing by increasing awareness. Drug bulletins, newsletters and journals also use re-educative techniques[99].

1.12.2 Persuasive strategies

Persuasive strategies are strategies, which attempt to bring about change partially through bias in the manner in which a message is structured and presented. They attempt to create a change by reasoning, urging, and inducement. Persuasive strategies can be based on rational appeal and can reflect fact accurately[120]. Most advertising and interpersonal communication is persuasive in nature[99].

The following should be considered when employing persuasive strategies[99]:

- ♠ The greater the need of a persuasive strategy, occurs when the degree of commitment to change in lower
- ♠ Persuasive strategies are implemented when a problem is not recognised, or when a recommendation is not perceived as potentially effective.

- ♠ Since it requires time to implement, if change is desired quickly, power strategies may be more appropriate.
- ♠ Persuasive strategies are potentially very effective in countering resistance to change as they allow for the use of two-way discussion with feedback. However, the presentation of many recommendations may be counterproductive and, therefore, an optimum number should be provided with a careful mixture of claims.

Persuasive strategies applied to prescribing practice must often use data based on authoritative sources. The use of promotional material quoting articles from respected journals, or written by authoritative workers is well known and the promotion of drugs by pharmaceutical companies relies heavily on this approach[99].

1.12.3 Facilitative strategies

Facilitative strategies involve the use of another person to assist an individual change his or her behaviour. The use of facilitative strategies 'assume that the target group: (a) recognizes a problem; (b) is in general agreement that remedial action is necessary; (c) is open to external assistance and willing to engage in self-help'[118].

The following should be considered when employing facilitative strategies[99]:

- ♦ The target group must be aware of the change agent's existence.
- ♦ Change is more likely to occur if the change agent is located within the organization.
- ♦ Developing a trust relationship between the change agent and target group influences the willingness to accept change

- The level of resistance to change must be very minimal, since the greater the resistance the less effective facilitative strategies will be. Facilitative strategies assume that target groups recognise a problem and are open to external assistance.
- Time requirements can be considerable, so that if time and willingness to change are limited, facilitative strategies are not appropriate.
- Follow-up assistance must be provided by the change agent according to the ability of the target groups
- Different subgroups may require different facilitative strategies. Therefore, the approach should be modified to meet specific needs
- Little success will be seen when the change attempts to alter firmly held attitudes or entrenched behaviour
- The greater the magnitude and complexity of change, the most important it is to use facilitative strategies.

Facilitative strategies have considerable potential for influencing prescribing. Personal contact between individuals allows for two-way discussion and feedback, and can engender commitment to change. Facilitative strategies also offer an adaptive alternative, which is readily responsive to changing needs[99].

1.12.4 Power strategies

Power strategies "involve the use of coercion to obtain the targets compliance"[118]. The exertion of power is based on the dependency of the target group on the change agent for the achievement of goals. The ability to use power strategies is high when goals controlled by the change agent are important motivational objectives of the target group. Rewards for compliance and punishment for non-compliance are to be considered[99].

The following should be considered when employing power strategies[99]:

- ♠ Power strategies generally result in compliance, but require continuous surveillance because of a lower degree of commitment.
- ♠ The greater need of a power strategy is when the target group feels a lower perception of need for change.
- ♠ Power strategies are very important where the target group is unwilling to implement change, or where immediate action is necessary.
- ♠ Power strategies will be ineffective if the skills are absent or assistance by the change agent is not given and the target group doesn't have the resources and skills to implement the desired change.
- ♠ Power strategies can be used to overcome high levels of resistance. They are most commonly used after a decision has been made and requires implementation, while education and persuasion are more often used as a means of influencing future decisions.
- ♠ The greater the power required by the change agent, the greater the magnitude of change. Therefore, if a major change is contemplated, it may be preferable to undertake it in different stages.
- ♠ Change may force a target group to compromise for a moderate change by threatening drastic change. In fact, the moderate change may have been the original goal that was desired.

Influencing prescribing through power strategies is practised at both national and local levels. Government regulatory control has a major impact on national drug usage patterns. This can be exercised through restrictions on the release and use of drugs and controls on prescribing applied to subsidized pharmaceutical benefits schemes. At a local level drug formularies and prescribing restrictions have been enforced within some hospitals. Prescribing can be restricted to certain groups of prescribers, individual drugs can be restricted by deleting them as stock lines, or use of a drug may require prior permission of a clinical specialist[99].

1.12.5 Combined strategies

Combined strategies use two or more of the preceding strategies simultaneously and/or sequentially. Most interventions are of the combined type[99].

There are many strategies that have been effective in improving drug use. Mainly their individual limitations and local circumstances determine their selection and implementation[112].

1.13 Selection criteria of a strategy

Ideally, the selection of a strategy should be guided by the following requirements[112]:

- ♠ Acceptability to the hospital and prescribers. It should be neither disruptive to hospital routine, nor impair the care or health outcomes of patients
- ♠ Efficiency in the improvements in drug use can outweigh the resources and efforts required achieving and sustaining them
- ♠ Specificity in impact on drugs and prescribers. The strategy should neither restrict the use of alternative, appropriate drugs, nor penalise prescribers who comply with therapeutic standards and hospital requirements
- ♠ The educational benefits for staff, particularly inexperienced prescribers should be considered. This aspect is sound in teaching hospitals
- ♠ Sharing of guidelines and policies to related hospitals which have proven successful in one hospital, may be easily and inexpensively introduced into another

The success of strategies will depend mainly on certain features of hospitals. The availability of staff and resources dedicated to improving drug use is important.

Pharmacologists, pharmacists and microbiologists have been frequently associated with successful DUR programs in hospitals[112].

1.14 Drug Bulletins

In 1958, Kallet and Aaron first released the Medical Letter on Drugs and Therapeutics, a biweekly newsletter for physicians and other health personnel[121]. According to guidelines released by the World Health Organization, hospital drug bulletins are publications whose content is intended to optimise drug treatment in the interests of both the patient and the society, which the hospital serves. The information in drug bulletins should be precise, specific to the needs of the target group, independent of the pharmaceutical industry, presented attractively, and distributed efficiently and punctually to the relevant staff in the hospital[122, 123].

Plumridge et al[103] concluded that bulletins are useful in increasing an awareness of specific prescribing problems and can achieve changes in prescribing patterns. According to the WHO drugs are frequently not used to their full potential, nor according to generally accepted criteria. Drug bulletins or newsletters are produced by many hospitals on the assumption that they improve the quality of drug treatment with a subsequent decrease in costs[104, 122].

May and colleagues in the USA[124, 125] demonstrated that information in drug bulletins had a short-term effect on prescribing patterns. Since 1960, Moir and associates have employed regular feedback of drug usage data to prescribers in hospitals. Drug usage surveys conducted at the Pharmacy Department, Fremantle Hospital are in consistent with the observations made by the WHO recommendation. “However good the surveillance systems, they will not contribute directly to safer and more effective therapy

unless physicians are continuously provided with accurate unbiased information on drug therapy"[126].

In the vibrant field of drug therapy the need to be current is essential. There are many ways to gather drug information, but prescribers generally prefer and use printed information sources such as journals and bulletins. Two decades ago several studies have been completed, with conflicting results, to assess the effects of printed drug information on prescribing behaviour[104, 108, 110, 127-129]. In general, it has been concluded that printed material alone may change knowledge but it rarely has a direct effect on prescribing behaviour without the addition of multiple strategies[122, 130-132].

Drug bulletins are mainly directed at transmitting information about treatment aspects such as efficacy, adverse effects, and cost. Such information is not the only factor influencing drug choice and prescribing behaviour: the value attached to the treatment aspects is also important[132-135].

1.15 The Pharmacist Role

Pharmacists should play a central role in the overall operation of DUE programs in addition to assisting in the performance of individual reviews. Suggested roles and responsibilities include[115]:

- Preparation of submissions for program justification;
- Program development, supervision and coordination;
- Education of hospital staff about DUE in conceptual and practical terms;
- Recommendation and promotion of the goals and objectives of DUE;
- Development/review of audit criteria, guidelines, study protocols and other educational material;

- Development of data collection instruments, field testing, data collection, analysis and report writing;
- Documentation of program outcome, effectiveness and cost benefit;
- Prospective/concurrent monitoring of drug usage;
- Participating as a member of hospital committees concerned with quality assurance in general and drug usage evaluation in particular;
- Presentation of DUE results at meetings and conferences.

Pharmacists should monitor quality assurance activities in all practice settings and assist in established guidelines to discourage unnecessary drug use. Pharmacists should also become directly involved in aiding physicians in the decision to use drug therapy by documenting important drug related information in medical charts, by participating in patient care rounds, and by providing in-service education to the medical staff[136].

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Chapter Two

Review of prescribed Antibiotic and Analgesic dosage and the impact of intervention at a pediatric teaching hospital in Western Australia

2.1 Introduction

Paediatric and neonatal therapeutics and toxicology deals with an immature subject in a continuous state of development of body and organ function. It is well recognised that children cannot be viewed as "little adults" with respect to either drug effects or drug disposition [1]. Children and adults respond to drugs differently. There are important differences in the absorption, distribution, metabolism, and excretion of drugs during infancy and childhood. Children's body systems are less developed; their gastrointestinal transit time varies, and their body composition changes with development [2]. Children often require and tolerate proportionally greater daily doses of many drugs to achieve similar pharmacodynamic effects as adults, whereas newborn and infants may require more or less of a drug for a comparable effect [1].

Prescribing medication to a child requires careful consideration. In comparison to an adult, there are both subtle and marked differences in the pharmacokinetic action of drugs in the developing child. Many current medications have not been tested in children, so rational prescribing poses many challenges [2].

A significant increase in the knowledge base in paediatric clinical pharmacology has occurred over the past two decades and has largely been the result of important scientific and sociological advances pertaining to paediatric therapeutics. Although the data on drug disposition in infants and children have increased considerably over the past few years, pharmacokinetic, pharmacodynamic interactions, particularly the effects dependent on pharmacodynamics, remain poorly understood [3].

Errors in calculating drug doses have long been recognised as a cause of morbidity and mortality. In infants and small children such errors are more likely to be life threatening. It could be argued that such errors may stem from many factors such as poor medical knowledge, excessive workload, and fatigue [4].

Antibiotics are one of the most commonly used treatments around the world [5]. Antibiotics differ from other drugs in at least two respects. First, the main action of antibiotics is only to inhibit or to kill microorganisms. They are unlikely to heal or to reverse the damage already inflicted by the infecting organisms. Second, misuse of antibiotics not only causes morbidity and mortality due to side effects and financial loss, but it may also induce antibiotic resistance [6].

Antibiotic resistance is a very important worldwide problem. Strategies for reducing the inappropriate use of antibiotics are being explored in order to minimise the development of antibiotic resistance and to maximise the efficiency of antibiotic use. A number of measures have been taken to influence the use of antibiotics in the hospital setting. Restrictive or administrative approaches may work in the short term, but by themselves may meet resistance from the prescribers. An educational strategy seems to be a useful strategy, and it has been shown to be effective in modifying the prescribing patterns of clinicians[6, 7].

Drug usage evaluation is one of the important services provided by pharmacists today in hospitals. The outcomes of these evaluations are designed to lead to improvements in prescribing, to better utilisation of limited resources and improved patient care. This service is in high demand as organisations are searching for methods of improving patient care and reducing their costs. A typical drug evaluation process generally entails an in-depth analysis of an agreed specific group of drugs. The method of analysis involves a

pharmacist screening the literature and clinical data, developing and evaluating the collected data against practice guidelines in conjunction with other related stakeholders. The results of the review will then be presented to the prescribers and strategies used where appropriate modification of their prescribing behaviour is sought.

This chapter describes a series of studies, which were carried out as a preliminary to the development of a major study. These consist of study one; a pilot study to survey the frequency of drugs prescribed across the hospital during a 24-hour period, study two; to identify the level of appropriateness of prescribing antibiotic and paracetamol-compound analgesic dosages by retrospectively reviewing the medical records for a period of four weeks and study three; to evaluate the impact of an educational intervention programme on physicians prescribing of flucloxacillin, ceftriaxone and Liquigesic Co® dosages. The series of studies were conducted at Princess Margaret Hospital for Children (PMH), Subiaco, Western Australia, a 250-bed pediatric teaching hospital.

2.2 Methods

The initial study was conducted prospectively over a single 24-hour period on all patients admitted in PMH. Since the entire data collection to cover 250-bed hospital is not possible in one day, some patients prescribing data were collected on the following day. The drugs prescribed during the previous 24-hour period are only recorded. Other drugs, which are prescribed outside the 24-hour period, were not collected in the form. The time of prescription written on the medical record is taken into account.

The second study was a retrospective study carried out in December 1999. A list of patients admitted at PMH for the month of October 1999 was obtained from the Clinical Coding (CC) department. A request was sent to the Patient Information and Management

Services (PIMS) department to randomly select 15-20% of all the records available on the list.

The third study was carried out in three stages. Initially, a pre-intervention study (Group 1) was conducted to evaluate the level of appropriate dose prescribing of flucloxacillin, ceftriaxone and Liquigesic Co® by retrospectively reviewing the medical records. An intervention strategy was then planned and implemented. Subsequently, a post-intervention study (Group 2) was carried out by prospectively reviewing the medication charts in the wards to evaluate the level of impact of the intervention programme on physician's prescribing.

The pre-intervention study was conducted for a period of six weeks in January and February 2000 and the post-intervention study for the same period in June and July 2000. The PIMS and CC Departments supplied the list of patient medical records available during January and February 2000 and the data was transcribed only from the patients prescribed any of flucloxacillin, ceftriaxone and Liquigesic Co®.

2.2.1 Data collected

In study-1, the name of each drug and number of times prescribed to a patient on that day was entered into a prepared form. In studies -2 and -3, a coded form was prepared to transcribe the data from the medical records. Data recorded included patient details (age, weight, sex, date of admission and date of discharge), clinical details (principal diagnosis, principal procedure and other procedures) and medication details (drug name, dose, frequency, route and number of doses administered).

In study-2, prescribing data related to all antibiotics and paracetamol and paracetamol with codeine analgesics were collected whereas in study three only data for flucloxacillin, ceftriaxone, and Liquigesic Co® drugs were collected.

2.2.2 Inclusion and exclusion criteria

In study-1, all prescriptions written from 4th October at 8.00 a.m. until 8.00 a.m. 5th October were included in the study and others were excluded. For study-2, all medical records where no antibiotics or analgesics were prescribed or the data was incomplete were excluded. Patients prescribed flucloxacillin, ceftriaxone and Liquigesic Co® in study-3 were included in the study.

2.2.3 Data analysis

The drugs prescribed were categorised according to the British National Formulary [8]. The prescribed dosage was evaluated against Australian Therapeutic Guidelines (ATG) for Antibiotics [9] [10] and for Analgesics [11]. Liquigesic Co® was evaluated according to the PMH in-house guidelines of 0.8 ml/kg/6-hourly (19.2 mg/kg of paracetamol and 0.8mg/kg of codeine). Each 5 ml of Liquigesic Co® contains 120 mg of paracetamol and 5 mg of codeine.

An appropriate dose was classified as one prescribed within ±25% of the recommended dose. The permitted dosage error of ±25% was based on the common variability allowed in dosage forms and bioequivalency studies. Statistical evaluations were performed using χ^2 analysis for patient categorical and other non-parametric data. The influence of the intervention was analysed by analysis of variance. The sample size was based on current prescribing being 60% appropriate, and if increased to 80% by the intervention at $\alpha = 0.05$ and $\beta = 0.8$, required a minimum of 80 patients in each group to achieve a statistically significant difference.

2.2.4 Intervention programme

The intervention strategy involved (i) releasing a newsletter to the relevant key prescribing medical and other appropriate staff in the hospital on 6th June 2000; (ii) personal discussion held with the appropriate key staff; (iii) the chief pharmacist gave a presentation to all prescribers and clinical pharmacists subsequently followed up on the wards regularly; (iv) this included a review and analysis of the prescribing data collected in the pre-intervention study along with current recommendations for ceftriaxone, flucloxacillin and Liquigesic Co® dosages.

2.2.5 Ethical issues

As this study involved an analysis of patient's prescription data, ethical issues arise in relation to confidentiality and release of data. A unique non-patient identifiable code was allocated to each medical record to enable re-identification if necessary. Any coded data to leave the hospital was kept secure in accordance with National Health and Medical Research Council guidelines{Grandis JR, 1992 #57} and only group data released from the research. Informed consent was not obtained, because the study was classified as a quality audit. The PMH and Curtin University of Technology Ethics Committees approved this study.

2.3 Results

2.3.1 Study-1

One hundred and thirty nine different drugs were prescribed during the selected 24-hour period. A total of 537 drugs were prescribed, which on average is 3.6 drugs per patient. Of the total prescriptions, 25.5% were antibiotics, 22% analgesics, and 11% antifungals and laxatives together (Table 2.1). Of 250 beds available at PMH, 146 were occupied.

It was evident from Table 2.1 that antibiotics and analgesics made up almost half of the prescribed medication. Antifungals a sub-group of antibiotics increased the total to in excess of 50% with laxatives the next most frequent group. This gives clear evidence that there is only a relatively small use of other drug treatments. The “Other Groups” category did include a range of treatment for serious pathologies such as cancer, and the need for pulmonary surfactants and antihypertensives. A total of 537drugs were prescribed, which was on average was 3.6 drugs per patient (Appendix 2.1).

As antibiotics and analgesics made up approximately 50% of total prescribing, these groups were then targeted for further evaluation. It was noteworthy that within the group of antibiotics at least 19 different agents were prescribed.

Table 2. 1 Classification of drug groups

Classification of drug groups and their percentages prescribed over 24 hours			
S.No	**Group**	**Total number of patients on this group of drugs**	**Percentage of this group in the total drugs prescribed**
1	Antibiotics	137	25.5
2	Analgesics	118	22.0
3	Antifungal	29	5.4
4	Laxative	29	5.4
5	Drugs used to treat nausea and vertigo	19	3.5
6	Supplements	15	2.8
7	Anti-epileptic	14	2.6
8	Anti-inflammatory	13	2.4
9	Bronchodilators	12	2.2
10	Diuretics	12	2.2
11	Drugs used for glucocorticoid therapy	12	2.2
12	Anxiolytics and neuroleptics	11	2
13	Anti-histamine	11	2
14	Anti-hypertensive	10	1.9
15	Vitamins	9	1.7
16	Anti-muscarinic	7	1.3
18	Local anaesthetic	7	1.3
19	Antiviral	7	1.3
20	Other groups	65	12.1
21	Total	537	100

2.3.2 Study-2

There were 2000 medical records available for the month of October 1999. Of these, 355 (17.7%) were selected at random for review. Prescribing data was incomplete in 8, no medication chart was available in 11, no drugs were prescribed in 78, no drugs were administered in 2 (drugs prescribed as PRN but not administered) and no antibiotics and/or analgesics were prescribed in 63 patient records. Of the initial 355, 193 (54%) medical records were analysed for antibiotic and oral analgesic dosage prescribing appropriateness. Ninety one females and one hundred and two males were included in this study (Table 2.2).

Fourteen different antibiotics and four paracetamol-compounded analgesics were prescribed. Of these, cotrimoxazole, erythromycin, gentamicin, roxithromycin and tobramycin were prescribed according to the guidelines at appropriate dosages. Whereas the other antibiotics and analgesics showed variable levels of lack of conformity with current guidelines (Tables 2.3&2.4). The level of their appropriateness data is provided in Appendices 2 & 3. Flucloxacillin, ceftriaxone and Liquigesic Co® were selected for further evaluation and the impact of an educational intervention programme was tested in study-3.

Table 2. 2 Demographic data from selected sample

Gender	Neonates (<30 days)	Infant (1m to 1y)	Toddler (1-2y)	Child (3-12y)	Teenager (13-17y)	Total
Female	3	21	6	46	15	91
Male	3	24	12	50	13	102
Total	6	45	18	96	28	193

Table 2. 3 Number of patients prescribed appropriate and inappropriate doses of antibiotics

Drug name	Appropriate dose	Inappropriate dose	Total	% of appropriate dose prescribing
Amoxicillin	13 (92)*	15 (134)	28 (226)	46.4
Augmentin®	1 (6)	5 (36)	6 (44)	16.7
Cefotaxime	21 (116)	2 (19)	23 (135)	91.3
Ceftazidime	3 (22)	1 (5)	4 (27)	75.0
Ceftriaxone	16 (32)	14 (48)	30 (80)	53.3
Cephalexin	10 (120)	9 (140)	19 (260)	52.6
Cotrimoxazole	1 (5)	-	1 (5)	100.0
Erythromycin	6 (75)	-	6 (75)	100.0
Flucloxacillin	20 (142)	26 (346)	46 (488)	43.5
Gentamicin	8 (12)	-	8 (12)	100.0
Metronidazole	3 (16)	16 (110)	19 (126)	15.8
Penicillin	10 (108)	4 (45)	14 (153)	71.4
Roxithromycin	4 (26)	-	4 (26)	100.0
Tobramycin	1 (1)	-	1 (1)	100.0

*Sum of doses in the parenthesis

Table 2. 4 Number of patients prescribed appropriate and inappropriate doses of analgesics

Drug name	Appropriate dose	Inappropriate dose	Total	% of appropriate dose prescribing
Liquigesic®	41 (95)*	11 (22)	52 (117)	78.8
Panadeine®	6 (11)	5 (14)	11 (25)	54.5
Panadeine Forte®	16 (54)	7 (23)	23 (77)	69.5
Paracetamol	103 (294)	49 (119)	152 (413)	67.7

*Sum of doses in the parenthesis

2.3.3 Study-3

Overall, the patients' ages ranged from six days to 17 years in Group 1 and ten days to 17 years in Group 2. One hundred and forty five females and 202 males in Group 1 and one hundred and five females and 161 males in Group 2 were included (Table 2.5). No significant difference was found between the distributions of genders between the two groups ($p = 0.712$). The mean age of the patients in Group 1 was 6.13 years and 6.29 years in Group 2 with no significant difference ($p = 0.638$).

In Group 1, 86 patients had been prescribed ceftriaxone, 157 flucloxacillin and 241 Liquigesic Co® doses. Seventy-six patients were prescribed ceftriaxone, 96 flucloxacillin and 192 Liquigesic Co® doses in Group 2. There was a significant improvement in the appropriate dose prescribing of ceftriaxone and flucloxacillin following the intervention ($p = 0.001$). No significant difference was found in the dose prescribing of Liquigesic Co® ($p = 0.535$) (Table 2.6). The level of dose prescribing appropriateness in Group 1 and Group 2 in study three is summarised in the Appendix 2.4.

Table 2. 5 Patient group statistics

Patient group	Group 1		Group 2	
	Male	**Female**	**Male**	**Female**
Neonate (<30 days)	2	2	-	1
Infant (1month -1year)	9	12	19	9
Toddler (1 –2 years)	26	13	14	15
Children (3- 12 years)	140	102	112	68
Teenager (13-17 years)	25	16	16	12
Total	**202**	**145**	**161**	**105**

Table 2. 6 Comparison data of drug dosage prescribing between Group 1&2

Drug code	Dose appropriateness	Group 1	Group 2	P
Ceftriaxone	Appropriate	50 (58.1%)	68 (89.5%)	0.001
	Inappropriate	36 (41.9%)	8 (10.5%)	
	Total	86	76	
Flucloxacillin	Appropriate	108 (68.8%)	87 (90.6%)	0.001
	Inappropriate	49 (31.2%)	9 (9.4%)	
	Total	157	96	
Liquigesic	Appropriate	178 (73.8%)	142 (74%)	0.535
	Inappropriate	63 (26.2%)	50 (26%)	
	Total	241	192	

2.4 Discussion

In Study-1, antibiotics comprised 25.5% (137/537) of the total prescriptions, of these cephalosporins constituted 18.9% (26/137). While studies have indicated that antibiotic purchases comprise 19-35% of total pharmacy drug budgets[13-15], it is the cephalosporins, which currently account for the highest antibiotic cost in hospitals[16, 17]. In Study-2, 43.8% of the total prescribed antibiotics dosages did not conform with the guidelines. Studies have shown that as many as 60% or more of the patients who are prescribed antibiotics in the hospital receive therapy, which is deemed "inappropriate [18-20]."

To enhance and provide an agreed basis for the rational use of drugs, most hospitals have developed and implemented drug policies[21]. However, development alone is not sufficient to ensure the quality of drug use[22]. Herman & Rodowskas[23] have suggested that programs meant to improve the quality of patient care and thus drug usage, can succeed only if practitioners adopt a positive attitude towards such programs. It has also been reported that attitude was the strongest predictor of whether or not pharmacists performed clinical pharmacy activities[24]. The attitudes of pharmacists and physicians to drug policies is likely to be one of the important factors that may affect compliance with, and hence the ultimate effectiveness of such policies[25].

The results of four studies carried out in the early 1980's suggested that educational measures can reduce less than optimal prescribing of drugs[26-29]. Avorn and Soumerai[26] reported that suboptimal prescribing of target drugs was reduced when physicians were detailed by clinical pharmacists. Schaffner et al.[27] and Ray et al.[28] found that clinical pharmacist drug educators who visited physicians had only a modest effect on reducing the use of target drugs[30]. In the intervention (Study-3), the appropriate dosage prescribing of ceftriaxone was increased from 58.1% to 89.4% ($p<0.001$) and flucloxacillin from 68.7% to 90.6% ($p<0.001$). This shows that the intervention, which included clinical pharmacist involvement in the education of prescribers, has resulted in a significant impact.

Several low (5 in Study-2 and 26 in Study-3 were more than 51% below the recommended dose) and high (8 in Study-2 and 3 in Study-3 were more than 51% above the recommended dose) antibiotic dosages were prescribed. Both overdose and underdose prescribing of antibiotics are inappropriate practices; overdose prescribing potentially is associated with increased side effects, and unnecessary expenditure, whereas underdose prescribing potentially leads to treatment failure and possibly resistant organisms[21].

In Study-2, the appropriateness of paracetamol with codeine analgesic (Liquigesic Co®) dosage was found to be 69.7%. Patients on low analgesic dosage (1 in Study-2 and 7 in Study-3 were more than 51% below the recommended dose) may suffer from preventable pain, complications leading to a longer duration of hospital stay and increased costs. While patients on high dosage of paracetamol / paracetamol with codeine analgesic (3 in Study-2 were more than 51% above the recommended dose) may potentially suffer from toxicity effects.

In this study, Liquigesic Co® dosage appropriateness did not show any significant improvement following the intervention ($p = 0.535$). This shows that the intervention, which was the same methodology as for antibiotics, showed success for antibiotics and had no effect on analgesic prescribing. On further investigation it was found that prescribers were using a monograph, which is not endorsed by the hospital and also did not match with the current guidelines for dosages of analgesics.

The overall proportion of antibiotic dosage prescribing adherence to ATG was 65% in the pre-intervention group in Study-3. This is similar to the other Australian DUE studies which show a 50-71% adherence [22, 31-34]. In the post-intervention group, the level was increased to 90.1%. When implementing educational strategies, time should not be a

pressing factor, as they often take time to work and may require additional resources to sustain the desired effect. This type of strategy is useful in creating initial awareness of a problem, when the prescribers lack knowledge of the problem. Re-educative strategies can be effective by offering solutions or recommendations to the problem. These strategies are not capable of affecting large-scale change in a short time scale when used alone if the motivation to change is low[35].

Pharmacists have an important role in monitoring drug utilisation in all practice settings and should encourage the use of existing hospital guidelines and discourage suboptimal drug prescribing. Pharmacists should also become directly involved in aiding physicians in the decision to use drug therapy by documenting important drug related information in medical charts, by participating in patient care rounds, and by providing in-service education to the medical staff[36].

This study has evaluated the influence of a comprehensive intervention strategy on a short-term basis. Clinical pharmacists regularly identify the need to maintain high levels of appropriate prescribing. Clearly this needs to include educational strategies at selected time intervals as prescribing occurs over the whole 24 hours and seven day a week whereas clinical pharmacists are in many settings available for 7.5 hours per day and five days per week.

2.5 Conclusion

This study has identified that since antibiotics and analgesics constitute around 50% of medications prescribed to children, attention should be placed on their appropriateness. Improvement in the prescribing of antibiotic dosages for ceftriaxone and flucloxacillin was achieved with a multifaceted educational program. This did not occur with Liquigesic Co® but identified another source that influenced that prescribing. It is

important for pharmacists to be constantly vigilant regarding prescribing and evaluate long-term strategies to maintain appropriate prescribing.

2.6 Reference

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2.7 Appendix

Appendix 2. 1 Names of drugs, their groups and number of times prescribed

S.No	Drug Name	Classification	No. of patients on this drug
	Liquigesic	Analgesic (compound)	27
	Panadeine	Analgesic (compound)	2
	Panadeine Forte	Analgesic (compound)	9
	Aspirin	Analgesic (NSAID)	3
	Paracetamol	Analgesic (NSAID)	56
	Morphine	Analgesic (opiod)	21
	Beclomethasone dipropionate	Anti-asthamatic	7
	Amoxycillin	Anti-bacterial	20
	Ampicillin	Anti-bacterial	1
	Augmentin	Anti-bacterial	6
	Bactrim (sulfamethoxazole + trimethoprim)	Anti-bacterial	16
	Cefotaxime	Anti-bacterial	9
	Ceftriaxone	Anti-bacterial	9
	Cephalexin	Anti-bacterial	7
	Cephalothin	Anti-bacterial	1
	Chloramphenicol	Anti-bacterial	4

	Ciprofloxacin	Anti-bacterial	3
	Cotrimoxazole	Anti-bacterial	2
	Erythromycin	Anti-bacterial	1
	Flucoxacillin	Anti-bacterial	8
	Gentamicin	Anti-bacterial	15
	Metronidazole	Anti-bacterial	11
	Penicillin	Anti-bacterial	5
	Rulide	Anti-bacterial	1
	Tobramycin	Anti-bacterial	7
	Vancomycin	Anti-bacterial	4
	Heparin	Anti-coagulant	3
	Zoloft	Anti-depressant	1
	Actrapid	Anti-diabetic	4
	Humulin	Anti-diabetic	1
	Carbamazepine	Anti-epileptic	2
	Clobazam	Anti-epileptic	1
	Epilim	Anti-epileptic	4
	Phenobarbitone	Anti-epileptic	6
	Vigabatrin	Anti-epileptic	1
	Canesten Cream	Anti-fungal	1
	Daktarin	Anti-fungal	1
	Econazole	Anti-fungal	3
	Fluconazole	Anti-fungal	12

	Flucytosine	Anti-fungal	1
	Itraconazole	Anti-fungal	1
	Nilstat	Anti-fungal	8
	Nystatin	Anti-fungal	2
	Benadryl	Anti-histamine	1
	Hydroxyzine	Anti-histamine	1
	Loratidine	Anti-histamine	3
	Promethazine	Anti-histamine	6
	Atenolol	Anti-hypertensive	2
	Captopril	Anti-hypertensive	2
	Catapress	Anti-hypertensive	1
	Diltiazem	Anti-hypertensive	1
	Enalapril	Anti-hypertensive	1
	Nifedipine	Anti-hypertensive	3
	Dexamethasone	Anti-inflammatory	6
	Ibuprofen	Anti-inflammatory	4
	Indomethacin	Anti-inflammatory	1
	Naprosyn	Anti-inflammatory	1
	Sofradex	Anti-inflammatory	1
	6-Mercaptopurine	Anti-metabolite	2
	Methotrexate	Anti-metabolite	2
	Thioguanine	Anti-metabolite	1
	Atropine	Anti-muscarinic	3

	Atrovent	Anti-muscarinic	1
	Benztroprine	Anti-muscarinic	1
	Oxybutynin	Anti-muscarinic	1
	Sucralfate	Anti-muscarinic	1
	Mycophenolate	Anti-proliferative immunosuppresant	1
	Tazocin	Antibiotic	2
	Timentin	Antibiotic	5
	Haloperidol	Anti-psychotic	1
	Omeprazole	Anti-secretory	1
	Rifampicin	Anti-tubercular	1
	Cimetidine	Anti-ulcer	1
	Ranitidine	Anti-ulcer	2
	Acyclovir	Anti-viral	2
	CMV-Ig	Anti-viral	2
	Fanciclovir	Anti-viral	1
	Ganciclovir	Anti-viral	1
	Valacyclovir	Anti-viral	1
	Diazepam	Anxiolytic	9
	Midazolam	Anxiolytic and neuroleptic	2

	Aminophylline	Bronchodilator	3
	Salbutamol	Bronchodilator	9
	Caffeine	CNS stimulant	2
	Ritalin	CNS stimulant	1
	Betadine drops	Dis-infectant	1
	Chlorhexidine	Dis-infectant	1
	Frusemide	Diuretic	8
	Hydrochlorthiazide	Diuretic	2
	Spironolactone	Diuretic	2
	Bonjela	Drug acting on oropharynx	3
	G-CSF	Drug used to treat neutropenia	2
	Gaviscon	Drug used for gastroesophageal reflux	1
	Hydrocortisone	Drug used for glucocorticoid therapy	3
	Prednisolone	Drug used for glucocorticoid therapy	9
	Prochloroperazine	Drug used for nausea and vertigo	1
	Tilade (nedocromil)	Drug used for prophylaxis of asthma	1
	Metoclopromide	Drug used for the relief of nausea	5
	Ondansetron	Drug used to treat nausea and vertigo	13
	Nitrofurantoin	Drug used to treat urinary tract infection	1
	Potassium Chloride	Electrolyte	2
	Sodium Chloride	Electrolyte	3
	Dermazole Cream	Emollient	1

	Chloral Hydrate	Hypnotic	3
	Nitrazepam	Hypnotic	1
	Temazepam	Hypnotic	1
	Azathioprine	Immunosuppressant	1
	Cyclosporin	Immunosuppressant	1
	Tacrolimus	Immunosuppressant	2
	Coloxyl	Laxative	8
	Lactulose	Laxative	1
	Magnesium asparate	Supplement (magnesium)	2
	Microlax	Laxative	6
	Parachoc	Laxative	8
	Senna	Laxative	1
	Sorbitol	Laxative	2
	Phosphate Enema	Laxative	1
	Bupivacine	Local anaesthetic	1
	Emla	Local anaesthetic	6
	Pancuronium	Muscle relaxant	1
	Suxamethonium	Muscle relaxant	3
	Permethrin	Parasiticidal preparation	2
	Calcium Carbonate	Phosphate binding agent	2

	Survanta	Pulmonary surfactant	3
	Calcium gluconate	Supplement (calcium)	1
	Calcium	Supplement (calcium)	2
	Carnitine	Supplement (carnitine)	1
	Erythropeotin	Supplement (erythropoietin)	1
	Ferrous gluconate	Supplement (ferrous)	1
	Folate	Supplement (folic acid)	1
	Pancrease	Supplement (pancrease)	1
	Phosphate Sandoz	Supplement (phosphorous)	4
	Sodium Bicarbonate	Supplement (bicarbonate)	2
	Calcitriol	Vitamin-D	2
	Vitamin- A+D	Vitamins	1
	Vitamin-C	Vitamins	1
	Vitamin-E	Vitamins	3
	Vitamin-K	Vitamins	1

Appendix 2. 2 Profile of dose prescribing of antibiotics in Study two

Drug name	Low dose		High dose			Appropriate dose	Total	Percentage of appropriateness
	26-50% low dose	51-75% low dose	26-50% high dose	51-75% high dose	76-100% high dose			
Amoxycillin	2 (4)*		12 (129)		1 (1)	13 (92)	28 (226)	46.4
Augmentin			2 (15)	3 (23)		1 (6)	6 (44)	16.67
Cefotaxime			1 (14)	1 (5)		21 (116)	23 (135)	91.3
Ceftazidime				1 (5)		3 (22)	4 (27)	75
Ceftriaxone	11 (40)	1 (6)		1 (2)		16 (32)	30 (80)	53.3
Cephalexin	8 (100)	1 (40)				10 (120)	19 (260)	52.6
Cotrimoxazole						1 (5)	1 (5)	100
Erythromycin						6 (75)	6 (75)	100
Flucloxacillin	15 (176)	2 (11)	9 (159)			20 (142)	46 (488)	43.47
Gentamicin						8 (12)	8 (12)	100
Metronidazole	9 (92)	1 (3)	5 (12)	1 (3)		3 (16)	19 (126)	15.8
Penicillin	4 (45)					10 (108)	14 (153)	71.4
Roxithromycin						4 (26)	4 (26)	100
Tobramycin						1 (1)	1 (1)	100

*Sum of doses in the parenthesis

Appendix 2. 3 Profile of dose prescribing of oral analgesics in Study two

Drug name	Low dose		High dose			Appropriate dose	Total	Percentage of appropriateness
	26-50% low dose	51-75% low dose	26-50% high dose	51-75% high dose	76-100% high dose			
Liquigesic®	10 (20)*		1 (2)			41 (95)	52 (117)	78.8
Panadeine®	4 (8)		1 (6)			6 (11)	11 (25)	54.5
Panadeine forte®	6 (16)		1 (7)			16 (54)	23 (77)	69.5
Paracetamol	32 (93)	1 (1)	13 (21)	2 (2)	1 (2)	103 (294)	152 (413)	67.7

*Sum of doses in the parenthesis

Appendix 2. 4 Profile of level of dose prescribing appropriateness in Group 1 and Group 2 in Study three

Level of appropriateness	Group 1			Group 2		
	Ceftriaxone	Flucloxacillin	Liquigesic®	Ceftriaxone	Flucloxacillin	Liquigesic®
26-50% low dose	32 (60)*	25 (152)	54 (129)	7 (19)	2 (7)	49 (128)
51-75% low dose	2 (9)	24 (93)	7 (112)		4 (15)	
76-100% low dose					1 (4)	
26-50% high dose	1 (5)		1 (168)	1 (1)		1 (2)
51-75% high dose	1 (1)				1 (1)	
76-100% high dose					1 (5)	
Appropriate	50 (126)	108 (705)	179 (1028)	68 (191)	87 (779)	142 (454)
Total	86 (201)	157 (950)	241 (1480)	76 (211)	96 (811)	192 (584)

*Sum of doses in the parenthesis

Chapter three

Impact On Surgeons Antibiotic and Analgesic Prescribing Following The Implementation Of Hospital Treatment Guidelines In Pediatric Appendectomy Procedures in Australia

3.1 Introduction

Appendectomy is the surgical removal of the appendix. Surgeons have been successfully performing appendectomies for more than 100 years, and it is now the most common type of emergency surgery. Approximately 60,000 US children are operated annually for the presumptive diagnosis of appendicitis[1]. About 10% to 30% of these have normal pathology and 30% to 45% have ruptured appendices, at least one third of all patients do not achieve optimal timing for the surgical intervention[2]. Fitz stated, "The vital importance of early recognition of perforative peritonitis is unmistakable…its eventual treatment by laparotomy indispensable[3]." In McBurney's treatise he proposes, "In the early stage no accurate diagnosis can be made as to whether the appendix is perforated or not. There is no reason to think…that diagnosis from symptoms alone will ever reach that perfection"[4].

The hallmark of the diagnosis of acute appendicitis is a compatible history and physical examination. Signs and symptoms of right lower quadrant tenderness and pain are anticipated for the vast majority of patients examined for acute appendicitis. However, the absence of right lower quadrant symptoms, it is very reliable for eliminating the diagnosis and therefore for avoiding surgery[5].

Despite technologic advances, the diagnosis of appendicitis is still based primarily on the patient's history and a physical examination. Prompt diagnosis and surgical referral may reduce the risk of perforation and prevent complications. The mortality rate in non-

perforated appendicitis is less than 1 percent, but it may be as high as 5 percent or more in young patients, where diagnosis may often be delayed, thus making perforation more likely[6].

3.1.1 Appendectomy in Western Australia

Appendectomy is one of the most common surgical procedures in Australian children. An increase in the incidence of appendicitis was reported during the early part of the 20th century, but a decline has been reported since about 1930[7].

Western Australia occupies one third of the Australian continent. It is sparsely populated. Seventy-three percent of the total population of 1.9 million reside in the capital city of Perth [7]. According to a study conducted by Donnelly et al, of the 59,749 appendectomies performed in WA during 1981-1997, 33,352 (58%) were performed on female patients and 26,397 (42%) on males. They found that a marked decline occurred in the rate of appendectomy during the study period; it was more marked in females than males which is consistent with trends reported from European countries [7-9]. Of the 30,934 appendectomies performed in WA during 1988-1997, 18,961 (61.3%) were acute emergency admissions, 3820 (12.3%) were other emergency admissions, 2192 (7.1%) were incidental procedures and 5961 (19.3%) were recorded as other appendectomy admissions [7].

Depending on the nature of the appendicitis, which can manifest with perforation, peritonitis, phlegmon, or abscess, treatment usually incorporates a combination of surgical and medical therapies in the form of antibiotics.

3.1.2 Misuse of antibiotic prophylaxis during surgery

Antibiotic use has soared in recent years. Furthermore, antibiotics appear to be used both in excess and inappropriately. The Center for Disease Control and Prevention in the USA has estimated that some 50 million of the 150 million prescriptions for antibiotics written for outpatients every year are unnecessary. A similar type of study, an evaluation of antibiotic use at Hacettepe University Hospital in Turkey in 1994 revealed that antibiotics were being used inappropriately in 23% of patients[10, 11].

Inappropriate antibiotic use has been shown to have implications for the cost-effectiveness of patient care. A study from Naples, Italy, examined surgeons' compliance with published international guidelines for surgical prophylaxis and evaluated the cost of the surgical prophylaxis against what it would have been had the guidelines been followed[12]. The first observation was that the duration of prophylaxis use was longer than recommended. Two hundred and twenty patients who underwent clean surgical procedures, for which prophylaxis was not generally recommended, received prophylaxis lasting from 1.1±0.3 days to 4.6±2.8 days. Similarly, 440 patients who underwent clean-contaminated surgical procedures, for which single-dose prophylaxis was indicated, received prophylaxis lasting from 3.6±2.4 days to 5.2±3.7 days. They found that 84% and 90.5% of patients' who underwent clean and clean-contaminated surgical procedures, received non-standard antibiotics. Third-generation cephalosporins were the most popular prophylactic agents for both clean and clean-contaminated surgery, even though these agents are not recommended in the guidelines. A study by Akalin, stated that if the recommendations regarding choice of antibiotic and timing of prophylaxis had been followed, approximately 10% of the actual cost would have been saved[11]. Gorecki et al supports the above statement with savings of $18,533 per patient due to excessive duration of antibiotic administration[13].

3.1.3 Principles of prophylaxis

Since infectious complications in surgical patients are responsible for prolonged wound healing, disability, deformity, prolonged hospitalisation, increased overall cost of hospital care and even death, and since the patients quality of life can be affected or even permanently altered by them, including very high human and economic costs, it is important to prevent them as far as possible. This can be done by improving the patients ability to overcome the microbial invasion, by improving the patients general conditions, by judicial surgical procedures and by using antibiotic prophylaxis[14].

Antibiotic prophylaxis for abdominal procedures has been used since antibiotics became available in the 1940s[15]. Since then, numerous investigations have attempted to define the optimal antibiotic, number of doses, risk factors, and cost-effectiveness of prophylaxis in this field of surgery.

Following the initial studies by Burke[16] in the 1960s, the basic principles of surgical prophylaxis established in that period are now widely accepted. Bacterial contamination of surgical wounds potentially occurs in every operation. The origin of the contamination may be exogenous or endogenous. Both may coexist, are usually minor, and are more likely to occur during than after a surgical procedure[17].

The objective of antibiotic prophylaxis in surgery is to prevent wound infection, in particular deep abscess, caused by intraoperative bacterial contamination. Success depends on the ability of the patients local and systemic defence mechanisms to resist the microbial invasion. Prophylaxis may be advisable in any patient undergoing an intra-abdominal procedure[14].

The likelihood of a wound becoming infected depends largely on the size of the bacterial inoculum, since infection only occurs when pathogens invade the tissues in a sufficient number to overcome the natural defences of the body. The surgeon can enhance host resistance by ensuring an adequate supply of blood and avoiding tissue haematomas and the entry of foreign materials to the surgical site. In this situation, the role of prophylactic measures is to reduce the number of 'invaders' as far as possible[17]. The key elements of surgical antibiotic prophylaxis are indications, choice of antibiotic, dosage, route of administration and timing.

The prophylactic use of antimicrobial agents is recommended for the prevention of a variety of post-operative infections[18], which represent 25% of all nosocomial infections in hospitals [19]. Since antibiotics were discovered, no single preventive measure contributed more to the decrease in post-operative wound infection than prophylaxis[20]. However, its appropriate application is a source of concern as it currently accounts for up to 30-50% of antimicrobial prescriptions in hospitals. Inappropriate antimicrobial prophylaxis adds to the pressure on microbial ecology within the hospital, and increases the risk of antimicrobial resistance. It contributes to the development of multiple antibiotic resistances, including resistance to newer agents, and antimicrobial resistance is associated with poor clinical outcome and increased treatment costs[21, 22].

The principles of surgical prophylaxis have been defined over the years: administration just prior to surgery, maintenance of sufficient tissue drug levels for the duration of the procedure and for not more than 24hrs, and the antimicrobial agent given is active against those organisms most likely to be encountered in the particular surgical field[23]. Antibiotic "prophylaxis" initiated after the operation is useless[13]. The timing of antibiotic administration relative to the time of surgery is the most crucial factor in the success of surgical prophylaxis[11].

3.1.4 Determinants of the need for prophylaxis

The decision to administer antibiotic prophylaxis during a given surgical procedure can readily be linked to the traditional classification of surgical procedures (Table 3.1)[24]. Prophylaxis is required usually for clean-contaminated procedures, and always for contaminated procedures. Aggressive therapy is obviously essential in the case of dirty-infected procedures[14].

Table 3. 1 Traditional classification of surgical procedure

Category	Infection risk (%)	Types and/or characteristics of procedure	Need for prophylaxis
Clean	1.5-4.2	Non-traumatic; no inflammation encountered; no break in technique; respiratory, alimentary, genitourinary tract not entered	Not required, except in high-risk patients
Clean-contaminated	<10	Gastrointestinal or respiratory tract entered without significant spillage; appendectomy, oropharynx or vagina entered, urinary or biliary tract entered in absence of infection; minor lapse in technique	Usually required
Contaminated	10-20	Major lapse in technique; gross spillage from gastrointestinal tract; fresh traumatic wound; infection of entry in urinary or biliary tract	Always required
Dirty and infected	20-40	Acute bacterial inflammation without pus; transection of clean tissue to enable collection of pus; traumatic wound with retained devitalised tissue; foreign bodies; faecal contamination; delayed treatment	Therapy required

Prophylactic antibiotics are effective in a wide range of surgical procedures and have contributed substantially to reducing postoperative wound infections rates. Moreover, financial savings may be associated with their use since wound infections are among the most expensive nosocomial infections. However, use of broad-spectrum antibiotics potentially contribute to the appearance of multi-resistant organisms, including strains resistant to newer agents, and antimicrobial resistance is associated with poor clinical outcomes and increased treatment costs[25]. The decision to prescribe antimicrobials has to be carefully balanced between immediate benefits and possible adverse effects as well as unfavourable medium-term impact on patient or hospital ecology[22].

3.1.5 Cost of intra-abdominal infections

Surgical site infection in the postoperative period can be very costly. The cost of surgical site infection is three fold: cost to the hospital, the community services and the patient[26].

Postoperative wound infections account for approximately 25% of all hospital-acquired infections and are the most expensive type of hospital-acquired infection[27]. Postoperative wound infections affect at least 920,000 of the 23 million patients who undergo surgery each year in the USA[11].

Despite considerable progress in the areas of prevention, diagnosis, and therapy, postoperative infections continue to be associated with considerable morbidity and mortality. Surgical patients can develop several postoperative infections; wound infections – representing more than 19% of all postoperative infections. These complications add 10-20% additional costs to the total hospital bill[28]. In the USA, for

any given type of operation, the development of a wound infection, will approximately double the cost of hospitalisation. These infections lead to 80,000 deaths and are associated with an annual treatment cost of US$ 2 billion. These data are similar in Italy, where nosocomial infections occur in 500,000 out of 8,000,000 hospital admissions per year and where the hospital antibacterial expenditure was about ITL 580 billion in 1997, which is 22% of the total drug expenditure[11, 29].

3.1.6 Need for surgical prophylaxis

The economic consequences of hospital-acquired infections are well known and have changed little during the past few years. In the USA in 1995, hospital-acquired infections account for approximately 2 million patients per year[11], with an increased hospital stay by an average of seven days, at a cost of $2434 per patient[26]. A similar study in the UK showed an increased stay of 8.2 days at a cost of £1041[30]. A recent report from the Public Health Laboratory Service identified a 2.5 fold greater cost for patients developing surgical site infection[31]. Many studies in other countries have found a similar cost per patient[11].

The effect of postoperative infections in prolonging the length of hospital stay and thereby increasingly the direct cost of patient care is especially noticeable for patients undergoing cardiothoracic, orthopaedic and gastrointestinal operations. The indirect costs can be very high in these patients, and are an important consideration in assessing the consequences of postoperative infection[11].

Postoperative infection is the major common avoidable cause of both morbidity and mortality in surgical procedures. Advances in overcoming this problem have transformed surgery from an activity associated with frequent infection and death into a discipline capable of extending patients' lifespan and quality of life with a high probability[32].

Given the high morbidity and mortality rates and high costs associated with the treatment of surgical infections, prophylaxis is the much preferred management option. The prophylaxis of surgical-site infections is based on four principles: preoperative patient preparation, surgical technique, perioperative antibiotic prophylaxis and postoperative wound care[11].

3.1.7 Effects of inappropriate antimicrobial use

Overuse or "inappropriate" use of antimicrobials is often cited as a risk factor for the emergence of antibiotic resistant bacteria. The use of vancomycin, of third generation cephalosporins and of antimicrobials with anaerobic activity has been cited as a risk factor for development of vancomycin resistant enterococcus[33, 34]. Third generation cephalosporins have been implicated as a risk factor for the development of multi-resistant Gram-negative bacilli[35, 36]. Most studies suggest that a correlation between antibiotic use and resistance rates have described the experience of single institutions[37].

Antibiotic use in common practice is excessive[38, 39]. Effects of antibiotics other than bactericidal are common and include drug interactions, toxic or allergic reactions, and release of endotoxins from enteric bacteria. Beyond these issues and excessive hospital costs, the spread of resistant microorganisms in the environment is a material concern[13].

3.1.8 Guidelines for improved quality of surgical prophylaxis

There are at least three reasons to promote the rational use of antibiotics: to improve the quality of patient care, to delay the development of antibiotic resistance, and to increase the cost-effective use of antibiotics. With regard to the quality of care, inappropriate

hospitalisation, medical treatments and/or surgical intervention clearly represent poor-quality medical care. In addition, large variations in practice patterns have implications for quality of care, as does variation in the way a treatment is applied[11, 40].

The current pediatric surgery environment demands the provision of quality health care at an affordable cost. Both payers and regulators are committed to lowering cost through initiation of best practice strategies that include practice guidelines, clinical pathways, and standards of care[13, 41].

Several studies have indicated that the implementation of guidelines can yield significant improvements in antibiotic use and hence quality of patient care[11]. In a study by Akalin, when compared with the previous practice, compliance with newer guidelines increased after their implementation, from 32% to 79%. The proportion of cases managed by single-dose prophylaxis also increased from 34% to 80%, there was a decrease in prophylactic antibiotic consumption from 0.75 to 0.53 DDD/patient. After intervention, only 16% of total antibiotic use was for prophylactic use, compared with 31% before intervention. The incidence of prophylaxis lasting more than 24 hours decreased from 21% to 8%[11].

The control of variation through quality processes such as pathway development, refinement of guidelines, and feedback of providers may improve the care of children with appendicitis[42]. By evaluating comparative data, physicians and hospitals may be able to identify and adopt best practices, improve outcomes, and perhaps decrease resource utilisation and the cost of care[43]. National databases have become an important resource for benchmarking and standardisation of care[44].

The best approach is the development of formal clinical practice guidelines (CPGs) to guide patient care prospectively within a select population. The development of CPGs is part of a larger trend toward evidence-based medicine and quality of care. A clinical practice guideline is defined as a systematically developed, evidence or consensus based, or both, multidisciplinary plan of care for a specific patient population that serves as a guide for clinical decision-making and as a method to ensure that all aspects of the care process are carried out in a timely fashion to best meet the patient's needs[45].

According to a survey by Chen et al. on current practice patterns in the treatment of appendicitis in children, a majority of surgeons (59%) base their clinical practices on individual surgeon's preferences. Another 24% of respondents used informal guidelines based on a consensus of surgeons in the practice group. Surprisingly, only 17% of surgeons have formal clinical practice guidelines to direct care of patients with perforated appendicitis[45].

Reduction in funds appropriated for health care forces physicians all over the world to take into consideration therapeutic costs[46]. Restricting antibiotic overuse is even more justified because expenses towards antibacterial agents constitute a major item in a budget of many hospitals[13].

Perioperative antimicrobial prophylaxis (PAP) accounts for more than one of every three antibiotic prescriptions in hospitals, and the dollar value of antibiotics used for this purpose is significant and an aggregate expenditure of several billion dollars per year results in the United States. The benefits that PAP produces are of substantial economic importance, because of the cost of postoperative infections. Hospitals in the United States usually recover a small net gain for surgical procedures; this profit is lost when the patient develops a postoperative infection[47]. PAP "may account for a substantial portion of hospital pharmacy antibiotic use that is regarded as inappropriate,"[48] so it

deserves attempts to improve usage. However, even if there was no cost rationale for its review, analysis of PAP still would be necessary because of its potential for selection of resistant organisms[49].

The purpose of this study is to evaluate drug use in appendectomy procedures in pediatric patients. This will be achieved by (i) determining drug usage and prescribing patterns for antibiotics in appendectomy patients (ii) identifying and establishing criteria and standards which describe appropriate use of these drugs (iii) promoting rational therapy by implementing treatment guidelines through education programs administered by targeted interventions (iv) evaluating the outcomes of the intervention and analysing the implications of any identified inappropriate drug use.

The uniqueness of this study is evaluating both drug usage and dosage prescribing appropriateness in pediatric appendectomy patients and implementing multifaceted educational intervention programme to improve surgeons prescribing behaviour.

3.2 Methods

3.2.1 Setting and patient population

The study was conducted at Princess Margaret Hospital for Children (PMH) (test-1&2), Subiaco, Western Australia a 250-bed pediatric teaching hospital. The control groups were identified at Fremantle Hospital (FH) (control-1&2), Fremantle, Western Australia and Royal Children's Hospital (RCH) (control-3&4), Melbourne, Victoria. FH is a 350-bed general hospital with 29 pediatric beds and RCH is a 350-bed pediatric teaching hospital.

A pre-intervention retrospective study (Group 1) of appendectomy procedures was carried out from April 2000 to August 2001 at PMH, FH and RCH. The Patient Information and Management Services Department supplied the patient medical records in each case. Post-intervention (Group 2) studies were conducted from December 2001 to April 2002 and data was collected retrospectively at all the hospitals. All pediatric patients undergoing treatment at PMH and RCH and patients under 18 years of age at FH were eligible to be included in this study.

3.2.2 Data collected

The data related to antibiotic prescribing were entered from the medical records into a coded prepared form. Patient details included age, weight, sex, date of admission, date of discharge, clinical details such as principal diagnosis and principal procedure, medication details including drug name, dose, frequency, route and number of doses administered.

3.2.3 Inclusion criteria

All pediatric patients undergoing treatment at PMH and RCH and patients under 18 years of age at FH were eligible to be included in this study.

3.2.4 Intervention

An intervention strategy involved (i) releasing a newsletter to the relevant key prescribing medical and other appropriate staff in the PMH hospital on 5th December 2001 detailing current recommendations for the prophylaxis and treatment of appendectomy (ii) Chief Pharmacist and the surgical ward pharmacist held personal discussions with the appropriate staff (iii) a senior pharmacist gave a presentation to surgeons and subsequent regular follow-up by clinical pharmacists regarding antibiotic treatments, this included a review and analysis of the prescribing data collected in the Group 1 study for analgesics

and with current recommendations of antibiotics for prophylaxis and treatment in appendectomy procedures (iv) any infections developed by patients due to inappropriate antimicrobial cover was discussed with the microbiologist and the recommendations made by him/her were presented to the physicians (v) this was re-inforced by the hospital clinical pharmacists (vi) guideline posters were displayed in the wards and operating theatres (vii) the principal goal was to achieve compliance with the developed guidelines in the hospital.

3.2.5 Ethical issues

As this study involved an analysis of patient records, ethical issues arise in relation to confidentiality and release of data. A unique non-patient identifiable code was allocated to each record to enable re-identification of the record if necessary. The key to the code was held by the Chief Pharmacist, which does not leave the hospital. Any coded data to leave the hospital was kept secure in accord with National Health and Medical Research Council [50] guidelines and only group data released from the research.

3.2.6 Patient groups

Patients were categorised into five groups based on their age. Patients of less than 30 days of age were neonates, one month to one-year infants, one to two years' toddlers, three to twelve years' children, and thirteen to eighteen years of age teenagers.

3.2.7 Definitions

An appropriate dose was classified as one prescribed within ±25% of the recommended dose. The designated dosage error of ±25% was based around common variability allowed in dosage forms and bio-equivalency studies. An appropriate choice of the drugs / combination of drugs were those prescribed as recommended in the Australian

Therapeutic Guidelines. Theatre antibiotics were the antibiotics prescribed in the theatre as a prophylactic cover. Ward antibiotics were the antibiotics prescribed postoperatively in the ward. Total antibiotic choice was the choice of the drugs / combination of drugs prescribed according to the guidelines in the theatre and ward combined. Theatre dosage was the dosage of theatre antibiotics. Ward dosage was the dosage of the ward antibiotics. Total dosage was the dosage of all the antibiotics prescribed in the theatre and ward together. Total appropriateness was the level of appropriateness of a combination of the choice and dosage of antibiotics prescribed in the theatre and ward in accordance with the guidelines. Total analgesic dosage was the dosage of all oral analgesics prescribed in the ward.

3.2.8 Statistical Evaluation

The study design was a pre-post time series incorporating control groups. Group 2 data was used to evaluate the antibiotic prescribing compared with a Group 1 population undergoing the same procedure. Populations were matched for number of patients included in each group, age and length of stay were tested using independent sample t-tests. Differences in the choice, dosage of antibiotic, and gender were evaluated using χ^2 analysis. One was added to the fields where zero was the result in a cell and analysed using χ^2 analysis. Bonferroni method was used to control the alpha level for multiple comparisons. Multiple regression analysis is used to evaluate the post-intervention group following the release of guidelines. Based on α=0.05 and β=0.2 and a 20% change in prescribing appropriateness estimated approximately from 60-80% require a sample of 80 patients in each group to achieve statistical significance. Control groups were analysed for any change over the pre and post total periods of the study.

3.2.9 Approvals

This study was approved by (i) Curtin University of Technology, Division of Health Sciences (ii) Cutin University of Technology, Human Research Ethics Committee (iii) Princess Margaret Hospital for Children, Head, Department of General Pediatric Surgery (iv) King Edward Memorial and Princess Margaret Hospitals Ethics Committee (v) Fremantle Hospital, Head, Department of Surgery (vi) Fremantle Hospital Ethics Committee (vii) Royal Children Hospital, Head, Department of General Pediatric Surgery (viii) Royal Women and Royal Children Hospitals Ethics Committee

3.3.0 Data analysis

The data was evaluated against Australian National Therapeutic Guidelines for antibiotics (ANTG)[51] and hospital in-house guidelines for appendectomy procedure, which was written in detail according to the ANTG. Physicians' prescribing of analgesic dosages was evaluated against Australian National Therapeutic Guidelines (ANTG) for paracetamol[52]. The stated dosage is: paracetamol - 15 mg/kg/dose orally, every 4 to 6 hours, to a maximum of 90 mg/kg/day. Analgesic and antibiotic dosage was calculated according to the product of the weight of the patient and the recommended dose per kilogram. Antibiotic guidelines were summarized in the Table 3.2.

Table 3. 2 PMH in-house antibiotic guidelines for appendectomy procedure

Category	Prophylaxis (at the time of induction)	Post-operative treatment	
		Inflamed appendix	Peritoneal soiling / peritonitis detected
Normal patient	Cefotetan 50mg/kg single dose (maximum dose 1g)	Ticarcillin / Clavulanic acid (Timentin®) 50mg/kg (as Ticarcillin) (maximum dose 3g) 2doses 6 hours apart	Ticarcillin / Clavulanic acid (Timentin®) 50 mg/kg (as Ticarcillin) (maximum dose 3g) four times daily for up to 5 days
Non-anaphylactic penicillin allergy patients	Cefotetan 50 mg/kg single dose (maximum dose 1g)	Ceftriaxone 50 mg/kg (maximum dose 1g) as a single dose with Metronidazole 12.5 mg/kg IV (maximum dose 500 mg) as single dose given 6 hours post-operatively	Ceftriaxone 50 mg/kg (maximum dose 1g) once daily with Metronidazole 12.5 mg/kg IV (maximum dose 500mg) twice daily for 5 days
Anaphylactic penicillin allergy patients	Clindamycin 10 mg/kg IV (maximum dose 600 mg) with Gentamicin 7 mg/kg IV single dose	Clindamycin 10 mg/kg IV (maximum dose 600 mg) 2 doses given 6 hours apart starting 6 hours post-operatively with Gentamicin 7mg/kg IV single dose (if Gentamicin has been given as prophylaxis at induction then no further dose is required)	Clindamycin 10 mg/kg IV (maximum dose 600 mg) four times daily with Gentamicin 7 mg/kg once daily for 5 days

3.4 Results

3.4.1 Patient demographic comparisons

3.4.1.1 Patient group comparisons

A total of 207 patients in test-1&2 groups, 125 in control-1&2 and 224 in control-3&4 groups were included in this study (Table 3.3). No significant difference was found between the gender and mean age of patients in each test and control groups ($p > 0.05$) (Table 3.4&3.5). There was a significant difference in the mean age of patients between test-1 & control-1 ($p < 0.001$) and test-2 & control-2 groups ($p < 0.001$) and no difference was found between test-1 & control-3 ($p = 0.196$) and test-2 & control-4 groups ($p = 0.138$) (Table 3.6).

Table 3. 3 Patient group comparisons in the test and control groups

Groups	**Test-1**			**Test-2**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Infant	-	-	-	1	-	1
Toddler	1	-	1	2	-	2
Children	38	32	70	45	31	76
Teenager	18	13	31	14	12	26
Total	57	45	102	62	43	105
	Control-1			**Control-2**		
Children	11	12	23	4	4	8
Teenager	31	45	76	11	7	18
Total	42	57	99	15	11	26
	Control-3			**Control-4**		
Toddler	-	-	-	2	2	4
Children	45	32	77	53	29	82
Teenager	28	14	42	9	10	19
Total	73	46	119	64	41	105

3.4.1.2 Gender comparisons

Table 3. 4 Patient gender statistics in the test and control groups

Groups	Male	Female	P value
Test-1	57	45	0.645
Test-2	42	43	
Control-1	42	57	0.164
Control-2	15	11	
Control-3	73	46	0.952
Control-4	64	41	

3.4.1.3 Mean age comparisons

Table 3. 5 Mean age of patients in each group

	Type	Number	Mean (years)	P value
Age in years	Test-1	102	10.72	0.437
	Test-2	105	11.04	
	Control-1	99	14.01	0.556
	Control-2	26	14.40	
	Control-3	119	11.30	0.052
	Control-4	105	10.37	

Table 3. 6 Comparison of mean age of patients between test and control groups

	Type	Number	Mean (years)	P value
Age in years	Test-1	102	10.72	0.000
	Control-1	99	14.01	
	Test-2	102	10.72	0.000
	Control-2	26	14.40	
	Test-1	102	10.72	0.196
	Control-3	119	11.30	
	Test-2	105	10.72	0.138
	Control-4	105	10.37	

3.4.2 Diagnoses and Histopathology

3.4.2.1 Principal diagnosis

The principal diagnosis of all the patients is summarized in the Tables 3.7-3.9.Appendicitis was diagnosed in 56% of patients in test-1&2, 40% in control-1&2 and 60% in controls-3&4 groups and acute appendicitis in 21% of patients in test-1&2, 57% in control-1&2 and 16% in control-3&4 groups.

Table 3. 7 Principal diagnosis of appendectomy patients in test-1&2 hospitals

Diagnosis	Test-1*		Test-2*		Total
	Female	Male	Female	Male	
Appendicitis	32	35	23	27	117
Acute appendicitis	5	10	11	18	44
Appendicitis with peritonitis	1	2	-	1	4
Gangrenous appendicitis	-	1	1	2	4
Perforated appendicitis	3	6	2	3	14
Acute suppurative appendicitis	4	3	-	6	13
Acute and gangrenous appendicitis	-	-	1	-	1
Acute inflamed appendix	-	-	4	2	6
Acute perforated appendicitis	-	-	1	1	2
Gangrenous and perforated appendicitis	-	-	-	2	2
Total	**45**	**57**	**43**	**62**	**207**

*Number of patients

Table 3. 8 Principal diagnosis of appendectomy patients in control-1&2 hospitals

Diagnosis	Control-1*		Control-2*		Total
	Female	Male	Female	Male	
Appendicitis	22	12	7	9	50
Acute appendicitis	35	30	2	5	72
Acute and perforated appendicitis	-	-	1	-	1
Acute suppurative appendicitis	-	-	1	1	2
Total	**57**	**42**	**11**	**15**	**125**

*Number of patients

Table 3. 9 Principal diagnosis of appendectomy patients in control-3&4 hospitals

Diagnosis	Control-3*		Control-4*		Total
	Female	Male	Female	Male	
Appendicitis	29	42	25	27	123
Acute appendicitis	6	14	6	11	37
Appendicitis with peritonitis	1	-	-	1	2
Gangrenous appendicitis	1	1	1	4	7
Perforated appendicitis	5	13	4	7	29
Acute suppurative appendicitis	1	-	-	4	5
Acute and gangrenous appendicitis	-	-	-	1	1
Acute suppurative and perforated	-	1	-	-	1
Acute perforated appendicitis	1	2	-	1	4
Gangrenous and perforated appendicitis	1	-	-	1	2
Appendix with faecolith	1	-	-	1	2
Acute inflamed appendix	-	-	1	-	1
Chronic appendicitis	-	-	-	2	2
Other complications	-	-	4	4	8
Total	**46**	**73**	**41**	**64**	**224**

*Number of patients

3.4.2.2 Histopathology descriptions

It was found that 14% of the patients in test-1&2 & control-3&4 and 10% in control-1&2 groups who were diagnosed as appendicitis were found to have a normal appendix. The histopathological descriptions are summarized in the Tables 3.10-3.12.

Table 3. 10 Histopathology descriptions of test-1&2 groups

Appendix pathology	Test-1*		Test-2*		Total
	Female	Male	Female	Male	
Normal appendix	6	8	8	7	29
Suppurative appendicitis	-	2	4	11	17
Appendix with perforation	1	1	1	-	3
Gangrenous appendicitis	1	1	2	-	4
Appendix with pin worms	3	2	3	-	8
Appendix with faecolith	1	-	-	-	1
Acute appendicitis	19	27	7	5	58
Acute appendicitis with peritonitis	3	1	-	-	4
Gangrenous appendix with peritonitis	1	2	-	-	3
Suppurative appendicitis with peritonitis	7	7	-	-	14
Acute appendicitis with pin worms	1	-	-	-	1
Gangrenous appendicitis with perforation and peritonitis	-	1	-	-	1
Acute and gangrenous appendicitis	-	1	2	5	8
Peritonitis appendicitis with pin worms	-	1	-	-	1
Gangrenous appendicitis with perforation	-	-	2	2	4
Gangrenous and suppurative appendicitis with peritonitis	1	-	-	-	1
Acute inflammation and perforation	1	-	-	-	1
Acute inflammation with peritonitis	-	-	-	1	1
Acute appendicitis with perforation	1	-	-	1	2
Acute inflamed appendicitis	-	-	-	2	2
Acute suppurative appendicitis	-	-	7	18	25
Minor changes of uncertain significance	-	-	1	2	3
Data not available	-	2	6	8	16
Total	**45**	**57**	**43**	**62**	**207**

*Number of patients

Table 3. 11 Histopathology descriptions of control-1&2 groups

Appendix pathology	Control-1*		Control-2*		Total
	Female	Male	Female	Male	
Normal appendix	10	2	-	-	12
Acute and gangrenous appendicitis	-	1	-	-	1
Acute appendix	-	2	-	-	2
Appendix with acute inflammation	1	2	-	-	3
Appendix with acute inflammation and pin worms	1	-	-	-	1
Acute suppurative appendicitis with perforation	-	1	-	-	1
Acute suppurative appendicitis	40	28	2	-	70
Appendix with faecolith	-	1	-	-	1
Appendix with pin worms	-	1	-	-	1
Gangrenous appendicitis	-	3	-	-	3
Perforated appendix	1	-	-	-	1
Data not available	-	1	13	11	25
Total	**42**	**57**	**15**	**11**	**124**

*Number of patients

Table 3. 12 Histopathology descriptions of control-3&4 groups

Appendix pathology	Control-3*		Control-4*		Total
	Female	Male	Female	Male	
Normal appendix	6	5	12	8	31
Acute appendicitis with inflammation	1	1	-	-	2
Acute appendicitis with perforation	2	3	1	-	6
Acute appendicitis	4	20	6	9	39
Acute appendix with pin worms	1	-	-	-	1
Acute inflammation	3	3	-	-	6
Acute inflammation and necrosis	-	2	-	-	2
Acute inflammation and perforation	3	1	-	-	4
Acute suppurative appendicitis	8	6	6	19	39
Gangrenous and suppurative appendicitis	-	1	-	-	1
Gangrenous appendicitis with perforation	3	12	3	4	22
Gangrenous appendicitis	5	6	6	8	25
Necrosis & perforation	4	-	-	-	4
Suppurative appendicitis with perforation	3	2	-	1	6
Suppurative appendicitis	3	7	-	6	16
Acute suppurative appendicitis with perforation	-	-	1	-	1
Appendix with pin worms and mild inflammation	-	-	2	1	3
Appendix with mild inflammation	-	-	1	1	2
Suppurative appendicitis with acute inflammation	-	-	1	-	1
Suppurative appendicitis with pin worms	-	-	-	1	1
Data not available	1	3	2	6	12
Total	**46**	**73**	**41**	**64**	**224**

*Number of patients

3.4.3 Theatre and ward antibiotics

3.4.3.1 Theatre antibiotic choices

Six different types of inappropriate prophylactic antibiotic regimens were prescribed in test-1, which was reduced to three inappropriate regimens in test-2, 7 to 2 from control-1 to control-2, and 5 in both control-3&4 groups. Prophylactic antibiotic administration in test and control groups is summarized in the Tables 3.13-3.15.

Table 3. 13 Prophylactic antibiotic administration in test-1&2 hospitals

Drug/s prescribed	Test-1*	Test-2*
Metronidazole	24	6
Ceftriaxone	4	6
Cefotaxime	3	-
Metronidazole + Ceftriaxone	44	-
Metronidazole + Cefotaxime	8	-
Metronidazole + Cephamandole	1	-
Cefotetan	-	68
Timentin	-	7
No prophylaxis	18	18
Total	**102**	**105**

*Number of patients

Table 3. 14 Prophylactic antibiotic administration in control-1&2 hospitals

Drug/s prescribed	Control-1*	Control-2*
Cefotetan	14	7
Metronidazole	2	4
Cephalothin	1	-
Amoxicillin	1	-
Ceftriaxone	2	-
Cephazolin	5	1
Cefotetan + Metronidazole	13	3
Metronidazole + Cephazolin	15	-
Cephazolin + Metronidazole	1	5
Cefotaxime + Metronidazole	1	-
Metronidazole + Ceftriaxone	26	-
Metronidazole + Amoxicillin + Gentamicin	1	1
Cefotetan + Cefotaxime + Metronidazole	1	-
Cephazolin + Amoxicillin + Gentamicin + Metronidazole	1	-
No prophylaxis	14	5
Total	**99**	**26**

*Number of patients

Table 3. 15 Prophylactic antibiotic administration in control-3&4 hospitals

Drug/s prescribed	Control-3*	Control-4*
Amoxicillin	1	1
Gentamicin	6	-
Cephazolin	8	14
Metronidazole	7	10
Metronidazole + Cephazolin + Gentamicin	3	3
Amoxycillin + Gentamicin + Metronidazole	7	2
Cephazolin + Metronidazole	50	47
Gentamicin + Metronidazole	2	1
Amoxycillin + Metronidazole	2	2
Amoxycillin + Metronidazole + Cephazolin	1	-
Ampicillin + Gentamicin + Metronidazole	-	4
Benzylpenicillin + Metronidazole + Gentamicin	-	2
Amoxicillin + Gentamicin	-	1
No prophylaxis	32	18
Total	**119**	**105**

*Number of patients

3.4.3.2 Theatre antibiotic choice comparisons

The number of patients receiving appropriate theatre antibiotics choice based on guidelines in test-1 was nil, control-1 46, and control-3 63. There was a significant improvement in the prescribing of appropriate theatre antibiotics in test-2 group patients following the intervention ($p < 0.001$), and neither of the control pairs (control-2 and 4) showed an improvement over the same period ($p > 0.05$) (Tables 3.16).

Table 3. 16 Comparison of theatre prophylaxis between test and control groups

Category	Appropriate prophylaxis*	Inappropriate prophylaxis*	No prophylaxis*	Total*
Test-1		84	18	102
Test-2	72	15	18	105
Total	72	99	36	207
P value	0.000			
Control-1	46	39	14	99
Control-2	16	5	5	26
Total	62	43	19	124
P value	0.187			
Control-3	63	24	32	119
Control-4	56	29	20	105
Total	119	53	52	224
P value	0.248			

*Number of patients

3.4.4 Comparison of prescribing of cephalosporin antibiotics before and after the release of health department circular in test-1 and control-1 groups

During the pre-intervention study a Health Department circular was released to all hospitals in Western Australia on 8th March 2001. It proposed, "supply of third generation cephalosporins (particularly ceftriaxone) to operating theatres should cease wherever possible, and that their use for surgical prophylaxis in operating theatres and for the purpose of peri-operative antibiotic prophylaxis use should be avoided". An evaluation of its effect in the pre-intervention period in test-1 was 35/77 (45.5%) patients were prescribed ceftriaxone prior to the circular and 13/25 (52%) following its release (p=0.367). In control-1 there were 23/72 (32%) patients prescribed it prior to the circular

and 6/27 (22.2%) following the its release (p=0.245). Both groups did not show any significant change (p>0.05) (Table 3.17).

Table 3. 17 Comparison of prescribing of cephalosporin antibiotics before and after the release of health department circular Test-1 and Control-1

Category	Control-1		Test-1	
	Before	After	Before	After
Number of patients on cefotaxime	1	1	9	2
Number of patients on ceftriaxone	23	6	35	13
Number of patients on appropriate prophylaxis	33	14	0	0
Number of patients on inappropriate prophylaxis	28	10	65	19
Number of patients on no antibiotic prophylaxis	11	3	12	6
Total number of patients in the study	72	27	77	25
% of patients on third generation cephalosporins among patients prescribed antibiotics	39.3	29.1	67.6	78.9

3.4.5 Comparison of patients on unnecessary prophylactic antibiotics between test and control groups

The number of patients on unnecessary (not recommended) prophylactic antibiotic doses other than inappropriate antibiotics prescribed were 52 in test-1, 45 in control-1 and 13 in control-3 and changed to 0 in test-2, 4 in control-2, and 13 in control-4 groups (Table 3.18). There was a significant improvement from test-1 and control-1 to test-2 and control-2 (p<0.05) and no change from control-3 to control-4 (p>0.05) found (Table 3.19).

Table 3. 18 Comparison of patients on unnecessary prophylactic antibiotic doses

Antibiotic	Test-1	Test-2	Control-1	Control-2	Control-3	Control-4
Ampicillin						4
Amoxicillin			2	1	10	2
Benzylpenicillin						2
Cefotaxime			1			
Gentamicin			1		3	3
Metronidazole	52		41	3		
Total*	52		45	4	13	13

*Number of patients

Table 3. 19 Prescribing pattern of unnecessary prophylactic antibiotic doses in the total doses

Groups	Number of unnecessary theatre antibiotic doses administered*	P value
Test-1	52/137	<0.001
Test-2	0/87	
Control-1	45/148	0.047
Control-2	4/31	
Control-3	13/163	0.961
Control-4	13/160	

*Number of patients

3.4.6 Theatre antibiotic doses

The number of theatre antibiotic doses prescribed out of the total number of patients on theatre antibiotics was 137/84 (1.6) in test-1, 148/85 (1.7) in control-1, 163/87 (1.8) in control-3 changed to 87/87 (1) in test-2, 31/21 (1.4) in control-2 and 160/87 (1.8) in control-4 group following the intervention (Table 3.20).

Table 3. 20 Number of theatre antibiotic doses out of number of patients on theatre antibiotics

Groups	Number of theatre antibiotic doses	Number of patients on theatre antibiotics	No. of doses/no. of patients	P value
Test-1	137	84	1.6	<0.001
Test-2	87	87	1	
Control-1	148	85	1.7	
Control-2	31	21	1.4	
Control-3	163	87	1.8	
Control-4	160	87	1.8	

3.4.7 Ward antibiotic choice comparisons

There was a significant improvement in the prescribing of appropriate ward antibiotic choices from 49/102 to 89/105 patients in test-1&2 ($p < 0.001$) and a non-significant diminution was noticed in the control groups ($p > 0.05$) (Table 3.21).

Table 3. 21 Comparison of ward antibiotics between test and control groups

Category	Appropriate ward antibiotics*	Inappropriate ward antibiotics*	No ward antibiotics*	Total*
Test-1	49	40	13	102
Test-2	89	4	12	105
Total	138	44	25	207
P value	0.000			
Control-1	24	17	58	99
Control-2	9	8	9	26
Total	33	25	67	125
P value	0.084			
Control-3	91	6	22	119
Control-4	75	3	27	105
Total	166	9	49	224
P value	0.335			

*Number of patients

3.4.8 Total antibiotic choice comparisons

None of the patients were on appropriate total antibiotic choices in test-1, 8 in control-1 and 43 in control-3 with a significant improvement as was evident in test-2 ($p < 0.001$) group following the intervention (Table 3.22).

Table 3. 22 Comparison of total antibiotic choices between test and control groups

Category	Appropriate total antibiotic choice*	Inappropriate total antibiotic choice*	No total antibiotics*	Total*
Test-1		100	2	102
Test-2	60	42	3	105
Total	60	142	5	207
P value	0.000			
Control-1	8	86	5	99
Control-2	6	20		26
Total	14	106	5	125
P value	0.058			
Control-3	43	73	3	119
Control-4	40	62	3	105
Total	83	135	6	224
P value	0.937			

*Number of patients

3.4.9 Antibiotic dosage

3.4.9.1 Individual theatre antibiotic dosage

Individual theatre drug dosage appropriateness was summarized in Tables 3.23-3.25.

Table 3. 23 Theatre antibiotic dosage appropriateness in Test-1&2 groups

Drug name		Test-1	Test-2
Cefotaxime	Appropriate	6	1
	Inappropriate	5	-
Ceftriaxone	Appropriate	10	4
	Inappropriate	39	1
Metronidazole	Appropriate	51	11
	Inappropriate	25	1
Cefotetan	Appropriate	-	67
	Inappropriate	-	3
Timentin	Appropriate	-	12
	Inappropriate	-	-
Gentamicin	Appropriate	-	5
	Inappropriate	-	1
Cephamandole	Appropriate	1	-
	Inappropriate	-	-
Amoxycillin	Appropriate	-	1
	Inappropriate	-	-

Table 3. 24 Theatre drugs dosage appropriateness in control-1&2 groups

Drug name		Control-1	Control-2
Amoxycillin	Appropriate	1	-
	Inappropriate	2	1
Cefotaxime	Appropriate	2	-
	Inappropriate		-
Cefotetan	Appropriate	6	6
	Inappropriate	23	-
Ceftriaxone	Appropriate	27	-
	Inappropriate	2	-
Cephalothin	Appropriate	-	-
	Inappropriate	2	-
Cephazolin	Appropriate	19	6
	Inappropriate	2	-
Gentamicin	Appropriate	2	1
	Inappropriate	-	-
Metronidazole	Appropriate	59	13
	Inappropriate	5	-

Table 3. 25 Theatre drugs dosage appropriateness in control-3&4 groups

Drug name		Control-3	Control-4
Amoxycillin	Appropriate	10	3
	Inappropriate	1	4
Cephazolin	Appropriate	48	40
	Inappropriate	14	22
Gentamicin	Appropriate	11	7
	Inappropriate	7	6
Metronidazole	Appropriate	59	44
	Inappropriate	13	25
Ampicillin	Appropriate	-	2
	Inappropriate	-	1
Benzylpenicillin	Appropriate	-	2
	Inappropriate	-	-

3.4.5.2 Total theatre antibiotic dosage comparisons

Appropriate theatre antibiotic dosages were increased from 68/137 to 100/106 prescriptions in the test groups ($p < 0.001$), and a significant diminution in the appropriateness of antibiotic dosage prescribing was seen in control groups 1&2 and 3&4 when evaluated individually ($p < 0.05$), which is summarised in Table 3.26.

Table 3. 26 Comparison of theatre antibiotic dosages between test and control groups

Category	Appropriate antibiotic dosage	Inappropriate antibiotic dosage	Total
Test-1	68	69	137
Test-2	100	6	106
Total	168	75	243
P value	0.000		
Control-1	118	38	156
Control-2	30	1	31
Total	148	39	187
P value	0.020		
Control-3	128	35	163
Control-4	99	58	157
Total	227	93	320
P value	0.003		

3.4.5.3 Individual ward antibiotic dosage

Individual ward drug dosage appropriateness is summarised in Tables 3.27-3.29.

Table 3. 27 Ward drugs dosage appropriateness in test-1&2 groups

Drug name		Test-1	Test-2
Amoxycillin	Appropriate	17 (40)*	12 (27)
	Inappropriate	13 (33)	7 (21)
Augmentin	Appropriate	2 (2)	5 (6)
	Inappropriate	4 (4)	2 (3)
Cefotaxime	Appropriate	40 (98)	6 (10)
	Inappropriate	9 (18)	-
Ceftriaxone	Appropriate	16 (16)	26 (29)
	Inappropriate	87 (90)	1 (1)
Gentamicin	Appropriate	7 (7)	42 (42)
	Inappropriate	20 (20)	1 (3)
Metronidazole	Appropriate	33 (120)	51 (100)
	Inappropriate	60 (369)	33 (68)
Timentin	Appropriate	-	226 (589)
	Inappropriate	-	10 (25)
Cephalexin	Appropriate	-	3 (5)
	Inappropriate	6 (11)	-
Cephalothin	Appropriate	-	-
	Inappropriate	3 (7)	1 (1)
Cefotetan	Appropriate	-	3 (3)
	Inappropriate	-	-

*Sum of doses are in the parenthesis

Table 3. 28 Ward drugs dosage appropriateness in control-1&2 groups

Drug name		Control-1	Control-2
Amoxycillin	Appropriate	-	4 (26)*
	Inappropriate	17 (40)	2 (7)
Augmentin	Appropriate	1 (1)	-
	Inappropriate	9 (13)	-
Cefotetan	Appropriate	-	1 (6)
	Inappropriate	4 (6)	-
Ceftriaxone	Appropriate	41 (41)	6 (19)
	Inappropriate	1 (1)	-
Cephalexin	Appropriate	5 (8)	-
	Inappropriate	5 (12)	-
Cephazolin	Appropriate	5 (10)	1 (4)
	Inappropriate	-	1 (2)
Gentamicin	Appropriate	13 (13)	2 (2)
	Inappropriate	-	-
Metronidazole	Appropriate	74 (117)	13 (57)
	Inappropriate	20 (38)	4 (22)
Roxithromycin	Appropriate	-	1 (5)
	Inappropriate	-	-
Timentin	Appropriate	-	1 (4)
	Inappropriate	-	-

*Sum of doses are in the parenthesis

Table 3. 29 Ward drugs dosage appropriateness in control-3&4 groups

Drug name		Control-3	Control-4
Amoxycillin	Appropriate	37 (272)*	6 (56)
	Inappropriate	18 (162)	8 (41)
Cefotaxime	Appropriate	4 (62)	3 (24)
	Inappropriate	-	-
Cephalexin	Appropriate	14 (41)	5 (8)
	Inappropriate	2 (4)	-
Cephazolin	Appropriate	63 (525)	43 (412)
	Inappropriate	32 (294)	20 (188)
Gentamicin	Appropriate	43 (137)	19 (78)
	Inappropriate	13 (29)	7 (24)
Metronidazole	Appropriate	68 (371)	27 (199)
	Inappropriate	95 (704)	60 (497)
Penicillin	Appropriate	2 (36)	-
	Inappropriate	1 (3)	-
Augmentin	Appropriate	2	2 (3)
	Inappropriate	12	-
Flucloxacillin	Appropriate	21	-
	Inappropriate	-	-
Ampicillin	Appropriate	-	-
	Inappropriate	-	1 (3)
Benzylpenicillin	Appropriate	-	7 (46)
	Inappropriate	-	-
Ceftazidime	Appropriate	-	-
	Inappropriate	-	1 (35)
Cephalothin	Appropriate	-	1 (3)
	Inappropriate	-	-
Clindamycin	Appropriate	-	1 (1)

	Inappropriate	-	-
Timentin	Appropriate	-	-
	Inappropriate	-	1 (14)

*Sum of doses are in the parenthesis

3.4.5.4 Total ward antibiotic dosage comparisons

The frequency of appropriate ward antibiotic dosages significantly increased in the test groups from 492/947 (52%) to 970/1047 (92.6%) and no significant change was noticed in control-1&2 from 392/491 (79.8%) to 70/81 (86.4%) and a statistically marginal improvement in control-3&4 from 525/750 (70%) to 320/454 (70.5%) (Table 3.30).

Table 3. 30 Comparison of ward antibiotic dosage between test and control groups

Category	No. of appropriate antibiotic dosages	No. of inappropriate antibiotic dosages	Total
Test-1	492	455	947
Test-2	970	77	1047
Total	1462	532	1994
P value	0.000		
Control-1	392	99	491
Control-2	70	11	81
Total	462	110	572
P value	0.378		
Control-3	525	225	750
Control-4	320	134	454
Total	845	359	1204
P value	0.048		

3.4.5.5 Total antibiotic dosage comparisons

The total antibiotic dosages (theatre and ward antibiotic dosage together) were significantly improved in test-1&2 and significantly decreased in control-1&2 groups and no effect was noticed in control-3&4 groups (Table 3.31).

Table 3. 31 Comparison of total antibiotic dosage between test and control groups

Category	No. of patients on appropriate total antibiotic dosage	No. of patients on inappropriate total antibiotic dosage	Total
Test-1	-	89	89
Test-2	60	43	103
Total	60	132	192
P value	0.000		
Control-1	9	85	94
Control-2	7	19	26
Total	16	104	120
P value	0.033		
Control-3	14	102	116
Control-4	4	99	103
Total	18	201	219
P value	0.084		

3.4.6 Total appropriateness

Patients achieving total appropriateness were 0/102 in test-1, 0/99 control-1 and 7/119 in control-3 changed to 46/105 in test-2 and 4/26 in control-2 and 1/105 in control-4. There was a statistical significant improvement was found in both test-1&2 and control-1&2 groups (Table 3.32).

Table 3. 32 Comparison of total appropriateness between test and control groups

Category	No. of patients on total appropriateness	No. of patients on total inappropriateness	Total
Test-1		100	100
Test-2	46	57	103
Total	46	157	203
P value	0.000		
Control-1		94	94
Control-2	4	22	26
Total	4	116	120
P value	0.000		
Control-3	7	110	117
Control-4	1	102	103
Total	8	212	220
P value	0.139		

3.4.7 Prescribing pattern of choice and dosage of antibiotics during the post-intervention period

There was no significant difference in the prescribing pattern of choice and dosage of theatre and ward antibiotic during the five month post-intervention study period in Test-2. Bonferroni method was used to control the alpha level for multiple comparisons. The data was summarised in the Table 3.33.

Table 3. 33 Monthly comparison of choice and dosage of theatre and ward antibiotic during the post-intervention period

Months	Category	Theatre antibiotics*	Ward antibiotics*	Theatre dosage*	Ward dosage*
December 01	App	15	16	20	1
	Inapp	5	1		2
January 02	App	14	17	16	4
	Inapp	3	2	1	3
February 02	App	20	25	25	4
	Inapp	5			6
March 02	App	12	21	13	3
	Inapp	3	1	2	2
April 02	App	9	10	8	1
	Inapp	1		2	1
P value		0.909	0.483	0.088	0.904

*Number of patients

3.4.8 Mean length of stay

The mean length of stay was 3.34 days in test-1, 3.83 in test-2, 2.27 in control-1, 2.65 in control-2, 4.4 in control-3 and 4.2 days in control-4 groups. There was no significant difference in the mean length of stay between test-1&2 (p = 0.139), control-1&2 (p = 0.102) and control-3&4 groups (p = 0.610) (Table 3.33). The mean length of stay between test-1&2 between perforated appendices 8.4 and 5.5 days (p = 0.289), gangrenous and/or perforated appendices 5.8 and 4.9 days (p = 0.518) and normal appendices 2.9 and 4.5 days (p = 0.121) is summarised in the Table 3.34.

Table 3. 34 Total mean length of stay in days in each group

	Type	Number	Mean (days)	P value
Length of stay in days	Test-1	102	3.34	0.139
	Test-2	105	3.83	
	Control-1	99	2.27	0.102
	Control-2	26	2.65	
	Control-3	119	4.4	0.610
	Control-4	105	4.2	

A significant different in the length of stay was found between patients identified as gangrenous and/or perforated and normal appendices in Test-1 ($p = 0.025$) and no significant difference in Test-2 ($p = 0.733$) was found.

Table 3. 35 Comparison of mean of length of stay in different pathologies of appendix

Category	Groups	Number	Mean (days)	P value
Normal appendix	Test-1	14	2.9	0.121
	Test-2	15	4.5	
Perforated appendix	Test-1	5	8.4	0.289
	Test-2	6	5.5	
Gangrenous and/or perforated appendix	Test-1	12	5.8	0.518
	Test-2	15	4.9	

3.4.9 Analgesic dosage

3.4.9.1 Individual ward analgesic dosage

Most of the patients were on paracetamol and/or paracetamol with codeine analgesics. Few patients were on ibuprofen alone or in combination with paracetamol and / or paracetamol with codeine analgesics (Table 3.36).

Table 3. 36 Analgesic dosage appropriateness in test and control groups

Category	Paracetamol	Liquigesic Co®	Panadeine®	Panadeine forte®	Ibuprofen
Test-1					
Appropriate	63 (217)*	15 (65)	25 (97)	13 (54)	43 (112)
Inappropriate	20 (80)	32 (97)	3 (10)	8 (31)	-
Test-2					
Appropriate	90 (511)	34 (111)	22 (90)	31 (111)	67 (222)
Inappropriate	2 (2)	7 (17)	3 (11)	2 (6)	2 (3)
Control-1					
Appropriate	57 (201)	13 (39)	19 (69)	27 (102)	9 (24)
Inappropriate	14 (40)	6 (9)	4 (11)	2 (4)	-
Control-2					
Appropriate	21 (93)	6 (25)	2 (7)	5 (14)	5 (9)
Inappropriate	2 (3)	1 (3)	-	1 (5)	-
Control-3					
Appropriate	81 (849)	-	1 (2)	-	19 (62)
Inappropriate	51 (527)	-	-	-	1 (7)
Control-4					
Appropriate	80 (765)	-	-	-	28 (58)
Inappropriate	33 (281)	-	-	-	2 (2)

*Sum of doses are in parenthesis

3.4.9.2 Total ward analgesic dosage comparisons

Analgesics dosage prescribing was significantly improved from 159/222 (71.6%) to 244/260 (94%) doses following the intervention in test-1&2 ($p < 0.001$) and non-significant from 125/151 (82.8%) to 38/42 (90.5%) in control-1&2 and 101/153 (66%) to 108/143 (75.5%) in control-3&4 groups ($p > 0.05$) (Table 3.37).

Table 3. 37 Patient analgesic dosage appropriateness in the test and control groups

Groups	Appropriate	Inappropriate	P value
Test-1	159	63	0.000
Test-2	244	16	
Control-1	125	26	0.205
Control-2	38	4	
Control-3	101	52	0.073
Control-4	108	35	

3.5.0 Microbiology results

3.5.1 Number of patient's culture results positive

There were seven patients cultured positive with 7 different microorganisms in test-1 and 17 with 33 in test-2, 9 with 12 in control-1, 1 with 1 in control-2, 21 with 29 in control-3 and 22 with 32 in control-4 groups (Tables 3.38 & 3.39).

Table 3. 38 Number of patients culture results positive

Group	Number of patients with organisms
Test-1	7
Test-2	17
Control-1	9
Control-2	1
Control-3	21
Control-4	22

3.5.2 Profile of organisms identified

Table 3. 39 Profile of organisms identified in the microbiology report

Organism found	Test-1	Test-2	Control-1	Control-2	Control-3	Control-4
Gram-positive	2	11	1	-	2	6
Gram-negative	1	9	2	1	15	13
Anaerobe/s	3	10	1	-	6	8
Mixed aerobes and anaerobes	1	3	8	-	6	5
Total*	7	33	12	1	29	32

*Number of organisms

3.6 Discussion

3.6.1 Patient demographics

There was no significant difference between patient demographic statistics within each group. But there was a significant difference in the mean age of patients between Test-1&2 and Control-1&2 groups, giving concerns of a varied population effect. And also,

there was a significant difference in the number of patients included between Control-1&2 groups. These were the only possible comparable populations available in Western Australia. Hence, a second control group (control-3&4) was identified in Victoria, which had similar patient characteristics to Test-1&2 groups.

Surgeons at PMH also practice at several other hospitals in Western Australia. This made it difficult to evaluate the impact of an intervention at PMH without a contaminated control group. Even though most of the surgeons at FH were different from PMH, the number of pediatric patients admitted for appendectomy surgery was much lower than PMH and they were more mature. This created a problem of insufficient and unmatched patient numbers. The investigators identified RCH located distant from PMH. This group would control for national influences on antibiotic prescribing during the study.

3.6.2 Diagnosis and Histopathology

The diagnosis of normal pathology in this study was 10 - 14%, which is in the similar to other studies of 10 - 30% [2]. Prompt treatment of appendicitis is important in preventing further morbidity and mortality; a margin of error in over diagnosis is acceptable. In this study, 13.8 – 20.6% of females (Test-1&2: 15.9%, Control-1&2: 13.8% and Control-3&4: 20.6%) and 3.7 – 12.6% of males (Test-1&2: 12.6%, Control-1&2: 3.7% and Control-3&4: 9.48%) had appendix specimens removed, which were histologically normal. This supports the Harding findings that pain from females is more likely to be misdiagnosed than for males[53]. He reported that 62% of appendix specimens removed from females aged 11-20 were histologically normal, and although he accepted that pain from the ovary might mimic appendicitis, he believed there might be a large psychological element because of the important changes that occur in the lives of females at this age [54].

The perforated appendix prevalence varied from 2 - 20% in this study (Test-1&2: 5.7%, Control-1&2: 2% and Control-3&4: 20.2%). This is in the lower end of the published studies, which are 30-45% [2]. The histopathological findings by a microbiologist (Test-1&2: 14.1%, Control-1&2: 6.25% and Control-3&4: 32.5%) of gangrenous and/or perforated appendicitis was higher than actual diagnosis (Test-1&2: 11.1%, Control-1&2: 0.8% and Control-3&4: 19.6%) by physicians in the test as well as in control groups in this study.

Appendiceal rupture accounts for a majority of the complications of appendicitis. Factors that increase the rate of perforation are delayed presentation to medical care, age, and hidden location of appendix. Brief periods of in-hospital observation potentially improve the diagnostic accuracy. Appendicitis poses special difficulties in young children due to their being unable to relate a history, often have abdominal pain from other causes and may have more non-specific signs and symptoms[6]. These factors contribute to a perforation rate as high as 50% in children[55].

Koepsell [56] and Arnbjornsson [57] noted the incidence of perforation to be firmly related to the duration of the pre-admission stage of illness, but not to the length of the post-admission stage. White et al. [58] have suggested that hospital observation of children in whom the diagnosis of appendicitis is uncertain can improve the diagnostic accuracy of appendicitis and safely reduce the incidence of negative laparotomies without increasing perforation. Ravitch [59], on the other hand, argues for prompt surgery "on every child with abdominal pain in whom tenderness, preferably right lower quadrant, can be elicited…provided there is nothing in the history, in the physical examination, or in the laboratory studies that is incompatible with the diagnosis [60]."

A delay in treatment of more than 36 hours after parents first noticed abdominal pain was associated with a 65% or greater incidence of perforation in children. This association

underlines the importance of a high index of suspicion of childhood appendicitis. Parents need to be educated regarding abdominal pain and its related diseases. This potentially reduces the number of perforations with prompt treatment for the patient [60].

Seventy years ago, the mortality rate for patients with perforated appendix was 10 to 20% [61, 62]; one death for every 940 children in 1960's and it decreased to 0.1% in the 1990's [63]. In this study, none of the patients died due to appendicitis in the test and control groups. The risk of death from a perforated appendix has now decreased dramatically, but the morbidity rate remains high.

3.6.3 Theatre and Ward antibiotics

Some 84/102 patients were prescribed non-recommended antibiotic prophylaxis in the Test-1 group, of them, 52 patients were prescribed ceftriaxone or cefotaxime and metronidazole. Metronidazole's activity is only against anaerobes, ceftriaxone and cefotaxime cover both Gram-positive and Gram-negative organisms, and each of the three drugs individually or in combination is considered an inappropriate choice for prophylaxis in appendectomy procedures since they are not recommended in the ANTG guidelines.

According to a study conducted by the Western Australian Drugs and Therapeutics Committee, the Health Department developed recommendations for prophylaxis in surgical procedures are cephalothin (with metronidazole) or cefotetan. They proposed, "supply of third generation cephalosporins (particularly ceftriaxone) to operating theatres should cease wherever possible, and that their use for surgical prophylaxis in operating theatres and for the purpose of peri-operative antibiotic prophylaxis use should be avoided". The committee also stated that use of third generation cephalosporins in non-approved indications significantly increased the probability of organisms to exhibit

multiple antibiotic resistance will emerge, particularly vancomycin-resistant enterococci. In this study, we found that 59/102 (57.8%) of the patients that were on prophylactic antibiotics in the test-1 group were on third generation cephalosporins.

This circular issued in Western Australia during the pre-intervention phase did not show any impact on the prescribing behaviour of the surgeons evaluated in the pre-intervention group in PMH and FH, located in Western Australia. The number of patients on third generation cephalosporins (cefotaxime and ceftriaxone) among patients prescribed antibiotics for surgical prophylaxis was 23/72 (32%) before the release of the circular and changed to 6/27 (22%) after the circular in control-1 and 35/77 (45%) before and 13/25 (52%) after in test-1 group patients (Table 3.17). However, following the introduction of local treatment guidelines and implementation of the educational intervention programme in this study, 6/87 (7%) of the patients on antibiotics were on the third generation cephalosporin (ceftriaxone) in test-2 and 0/21 and in control-2. However, there was no significant improvement in control-2 in the prescribing of appropriate theatre antibiotics. This supports that locally developed guidelines are more likely to be accepted and followed than those developed regionally or nationally without local input.

The level of pre and post-operative non-recommended antibiotic combinations prescribed was common before the introduction of the intervention. These occurrences were significantly reduced following the intervention for the test group (Table 3.13). The number of prophylactic antibiotic doses prescribed was significantly reduced and equaled the number of patients in test-2 compared with the test-1 group. This was in accordance with the guidelines recommending a single dose of cefotetan as prophylaxis. This reduces the cost of antibiotics, administration costs, nursing, pharmacist and surgeon's time and potentially less adverse effects (Table 3.20).

There was a significant reduction in the number of patients on unnecessary prophylactic antibiotic doses following the intervention in test-2 and also in the control-2 group. Due to the low sample size in control-2 and the p value (p=0.047) although slightly lower than 0.05, it cannot be considered a clinically significant change. No significant change was observed in control-4 compared to control-3 group (Table 3.19). This shows clearly that the intervention had an impact on this aspect of the prescribing behaviour of surgeons.

There was a significant improvement in the prescribing of post-operative and total antibiotic choices following the intervention in this study. The number of patients on appropriate total antibiotic dosage was improved from zero to 57% (60/105). Several studies have evaluated drug usage in children[64-69], and in pediatric appendectomy[70-72], but none of the studies considered dosage prescribing appropriateness in children. Our study has identified that pharmacist intervention can influence drug dosage-prescribing appropriateness of pediatricians in pediatric settings. This study is the first of its kind to be carried out in Australia or elsewhere to include dosages.

The number of prophylactic antibiotic prescriptions on 26-50% below were 51/137, 26-50% above the recommended dose were 18/137 in Test-1 which was decreased to 2/107 on 26-50% below, 3/107 on 26-50% above, and one prescription on 76-100% above the recommended dose in Test-2. Sub-optimal dosing of antibiotics has two potential consequences: therapy failure and the possible emergence of resistance. High dosage can lead to unwanted side effects and unnecessary costs both to the patient and the society. The clinician has the ultimate responsibility to optimise the delivery of an appropriate antimicrobial agent to the site in concentrations that exceed those needed to inhibit the growth of the pathogen involved. Inappropriate use of antibiotics can lead to microbial resistance and may expose the patient to adverse effects. A continuously maintained bactericidal level of an antibacterial agent is particularly important for curing an infection and speedy recovery of the patient.

3.6.4 Total appropriateness

The total appropriateness of the prescribing was a combination of the following factors: (i) the surgeon prescribed an appropriate theatre antibiotic regimen (ii) an appropriate postoperative antibiotic regimen (iii) an appropriate theatre antibiotic dosage and (iv) an appropriate ward antibiotic dosage. In the pre-intervention test group (Test-1) none of the patients achieved total appropriateness, which changed to 22% in the post-intervention group (Test-2) following the extensive intervention undertaken (Table 3.32). It is a shared responsibility of the hospital including clinical pharmacists to maintain the local guidelines effectively in the long-term.

3.6.5 Length of stay

Patients in Test-1&2 stayed a day longer than Control-1&2, and a day less than Control-3&4 groups, showing a significant difference. The mean length of stay for patients with normal appendices and acute appendicitis was 3.8 and 3.4 days, respectively. Patients with perforated appendicitis had a significantly longer hospital mean length of stay of 7.2 days. A significant difference in the length of stay was found between patients identified as gangrenous and/or perforated and normal appendices in Test-1 and no significant difference in Test-2 was found showing probably that appropriate antibiotic administration reduced the hospital stay in patients identified as gangrenous and/or perforated appendices (Table 3.35).

The mean length of stay of patients from Controls-1&2 was shorter and mean ages were higher than other groups. When a similar population (5.4 – 18 years) was compared across all the groups for mean length of stay there was a longer length of stay in the other groups compared to Controls-1&2. There was a significant difference between mean age Controls-1&2 and test groups ($p < 0.001$). When a normal population (0 – 18 years) is compared with a similar population as in Test-1&2 and Controls-3&4 for mean length of

stay and mean age showed no significant difference between them ($p > 0.05$) except in Control-4 where a significant change was just evident ($p = 0.045$). This is probably due to the different regimens of antibiotic prescriptions and varied patient conditions in the Test and Control groups. Some of this difference may relate to hospital policy or procedure rather than different patient outcomes.

3.6.6 Microbiology

The distribution of wound infections was not significantly affected by gender or age in this study. Intraoperative cultures were obtained for all patients in the study as a standard procedure at the hospital; one patient in each test group developed an infection and was readmitted to the hospital and another patient was readmitted due to pain. The infection results were irrespective of the diagnosis of the patient. Even though there was a difference in the pattern of antibiotic usage in the groups, no difference in the infection rate was found. The inappropriate antibiotics identified in the pre-intervention group however would be expected to be effective but were not an appropriate choice. The infection results were lower than reported by Hale et al. [73] on cultures obtained on 88 patients, in whom a wound infection developed subsequently and the risk of a wound infection increased markedly with perforated appendicitis (6.4%) compared to the rate associated with normal appendices (1.8%) and acute appendicitis (1.4%), respectively.

In this study, a small number of patients were identified with microorganisms (streptococcus sps 6.2%, mixed anaerobic 5.7%, aerobic 0.4%, E.coli 4.8%, pseudomonas 0.4% and mixed coliforms 0.4%) in perioperative samples in the test group, but according to the department of microbiology, those are not clinically significant. Those cultures were the reflection of the normal bowel flora. But, in a study by Hale et al [73], the spectrum of organisms identified from the cultures (no growth 23%, Escherichia coli 28%, Bacteroides fragilis 10% Pseudomonas 7%) were treated for infections.

3.6.7 Analgesics

This study found that most of the patients were prescribed paracetamol and/or paracetamol with codeine analgesics. Paracetamol is an analgesic widely used in children and does not induce nausea and vomiting. It has a good reputation for safety within the recommended dosage. The analgesic effect of paracetamol is directly related to its plasma concentration.[74] The addition of codeine gives a theoretical advantage of two analgesics with different mechanisms of action combined to enhance analgesia.[75] In a meta-analysis of 19 trials, De Craen et al.[76] found that the addition of codeine to paracetamol produced a 5% increase in analgesic effect.

In this study, surgeons prescribed paracetamol 28/83 times 26-50% above and 35/83 times 26-50% below the recommended dose in the test-1 group. It then decreased to 1/92 times 26-50% above, 14/92 times 26-50% below and 1/92 times 50-75% below the recommended dose in test-2 group. High dosages of paracetamol potentially lead to toxicity and low dosages leads to preventable suffering of pain and potentially longer lengths of stay in the hospital.

3.6.8 Intervention

On the basis of this study, the majority of clinical and pharmacy departments have adopted drug utilisation programs which have resulted in the introduction of various strategies in an attempt to modify physician prescribing habits. These attempts can be generally classified as educational strategies.

Girotti et al[77] reported on the introduction of a purely educational strategy in the form of an antibiotic handbook showed only a marginal improvement in the overall compliance with their recommendations on the surgical services. However, when they

introduced a control strategy through the use of a pre-printed physician order form in the perioperative period it resulted in a dramatic improvement in compliance with recommended antibiotic regimens. Employing a similar handbook, D'Eramo et al[78] reported a short-term improvement when their handbook was introduced into a hospital setting in an attempt to modify the patterns of physician drug use for empirical therapy. In this study, the compliance with the antibiotic guidelines was improved without any restrictions evident in the above studies. Clinical pharmacists in conjunction have developed the guidelines with clinical microbiologists and the division of surgical services. The multifaceted intervention consists of a newsletter, presentations, formal discussions, guidelines posters in ward and theatre and reminders by clinical pharmacists in the wards. Strategies, which involve all of the stakeholders, have been shown to the effective in other settings.[79, 80]

One of the principal reasons for restrictive antibiotic policies is to preserve the effectiveness of a limited number of antibiotic drugs. The Malthusian prediction that antibiotic-resistant bacteria would develop more rapidly than the rate at which new antibiotic drugs could be manufactured has proved thus far to be untrue. In fact, the drug industry has outsmarted bacteria by producing new compounds at a much-faster rate than that at which bacteria have developed new mechanisms of resistance. Consequently, too many antibiotic drugs have been developed rather than too few, and this is an area where antibiotic guidelines have been useful. Where there are many antibiotic agents with similar names, overlapping properties and different dosage regimens and costs, it seems sensible to have restrictive antibiotic policies [81].

Review is an essential element of drug policies in hospitals, but as far as antibiotic agents are concerned such a review should include a reconciliation of the guidelines and usage with antibiotic resistance and cost. The application of antibiotic policies has resulted in improved practices and reduced costs. However, the advocates of such policies should be

aware that considerable scope still exits for improvements in the outcome of treating infections [81].

Providing feedback to clinicians regarding their own antibiotic prescribing practices has been a successful technique for achieving behaviour change. Feedback can entail comparisons with peers or standards. As with practice guidelines, feedback may be most effective when the system is developed with local input, where clinicians accept the measures as important, fair, and relevant to their own practices.[79]

The duration effect of the intervention during the five-month period of data collection following the implementation of intervention shows that there was no significant diminution of the effect of the intervention on the prescribing behaviour for theatre and ward antibiotic choices and theatre and ward antibiotic dosages. In a randomised controlled trial of academic detailing by Avorn and Soumerai[82], indicated that face-to-face education of the practicing physician is an effective means of reducing less than optimal prescribing decisions and the differences in prescribing remained highly significant, with no sign of diminution in effect nine months after the start of the office-based intervention.

Ideally, the pharmacist should be involved in pursuing the above objectives through continually monitoring prescribing, providing information to new doctors and nurses and assisting in the process of drug use review. This will depend on improved communication with all newly arrived surgical and other related staff, and providing them with information about local antibiotic policies.[83]

3.7 Conclusion

The introduction of local guidelines has resulted in improved practices. A multifaceted educational intervention by pharmacists can have a significant effect on surgeons prescribing. The choice and dosage of pre-operative and post-operative antibiotics and dosage of analgesics were significantly improved following a multifaceted intervention. Locally developed guidelines are more likely to be accepted and followed than those developed nationally without local input. There was no significant diminution of the effect of the intervention on the prescribing behaviour of surgeons during the five month post-intervention. Development of clinical practice guidelines should therefore be supported by other educational activities. The effectiveness of ceftriaxone and cefotaxime was preserved.

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Chapter four

Liquid Medication Dosing errors: A pre-post time series in India

4.1 Introduction

4.1.1 Medical errors

Patient safety is a significant problem in health care. As we know medication-related problems are a significant cause of adverse medical events[1]. According to the Harvard Medical Practice Study, adverse drug events are more common than infectious complications in hospitals[2]. Most hospitals invest considerably more time and money in infection control than they do in improving medication safety[1]. It has been estimated that 44,000 to 98,000 people die each year as a result of medical errors. That is more than the number of people who die either from breast cancer, AIDS, or motor vehicle accidents in the U.S.A[3].

Adverse events are injuries arising from medical treatment. Not all adverse events are caused by errors; some result from differences among patients and their responses to treatment. However, about half of all adverse events are believed to be preventable[3]. In the past, an optimal therapeutic outcome has been defined as "the right drug, for the right patient, at the right time." Currently an optimal therapeutic outcome also implies the absence of drug-related problems (DRPs). A DRP is defined as an event or circumstance involving patient's drug treatment that actually or potentially interferes with the achievement of an optimal outcome. Unresolved DRPs may manifest as drug-related morbidity and, if left untreated, may eventually lead to drug related mortality[4].

Information regarding the epidemiology and prevention of medication errors and adverse drug events (ADEs) in pediatric inpatient settings is scarce[5]. Children pose unique challenges to the system for ordering, dispensing, administering, and monitoring

medications. Kaushal et al[6] found that the errors with a potential for harm occurred most often in the youngest and most vulnerable patients. Drug dosages often must be calculated individually in children, leading to increased opportunities for error with a relatively high risk of 10-fold errors. Furthermore, weights can change rapidly and dramatically over time, especially in small infants, requiring frequent dosing re-calculations. Medicine dispensing in children is complicated by the fact that stock solutions of medicines are often available only at adult concentrations and must be diluted for use in children. Children, particularly those who are young and critically ill, may be more prone to ADEs than adults because they have less physiologic reserve with which to buffer errors such as overdoses[7].

Errors in the prescribing and management of drug therapy are common and have been identified as a major cause of adverse drug events. Understanding the many factors contributing to errors should assist in implementation of more effective error prevention strategies[8]. Leape et al[9] found lack of knowledge and lack of timely access to patient information to be the major root causes of medication prescribing errors. Many specific factors have been associated with prescribing errors including calculations of drug dose, errors in decimal points, medications with similar names, medication dosage forms, use of abbreviations, unusual routes of drug administration, uncommon dosage regimen frequencies, complicated dosage regimens, and poor patient history taking[8].

Poisoning in the small child is commonly equated with a toddler ingesting tablets belonging to someone else, generally a family member. The prospect of health professionals poisoning children is traumatic from various aspects, and perhaps this is one of the reasons this area has been sparsely researched[10].

In an anonymous written test conducted by Koren and Haslam to evaluate the performance in calculating pediatric drug dosages among neonatal and pediatric staff

found that on average 60% of them had calculation errors. About 6% of the errors were of tenfold magnitude, due to misplacing the decimal point[10]. Parents are an additional link between the prescribing physician, the pharmacist, and the patient, and medications are frequently administered to the child by parents without medical background. Moreover, there are only a few formulations available that are adapted for children[11]. These issues highlight the importance of pediatric-specific prevention strategies for medication errors[6].

In the United States, estimates of personal total expenditures for prescription medications in 1995 exceeded $77 billion{Grandis JR, 1992 #59}. Recent studies, indicate that the substantial costs associated with inappropriate drug use are likely to exceed the initial outlays for drug therapy. Johnson and Bootman[13] estimated the cost of drug-related morbidity and mortality in the ambulatory setting was $76.6 billion and that, with the provision of pharmaceutical care, this figure could be reduced to $45.6 billion[4].

It was estimated that approximately $3 billion was spent annually for drug therapy in nursing facilities, indicating that the estimated health care cost of drug-related morbidity and mortality exceeds the original outlay for drugs by $1 billion i.e., for every dollar spent on drugs, $1.33 is consumed in the treatment of drug related morbidity[4].

The total costs of preventable medical errors are in the range of $17 to $29 billion per year in hospitals in United States. Errors also are costly in terms of loss of trust in the health care system by patients and diminished satisfaction by both patients and health professionals. Patients who experience a long hospital stay or disability as a result of errors pay with physical and psychological discomfort. Health professionals pay with loss of morale and frustration at not being able to provide the best care possible. Society bears the cost of errors as well, in terms of lost worker productivity, reduced school attendance by children, and lower levels of population health status[14].

In a meta-analysis study Lazarou et al[15] estimated that 702,000 hospitalised patients experienced a serious adverse drug reaction (ADR) and 1,547,000 patients were admitted to hospitals due to ADRs in the United States. They calculated 106,000 deaths were caused by ADRs, which could account for 4.6% of the 2,286,000-recorded deaths from all causes during the study period. ADRs constituted the fourth leading cause of death in the United States, after hearth disease (743,460), cancer (529,904), stroke (150,108) followed by pulmonary disease (101, 077), accidents (90,523); pneumonia (75,719) and diabetes (53,894)[16].

Another meta-analysis study reported an overall incidence of 6.7% for serious adverse drug reactions. For every 1000 patients admitted to a hospital, approximately 3 will die and 1 will suffer serious long-term disability due to ADEs. The mean direct cost of an inpatient ADE ranges from $1900 to $5900[17].

According to the Harvard Medical Practice Study conducted on 30,000 inpatient hospitalisations found that ADEs were the most common type of adverse event experience by patients at several hospitals in New York State[2]. The study documented that at least 3.7% of all hospitalised patients developed a serious, disabling, and clinically important adverse event during their hospitalisations, of which almost 20% were ADEs[18].

The most common adverse events were complications of medication use. Thirty percent of patients with drug-related injuries died or were disabled for more than 6 months[19]. Most medication errors were dosing errors (28%), followed by route of administration, medical administration record and documentation, date, and frequency of administration errors. The most potential ADEs were due to dosing errors (34%), followed by frequency

and route errors. Physician ordering, followed by transcription and nurse administration were the most common stages for medication errors and potential ADEs. The most common drugs involved in medication errors and potential ADEs were anti-infective agents, analgesics and sedatives, electrolytes and fluids, and bronchodilators[6].

In response to the above findings, the Adverse Drug Event Prevention Study addressed medication errors and adverse drug events (ADEs) in hospitalised adults[9, 20]. It found that ADEs were occurring at a rate of 6.5 per 100 adult admissions and they were costly, and often had severe sequelae[20, 21]. Other studies largely confirmed these findings[15, 18].

Medication errors are of two main types, prescribing errors and medication administration errors[22]. Approximately 3% of medication-error reports submitted in 1999 to the United States Pharmacopeia national database described actual harm to patients. Nearly half of the errors recorded referred to doses not administered or drug products not given at the proper dose or in the correct quantity. "Performance deficit" was the most frequently cited cause of errors, often in combination with another cause. In the medication-use process, "administering" was identified most frequently (40%) and prescribing (11%) of the time of the medication-error reports[23].

Medication order writing constitutes 5% of the drug related errors. Of these, 28% to 56% are preventable. Prescription of the wrong drug or wrong dose is often due to lack of information regarding the drug or the patient[17]. A study by Leape et al[9] concluded that 78% of errors leading of ADEs are due to system failures that could be corrected by improved information systems[17].

In a study by Bates et al[24] found that a large difference in length of stay and resource utilisation between preventable ADE and nonpreventable ADEs. Analgesics (30%) and

antibiotics (30%) accounted for the largest percentages of nonpreventable ADEs, followed by antineoplastic agents (8%) and sedatives (7%). The largest percentages of preventable ADEs were caused by analgesics (29%), sedatives (10%), antibiotics (9%), and antipsychotics (7%). Patients with long stay tend to be sicker and receive more medications and therefore had substantially greater rates of exposure per admission than other patients. They estimated an additional cost of $2595 to the hospital for preventable ADEs per patient. Thus, ADEs are costly, and interventions to reduce their frequency can be justified economically as well as to improve the quality of care[24].

In a case-control study performed by Evans et al[25] at a Hosptial in Salt Lake City, Utah, found an attributable increase in length of stay of 1.9 days and increased costs of $1939 for ADEs per patient.

Medication errors are quite frequent compared with accidental intoxications according to a survey of Poison Control Centres. Studies have shown that errors resulted in 4-11% of hospitalisations for intoxication in children. Seven hundred errors occurred with over-the-counter drugs, which accounted for 63% of all the medications. 7.8% of 459 patients prescribed acetaminophen was misused. Wrong dosage was prescribed in 31.5% of 1082 patients. The most frequent causes of error were parental prescribing (31.5%) and incorrect execution of the prescription (30%). The wrong dose often resulted from a wrong execution of the prescription, whereas drug errors were more frequently related to parental prescribing. In most of the cases of medication error (84.5%), the error was detected by family members who were also responsible for the majority of the wrong administrations[11].

The study by Folli et al[5] demonstrated that pharmacy review of medication orders could prevent erroneous orders from being implemented at a rate of 14 to 18 per 1000 patient-days. Fortescue et al[7] concluded in their study that the presence of clinical pharmacists

to monitor ordering might have prevented 58.3% of errors, whereas pharmacists monitoring transcribing and administering might have prevented an additional 19.6% and 5.8% of errors. In all clinical pharmacists performing these functions could have resulted in a total medication error rate reduction of 81.3%. The high risk of medication errors highlights the importance of developing, testing, and implementing effective error-prevention strategies in pediatrics[6].

4.1.2 Liquid medication dosing errors

In 1975, the American Academy of Pediatrics Committee on Drugs described unacceptable levels of inaccuracies in administering liquid medication by household spoons.[26] When recommended 27 years ago the use of an oral dosing syringe, was then described as novel and innovative. Subsequently, a range of liquid medication dosing devices have been developed and become widely available, each of which has its advantages and disadvantages.[27]

A study reported from poison control centers in the United States of America found two major causes of dosing errors using dispensing cups which were commonly provided attached to liquid medication: the assumption was made that the entire cup was the unit of measure; and secondly the misinterpretation that one cupful was the recommended dose.[28] Household measuring devices, such as teaspoons and tablespoons, were not recommended for measuring drugs because they are neither accurate nor consistent. The volume contained in a household teaspoon has been reported to range from 2.5 to 9.7 ml.[26, 29, 30] Research has suggested that parents may be confused about differences among teaspoons, tablespoons, and dose cups.[11, 28, 31] Problems can also result from spillage and medication left in or on the measurement device rather than being administered to the child.[27, 32] After receiving reports of inappropriately marked plastic dosing cups, the Food and Drug Administration began a public education campaign in

1994 to increase health professional and consumer awareness of dosing hazards with liquid medicines.[33]

When the oral dosing syringe was introduced in 1975, 75% of parents used a household teaspoon or other measuring device when dosing liquid medication.[29] A study from Israel in 1989, reported that 80% of children were still given medications by a household teaspoon.[34]

Optimal administration of liquid mediations to children requires the delivery system to be effective, safe, and acceptable to the parent. It also needs to be able to deliver the dose correctly to the child once measured. However, traditional techniques for administering pediatric oral liquid medications are not optimal because of the variability of the volume measured, incomplete delivery of the dose, or infant resistance and refusal.[26, 27, 30, 32, 35, 36]

Oral dosing syringes are considered the best device for the delivery of liquid medication.[27] Oral syringes can accurately measure liquids and may reduce drug dosage errors if the syringe is marked correctly and parents are trained.[32, 35] Its advantages include accuracy, expediency, availability in various sizes, and relatively low expense. The syringe permits the user to direct the delivery of the medication to the side of the mouth of an infant or small child, thus minimizing spillage. It also reduces the risk of possible gagging and aspiration of medication.[37]

Although a range of methods have been used to study medication administration errors, the observation-based method developed 40 years ago by Barker and McConnell[38] is generally accepted as the most reliable[39, 40]. In this approach, a researcher accompanies nurses preparing and administering drugs, records details of all doses administered, and

compares this information with the doses prescribed[22]. This approach can also be applied to measure the efficiency of parents administering a liquid medication dose. Less is known about the level of liquid medication dosing errors in India, the second largest populated country in the world. So the authors designed this study to evaluate the accuracy with which parents administered a paracetamol suspension prescribed for pyrexia because of the frequent diagnosis and use of liquid medication for this condition. This study was intended to determine whether parents could administer the prescribed dose correctly and also, to identify if the dose was medically appropriate for pyrexia for each patient.

The objectives of this study were (i) to study the impact of a liquid measurement device and pharmacist intervention on parent dosing accuracy and, (ii) to evaluate the effect of pharmacist intervention on pediatric prescribing of paracetamol dosages using an education program.

4.2 Methods

4.2.1 Setting and patient population

Children less than 10 years of age diagnosed with pyrexia and prescribed paracetamol suspension by a doctor were the subjects for the study. Patients received care in the Srujan Hospital for Sick Children (SHSC), Sirsilla, Andhra Pradesh, India. SHSC is a 60-bed pediatric hospital. It is the only pediatric hospital for a small town and fifteen villages (approximate population 100,000). SHSC contains a pharmacy where most of the patients will have their medications dispensed. To participate in the study, the patient's prescription had to be filled at the hospital pharmacy. The study sample was collected during the hospital visiting hours i.e., 7.00 a.m. to 9.00 a.m., 12.00 p.m. to 4.00 p.m. and 6 p.m. to 9.00 p.m. The researcher is a qualified pharmacist in that country. He spoke medical Telugu, however, all nursing assistants in the hospital were bilingual. The nursing assistants notified the researcher whenever the diagnosis of pyrexia was made

and a paracetamol suspension was prescribed. The weight for most patients was not available on the prescription. The researcher weighed each patient in his office in Group 1. In Group 2, the nursing assistants weighed each patient and it was written on the patient notes before the pediatrician wrote the prescription. The hospital does not normally employ a qualified pharmacist nor nurses.

4.2.2 Exclusion and inclusion criteria

All outpatients prescribed a paracetamol suspension and less than 10 years of age were included and classified into two groups. Group 1 was studied initially and received standard care. Patients from Group 1 were excluded from Group 2. Since it was a time series study, Group 1 data were collected in week one and Group 2 data a week later following the intervention to the pediatricians.

4.2.3 Data collected

Data collected included patient details such as age, weight and sex; parent details such as type of carer, level of education, number of children and order of the child in the family; prescription details such as drug name, dose prescribed and number of doses prescribed; measurement details such as volume of paracetamol suspension prescribed, volume measured, difference and the device used for measurement.

4.2.3.1 Data collection methodology

In Group 1 participants received the prescription, paracetamol suspension and verbal instructions from the hospital staff. This was the usual care practiced at SHSC. Data were collected directly from the patient's prescription. The parents were asked to give the first dose of paracetamol suspension to the patient in the presence of the researcher. The researcher had a range of measuring devices available including household teaspoons,

dosing spoons, droppers, measuring cups and syringes. The parent was asked to select and use the item most similar to what they usually used for the measurement of the dose. The researcher then measured that dose volume to the nearest 0.5 ml, using a calibrated syringe to suck up the dose to determine the reading of the dose and confirmed the volume by expulsion into a measuring cylinder calibrated to 0.1 ml to validate the syringe. If the parent measured an incorrect dose, the researcher reinforced the verbal instructions previously given and the dose measurement was corrected and demonstrated how to measure the dose. Parents were counseled on the advantages of oral dosing syringes and asked if they wanted to use the syringe to administer the medicine. If they were interested, the syringe was labeled at the prescribed dose with a "⊥". The inverted "⊥" was marked from the inlet of the syringe with the line showing the mark for the prescribed dose. This gave a clear instruction to the parent from the point of drawing up to the suspension to the point which was the dose volume. Use of dosing cups available attached to the medication where selected was discouraged.

In Group 2, participants received the prescription for paracetamol suspension, and the intervention included the marked syringe as previously described, verbal instructions and a demonstration by a qualified pharmacist, who was the researcher. The pediatricians also received feedback of Group 1 results for paracetamol dosages. A dosing chart was provided to the prescribers describing according to weight, the appropriate dose in millilitres of paracetamol suspension. Similar data were collected as in Group 1. In Group 2, each patient was weighed and data were provided to the pediatrician before prescribing the dose. The researcher explained to parents the advantages of using the oral dosing syringe. If they were prepared to volunteer, they were asked to measure the dose. As in Group 1, where an incorrect dose was measured, the dose was corrected.

4.2.4 Pharmacy survey

A survey of 16 pharmacies located in that area was conducted to identify the type of devices general practitioners (GP) were recommending to measure the dose. The researcher visited all the pharmacies and introduced himself, and asked the question what devices they provided with pediatric suspensions. Every pharmacy was located near to a GPs clinic. Most patients' visited a GP, and got their medicines dispensed at any of the 16 pharmacies located nearby.

4.2.5 Definitions

In this study an appropriate volume measurement was classified as a volume within ± 0.5 ml of the recommended volume. An appropriate dose was classified as one prescribed within ± 25% of the recommended dose. An educated person was defined as one who could read, write and speak any of the 18 languages listed in the constitution of India. A person without formal education was defined as one who cannot read or write but can speak any of the 18 languages listed in the constitution of India.

4.2.6 Data analysis

Physicians' prescribing of antipyretic dosages was evaluated against Australian National Therapeutic Guidelines (ANTG) for paracetamol.[41] The stated dosage is: paracetamol - 15 mg/kg/dose orally, every 4 to 6 hours, to a maximum of 90 mg/kg/day. Paracetamol dosage was calculated according to the product of the weight of the patient and the recommended dose per kilogram.

4.2.7 Statistical Evaluations

Using Students' t-test tested data for age differences and other population data were differentiated using χ^2 analysis. Difference in choice of device used, number of children,

order of the child, and level of education status of the parent for the appropriate measurement of liquid medication and physician prescribing were evaluated by χ^2 analysis. Other parametric data differences were tested using Student's t-test. Outcomes of the study were communicated to the pharmacy and relevant units at SHSC. Based on α=0.05 and β=0.2 and a 20% change in prescribing and dose measurement outcomes required a minimum sample of 80 patients in each group to achieve statistical significance.

4.2.8 Ethical issues

As this study involved an analysis of patient's prescription data, ethical issues arise in relation to confidentiality and release of data. A unique non-patient identifiable code was allocated to each prescription to enable re-identification if necessary since the hospital holds a duplicate copy of the prescription. The coded data was kept secure in accord with National Health and Medical Research Council {Grandis JR, 1992 #40} guidelines and only group data released from the research. Informed consent of parents was not obtained, because the study was a quality assurance audit to determine the number of patients using measuring devices correctly. The treatment was within the standard of care for pyrexia.[41] The Curtin University of Technology Ethics Committee approved this study.

4.3 Results

The study population consisted of 337 children of which 220 parents had no formal education and 117 were educated (Table 4.1). They were chosen consecutively by having received a prescription for paracetamol suspension for pyrexia. The number of parents in Group 1 is 175 and Group 2 162 with no significant difference between them (p = 0.103).

Table 4. 1 Parent educational status comparison statistics

Educational description	Number of patients		Total	P value
	Group 1	Group 2		
No education	117	103	220	0.528
Education	58	59	117	
Total	175	162	337	

Out of 337 patients, eighty-eight (50.3%) were females and eighty-seven (49.7%) were males in Group 1 and sixty-eight (42%) were females and ninety-four (58%) were males in Group 2. There was no significant gender difference between the two groups (p = 0.190). Patients were grouped according to their age for convenience and summarised in the Table 4.2.

Table 4. 2 Patient group statistics

Group	Group 1			Group 2			P value
	Male	Female	Total	Male	Female	Total	
Neonate	2	2	4	3	2	5	0.103
Infant	23	32	55	42	27	69	
Toddler	17	21	38	11	10	21	
Children	45	33	78	38	29	67	
Total	87	88	175	94	68	162	

The mean age of patients in Group 1 is 3.45 years and in Group 2 3.44 years with no significant difference (p=0.756) between them. The parents in Group 2 were all mothers, whereas in Group 1, mothers attended for 157 children and fathers for five (p=0.017).

Although a significant difference is evident this only arises from the zero in one of the Group 2 field.

Of the educated parents 19 were educated to primary, 32 to secondary and seven were educated to tertiary levels. In Group 2, 27 were at primary, 29 secondary and three parents at tertiary levels(Table 4.3).

Table 4. 3 Parents level of education

Level of education	Group 1	Group 2	Total
No education	117	103	220
Primary	19	27	46
Secondary	32	29	61
Tertiary	7	3	10
Total	175	162	337

Group 1 consisted of 63 parents with one child, 80 with two, 31 three, and one parent had five children. In Group 2, 57 parents had one child, 75 two, 23 had three and seven had five children. There was no significant difference in these data between Groups 1 and 2 ($p = 0.130$) (Table 4.4).

Table 4. 4 Number of children to the parent comparison statistics

Number of children	Number of parents		Total	P value
	Group 1	Group 2		
One	63	57	120	0.130
Two	80	75	155	
Three	31	23	54	
Other	1	7	8	
Total	175	162	337	

One hundred and thirteen (>64%) children were the first child in their family, 47 (27%) were the second child, and 15 (<9%) other children were the third child in Group 1. In Group 2, 106 (>65%) children were the first child, 42 (26%) were the second, 14 (9%) other children were the third child. There was no significant difference in these data between Group 1 and Group 2 (p = 0.981) (Table 4.5).

Table 4. 5 Order of the child in the family comparison statistics

Order of the child	Number of patients		Total	P value
	Group 1	Group 2		
First	113	106	219	0.981
Second	47	42	89	
Other	15	14	29	
Total	175	162	337	

The device initially selected by all parents to measure the paracetamol suspension in Group 1 was the measuring cup. This device was often attached to the closure of the

bottle. An oral dosing syringe was provided as part of the study intervention to Group 2 participants ($p<0.001$).

4.3.1 Parents dosing

The detailed overall outcomes of parent dosing are listed in Table 4.6. In Group 1, 85 measured the dose accurately (±0.5ml), 58 measured 0.6 to 1ml above or below the recommended dose, 7 measured 1.1 to 1.5ml above or below the recommended dose, 10 measured 1.6 to 2ml above or below the recommended dose and 15 other measured inappropriately. In Group 2, 160 parents measured the dose appropriately and two inappropriately with a statistically significant improvement from Groups 1 to 2 ($p < 0.001$).

Table 4. 6 Parents measurement appropriateness

Dose appropriateness description in ml	**Number of patients**	
	Group 1	**Group 2**
0 to 0.5 above the recommended dose	65 (appropriate)	136 (appropriate)
0 to 0.5 below the recommended dose	20 (appropriate)	24 (appropriate)
0.6 to 1 above the recommended dose	37	1
0.6 to 1 below the recommended dose	21	
1.1 to 1.5 above the recommended dose	3	1
1.1 to 1.5 below the recommended dose	4	
1.6 to 2 above the recommended dose	6	
1.6 to 2 below the recommended dose	4	
2.1 to 2.5 below the recommended dose	14	
2.6 to 3 above the recommended dose	1	
Total	**175**	**162**

4.3.2 Pediatrician prescribing

Pediatricians prescribed appropriate doses for 67 patients, 26-50% above or below the recommended dose for 31, 51-75% above or below the recommended dose for 34, 76-100% above the recommended dose for 19, 101-150% above the recommended dose for 13, 151-200% above the recommended dose for 5 children. It is notable that 6 children received doses, which were more than double to five-fold that of the recommended dosages in Group 1. In Group 2, 2 patients were prescribed 26-50% below the recommended dose and 160 were prescribed an appropriate dose with a significance improvement from the pre-intervention to post-intervention groups ($p < 0.001$) (Table 4.7).

Table 4. 7 Pediatricians prescribing appropriateness

Dose appropriateness description	**No of patients (sum of doses)**	
	Group 1	**Group 2**
26-50% below the recommended dose	13 (159)	2 (24)
51-75% below the recommended dose	1 (12)	
Appropriate dose	67 (807)	160 (1923)
26-50% above the recommended dose	18 (216)	
51-75% above the recommended dose	33 (399)	
76-100% above the recommended dose	19 (240)	
101-150% above the recommended dose	13 (162)	
151-200% above the recommended dose	5 (69)	
201-250% above the recommended dose	2 (27)	
251-300% above the recommended dose	1 (12)	
301-350% above the recommended dose	1 (12)	
451-500% above the recommended dose	2 (27)	
Total	**175 (2142)**	**162 (1947)**

4.3.3 Overall appropriateness

In evaluating the overall appropriateness of the dose administered (combination of pediatrician prescribing and parents measurement), 76 patients received an appropriate dose in Group 1 and 160 in Group 2 with a statistically significant improvement ($p < 0.001$) (Table 4.8). Some additional appropriate doses were fortuitously achieved as a result of incorrect measurements of inappropriate doses (Table 4.9). Hence irrespective of the parent's educational status, order of the child in their family, and number of children in a family, there was a marked improvement in the measurement of the appropriate dose (Tables 4.10-4.12).

Table 4. 8 Overall appropriateness

Dose appropriateness description	Number of patients (Sum of doses)	
	Group 1	**Group 2**
26-50% below the recommended dose	10 (123)	2 (24)
51-75% below the recommended dose	4 (48)	
Appropriate dose	76 (921)	160 (1923)
26-50% above the recommended dose	14 (171)	
51-75% above the recommended dose	30 (372)	
76-100% above the recommended dose	20 (240)	
101-150% above the recommended dose	12 (150)	
151-200% above the recommended dose	2 (27)	
201-250% above the recommended dose	3 (39)	
251-300% above the recommended dose	1 (12)	
401-450% above the recommended dose	1 (12)	
451-500% above the recommended dose	2 (27)	
Total	**175 (2142)**	**162 (1947)**

Table 4. 9 Parents measurement Vs Physician prescribing

Category	Dose prescribed appropriately		Dose prescribed inappropriately	
	Group 1	Group 2	Group 1	Group 2
Volume measured correctly	31	158	54	2
Volume measured incorrectly	29	2	61	-

Table 4. 10 Level of education Vs Appropriate measurement of dose

Level of education	Number of parents		Percentage	
	Group 1	Group 2	Group 1	Group 2
No education	58	102	49.5% (58/117)	99% (102/103)
Primary	9	27	47.4% (9/19)	100% (27/27)
Secondary	13	29	40.6% (13/32)	100% (29/29)
Tertiary	5	2	71.4% (5/7)	66.7% (2/3)
Total	85	160		

Table 4. 11 Order of the child Vs Appropriate measurement of dose

Order of the child in the family	Number of patients		Percentage	
	Group 1	Group 2	Group 1	Group 2
First	60	105	53% (60/113)	99% (105/106)
Second	19	41	40.4% (19/47)	97.6% (41/42)
Third	6	13	40% (6/15)	100% (13/13)
Fourth	-	1	-	100% (1/1)
Total	85	160		

Table 4. 12 Number of children to the parent Vs Appropriate measurement of dose

Number of children to the parent	Number of parents		Percentage	
	Group 1	Group 2	Group 1	Group 2
One	30	57	47.6% (30/63)	100% (57/57)
Two	41	73	51.2% (41/80)	97.4% (73/75)
Three	13	23	42% (13/31)	100% (23/23)
Four	-	6	-	100% (6/6)
Five	1	1	100% (1/1)	100% (1/1)
Total	85	160		

4.3.4 Pharmacy survey results

A survey of 16 pharmacies located in this rural area found that none of them supplied or had for sale an oral dosing syringe. The eight physicians practicing in this area appeared not to be aware of this device, hence did not make any recommendations for its use. All pharmacies were supplying either dosing spoons or dispensing cups.

4.4 Discussion

The overall inappropriateness of the medication, was a combination of the following factors: (i) the parent measured the dose inappropriately or (ii) the physician prescribed an inappropriate dose of paracetamol suspension and (iii) the overall combination of dose measurement and prescribed dose lead to an inappropriate dose being administered. There was in a small number of fortuitous situations where an inappropriate dose was incorrectly measured to overall result in an appropriate dose being administered. These cases have been counted as overall appropriate although achieved by inappropriate procedures.

In this study ±0.5ml was deemed an acceptable measurement error as the suspension is viscous. This is a high percentage error at low dosages (e.g. 2ml) but is acceptable at common dose volumes of 5 to 10ml. The designated dosage error of ±25% was based on the common variability allowed in dosage forms and bioequivalency studies. In India national guidelines are not available to prescribers. It is noted however the dosage errors do not relate to the use of a different dosage standard since the results show wide variability presumably arising from not knowing the weight.

Several very high dosages (150mgkg^{-1}day^{-1} to 250mgkg^{-1}day^{-1}) were prescribed. Penna & Buchanan[43] reported in 1991 7 deaths and 11 cases of hepatotoxicity associated with paracetamol. Survival was usually seen in those children suffering hepatotoxicity due to paracetamol greater than 150mgkg^{-1}day^{-1} for two to eight days.[43] However, toxicity has been reported rarely with therapeutic doses when administered over several days in children who have concurrent illnesses such as fever, vomiting, and diarrhoea.[44]

In this study 54% of the children in Group 1 received doses above that recommended. Of particular concern were 6 children being prescribed more than double to five-fold of the recommended dose. In addition to the immediate concern, medically prescribed dosages

of medicines that are easily purchased such as paracetamol may lead to these dosages being continued beyond only the contents of the suspension provided from the hospital consultation.

This study has found that irrespective of educational status or previous experience with other children that an appropriate intervention by a pharmacist can markedly improve the accuracy of measurement (Table 1). Pharmacist intervention involving parental and targeted physician education can be very effective in markedly improving the appropriateness of medication dosing and prescribing in a developing country. This study has demonstrated that the overall improvement is very substantial from 43.4% to 98.7%. With regard to providing parents' with verbal instructions, and a syringe marked for the prescribed dose and a demonstration by a qualified pharmacist caused a significant improvement from 48.5% to 98.7% able to achieve an acceptable accuracy. This study shows results similar to a recent study by McMohan and colleagues of 90 English-speaking and Spanish-speaking families, 100% of them dosed medication correctly when given instructions and a syringe with a line marked at the prescribed dose.[35]

A study conducted by Mattar, Markello and Yaffe (1975) found that difficulties with administration of liquid medications occurred with 28-40% of children.[29, 45] Because traditional oral liquid medication delivery devices may cause problems with drug administration, these devices may adversely affect compliance.[45] It is harder to feed the child with the dispensing cup than with the syringe. There is a greater chance of spillage of the liquid during administration compared with the oral dosing syringe.

This method of drug administration requires correct placement of the liquid in the cheek pouch of the patient's mouth for the medication to be correctly swallowed. If the liquid is placed too close to the front of the mouth, the medication can be expelled. If the liquid is administered too close to the back of the throat or too rapidly, the patient may choke or

aspirate.[27, 46] None of the patients in this study choked or aspirated during the trial administration. This shows that pharmacist involvement as counsellor and demonstrator of oral dosing syringes and practical reinforcer of the dosing instructions has worked well. Good communication and verbal skills are important and is a vital role of the pharmacist's activities in hospital settings.

Matter et al[29, 45] found that when no dispensing device was given, 71% of parents used a teaspoon. In this study, everybody normally used dispensing cups for measuring the suspension. This practice can be eliminated through better parent education and by providing labeled measuring devices.

Even though oral dosing syringes have been available in developed countries since 1975, none of the pharmacies in the survey conducted in this study, were supplying nor the physicians appeared to knew about this device. This reflects that there is a great need for pharmacist intervention and greater involvement in practice.

Herman & Rodowskas[47] have suggested that programs meant to improve the quality of patient care and thus drug use, can succeed only if practitioners adopt a positive attitude towards such programs. It has also been reported that attitude was the strongest predictor of whether or not pharmacists performed some clinical pharmacy activities.[48] The attitudes of pharmacists and physicians to policies is likely to be one of the important factors that may affect their compliance with, and hence the ultimate effectiveness of such policies.[49]

Although several studies have evaluated the accuracy of measuring medicines in various devices in several countries, this study has also linked this with the prescribing of appropriate doses. It is only with this combination that the administration of an

appropriate dose can be ensured. In addition, doses commenced in a hospital setting are likely to be continued when paracetamol is used or obtained in other circumstances, perpetuating the findings of Group 1 patients. The current situation can often lead to either drug toxicity or treatment failure dependent upon the combination of dosages prescribed and administered.

4.5 Conclusion

In this study we found that dosing by parents from rural areas of a developing country can be improved by a targeted pharmacist intervention. Health care professionals should ensure that parents understand liquid medication dosing procedures. Treatment failure from underdosage or adverse effects can potentially arise from overdosage. A syringe provides an appropriate device for dosage administration: it is easy to control, causes minimal spillage, and is useful for pediatrics because it initiates sucking compared with use of a dosing spoon. Irrespective of parents education status, number of children and order of the child, pharmacist intervention through patient education significantly improved parents accurate dosing and physicians prescribing of an antipyretic suspension in a country like India where pharmacist involvement thus far is minimal. This study strongly supports the roles that pharmacists can perform in developing countries in improving the quality use of medicines.

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Chapter five

Evaluation of Pharmacist Intervention for Drug Treatment of Severe Community-Acquired Pneumonia at a Rural Indian Pediatric Hospital

5.1 Introduction

Lower respiratory tract infections (LRTI) are a common cause of mortality in developing countries and represent a major source of morbidity among children worldwide [1]. Although the overall incidence of acute respiratory infections is similar in developed and developing countries, there are marked differences in the proportions of patients with specific infections [2]. The incidence of pneumonia in the developing world is up to 10 times higher than in developed countries such as the United States. Pneumonia can be associated with severe morbidity, and place an enormous burden, both economically and as a public health issue, on the entire health care system [3, 4].

Children under the age of five years are most commonly affected by LRTI. Children in the developing world have a high incidence of bacterial pneumonia, have risk factors that predispose to more severe infections, and often have a limited access to effective medical care. The risk factors include large family size with overcrowding, lateness in birth order, low birth weight, lack of breast feeding, malnutrition, vitamin A deficiency and exposure to smoke from cooking on open stoves with biomass fuels.[5, 6]

Pneumonia remains the most common infectious cause of death in the United States and incurs substantial morbidity-related costs to society and the health care system [7-9]. It is the sixth leading cause of death and the number one cause of death due to infections [10]. Pneumonia-associated mortality has declined over the decades since penicillin was introduced [11, 12].

It is estimated that the cost of treatment of community-acquired pneumonia (CAP), including direct patient-care costs and lost wages, is more than US$20 billion per year [13]. In the UK the cost of treatment is estimated to be £440.7 million per year, and 32% of CAP patients need hospital treatment, which accounts for 96% of this cost [14]. CAP is thought to account for 10 million physician visits per year in Unites States [15]. Despite the introduction of newer antimicrobial agents, vaccines and more sophisticated intensive care facilities, the mortality rate associated with pneumonia as reported between 1982-1990 appears to be increasing, after remaining steady during the 1950-60's [10, 16-19].

The risk factors predisposing to more severe disease can possibly be prevented in developing countries also, if the initial infection was identified and treated. This is important in the light of the knowledge that current therapeutic approaches are over time likely to be become less effective in reducing mortality, though they represent the standard approach at present.[20]

5.1.1 Classification of pneumonia

Pneumonia refers specifically to an inflammatory disease process involving the lung parenchyma rather than disease of the conducting airways, although both may occur at the same time [21]. CAP refers to pneumonia caused by a pathogen acquired in the community [10]. The classification of pneumonia can be categorized based on the source of infection (Table 1), the infectious agent (Table 2) or the major site of the pathological process (Table 3).

Table 5. 1 Classification of pneumonia by source of infection

Classification of pneumonia by source of infection [21]	
Classification	Features
Community-acquired	Pneumococcal pneumonia – most common in adults Haemophilus pneumoniae pneumonia – common in children Mycoplasma pneumoniae pneumonia – common in both
Hospital acquired	Increased incidence of Gram-negative infections Higher mortality
Aspiration pneumonia	More common in infancy and childhood May cause chemical pneumonitis Anaerobic bacteria likely May be 'silent' in the elderly
Immunocompromised	Wide range of organisms May rapidly become life threatening Often requires invasive diagnostic procedures

Table 5. 2 Classification of pneumonia by infectious agent

Classification of pneumonia by infectious agent [21]	
Classification	Features
Bacterial pneumonia	Common in all ages Many organisms can cause pneumonia in healthy people Most are curable by appropriate medication
Atypical pneumonia	Due to Mycoplasma, Legionella, Chlamydia, Rickettsiae The older child and young adult are most commonly affected Requires a macrolide or tetracycline and does not respond to β-lactam antibiotics
Viral pneumonia	More common in infants and children More likely to be serious in patients with weakened resistance Few are susceptible to therapy

Table 5. 3 Classification of pneumonia by site of infection

Classification of pneumonia by site of infection [21]	
Classification	Features
Lobar pneumonia	More common in bacterial pneumonia Less common in infancy and elderly May be secondary to bronchial obstruction
Bronchopneumonia	Patchy and widespread Due to bacteria or viruses Common in infancy and elderly Unlikely to be associated with bronchial obstruction
Interstitial pneumonia	Typical of opportunistic infection Typical of non-infective pneumonias

5.1.2 Etiology of pneumonia

Identifying the etiologic agent(s) responsible for pneumonia remains a challenge, primarily because of difficulty in obtaining adequate samples for culture and in differentiating infection from colonisation and lack of reliable diagnostic methods [22, 23]. Although several factors such as age, underlying disease and environment have a substantial influence on the microbial etiology of pneumonia, Streptococcus pneumonia continues to be an important bacterial cause of pneumonia, especially in infants and young children [24, 25]. More recently Chlamydia pneumoniae and Mycoplasma pneumoniae have been recognised as pathogens responsible for mild to severe pneumonia, particularly in children older than 4 to 5 years [25]. In younger patient's, pneumonia is mostly caused by respiratory viruses [26]. Bacterial pneumoniae are commonly caused by Streptococcus pneumoniae, Haemophilus influenzae, and Streptococcus aureus [27, 28].

5.1.3 Causative agents

Most of our knowledge on the etiological agents of pneumonia in children is derived from observations in developed countries where viral infections represent a considerable proportion. However, the finding of a viral pathogen does not rule out a bacterial causative agent, since viruses may predispose to secondary bacterial infection by several mechanisms including local and systemic immunodeficiency, acute malnutrition, and nosocomial infections [29].

Evidence is accumulating that bacterial pathogens play a greater role as a primary or secondary cause of pneumonia in developing than in developed countries [30]. Lung aspiration performed in children with pneumonia who had not received previous antibiotic treatment in developing countries yielded bacterial pathogens in up to 62% of cases [29-31].

It is difficult to draw consistent conclusions from such studies since they differ in many aspects such as their design, location, type of patients and patient's age. In addition, there is no evidence that in the developed world the bacterial causative agents are similar to those in the developing world. Furthermore, most of these studies were performed many years ago, and epidemiology tends to change, at least in part, with time [29].

Current microbiology methods are cumbersome, time consuming, and costly and the majority of patients treated parenterally are discharged without the causative agent being identified. Traditional lung aspiration could be informative in cases of pneumonia, but it is rarely used [32].

5.1.4 Medical Practices in India

India is a country of over one billion population with a vast diversity in cultures, traditions and religion. From North to South & East to West, the people are different. India is not only vast but is also has the distinction of being the second most populous nation in the world.

5.1.4.1 Public Hospitals

Health-care is free in India. Public hospitals are located in every town and city. Full time working medical practitioners are available 24 hours and seven days a week. Most of the hospitals contain specialists. Public hospitals located in the district headquarters have proper facilities with doctors specialized in various areas and with a capacity of 500-1000 beds. They perform all procedures free of charge. Even though health-care is free, due to a lack of proper funding, patients sometimes may need to buy drugs from the pharmacy. Each town contains only one public hospital for a population over 50,000. The number of public hospitals does not meet the public requirements. Most people belonging to the lower socio-economic class will visit public hospitals. The hospitals are not always properly maintained.

5.1.4.2 Private hospitals

The level of care in private hospitals is better than public hospitals. But most of the hospitals contain one or two doctors working full time. Each hospital is specialized in a particular area. Most of the private hospitals are located in the densely populated areas. People living in villages do not have access to private hospital services.

Some private hospitals located in the cities are very well equipped with modern equipment. They have a wide variety of specialists. Their quality of patient care meets the western standards. Similarly their charges are very high. Only wealthy people can afford

treatment in these hospitals. Most of the public and private hospitals do not perform routine pathological and diagnostic testing. Some doctors who perform tests have business links with diagnostic services.

On the other hand, doubtful medical practices are widespread at the village level. This arises from “so called” rural medical practitioners; who have no qualification, and title themselves as doctors. They are not allowed to prescribe any drug and to treat any patient but they do without holding any medical qualifications. The government does not recognise rural medical practitioners but also does not institute any restraint. Rural medical practitioners (RMP) are persons who have experience working under a qualified medical practitioner (QMP) for some time and gain some drug knowledge and then start their own clinic as a RMP. They usually charge less than QMPs. Their main goals are to prescribe as many drugs as possible and administer intravenous fluids to most of the patients as a method of achieving patient confidence. Generally, people from villages and small towns where 74% of India’s population lives will visit RMPs. The public doesn’t know the difference between a QMP and RMP. Even if they do, most cannot afford or have access to a QMP, who are not located in villages.

RMP's will use stethoscopes and blood pressure apparatus for every patient. Whether they know how to use it is not questioned. For most patients, they will prescribe parenteral drugs. They can then charge for the drug and the administration procedure. If the patient looks weak, they will administer intravenous fluids. Most of the patients feel very satisfied once the RMP's have administered fluids. Neither the RMP nor the patients understand the role of intravenous fluids. Some RMP’s have facilities like a rudimentary operating theatre. They are performing procedures like cesarean, and delivery. If the RMP cannot manage, he/she will recommend the patient to the nearest QMP located in towns who is in favour to him. So, that he/she can collect commission for each patient from the QMP. If the patient is lucky enough, the QMP treats; otherwise the patient dies.

Since both are dependent on each other for their businesses, even though the patient died because of RMP's inappropriate treatment, the QMP does not lodge a compliant.

Almost all the present knowledge on prescribing trends is derived from studies conducted in prosperous societies and these may not be relevant for developing countries in view of differing health problems and priorities. Lack of adequate information about prescribing patterns in less developed countries promoted the present investigators to study drug use in severe community-acquired pneumonia (SCAP) in a rural pediatric hospital, Sirsilla, Andhra Pradesh, India.

5.2 Methods

5.2.1 Setting and patient groups

A prospective study was conducted at Srujan Hospital for Sick Children (SHSC), Sirsilla, Andhra Pradesh, India, a 60-bed rural pediatric hospital. This study was categorised into two groups; Group 1 a pre-intervention cohort studied for three weeks and Group 2 a post-intervention group, studied for a similar period following the intervention.

5.2.2 Exclusion and inclusion criteria

All outpatients under 18 years of age diagnosed with SCAP were included in the study. If the patient was admitted as an in-patient, they were excluded from the study. Group 1 patients were excluded from Group 2.

5.2.3 Data collected

Data collected were patient demographic details such as age, weight, sex; and prescription related details such as drug name, dose, frequency, route and number of doses prescribed. The weight of most patients was not available on the prescription. The investigator weighed each patient in his office in Group 1. In Group 2, the weight was taken and written on the empty prescription form by nursing assistants before the patient visited the pediatrician. The nursing assistants notified the investigator whenever the diagnosis of SCAP was recorded. The hospital does not have a qualified pharmacist or qualified nursing staff. All prescribing was by medically qualified pediatricians.

5.2.4 Data collection methodology

The researcher collected the data from the prescription while the patients were paying the fees at the counter after visiting the pediatrician. SHSC contains a pharmacy where most of the patients will have their medications dispensed. The patients however, have no insurance or fee-for-service coverage. The study sample was collected during the hospital visiting hours i.e., 7.00 a.m. to 9.00 a.m., 12.00 p.m. to 4.00 p.m. and 6 p.m. to 9.00 p.m by the investigator who was a qualified pharmacist in that country.

5.2.5 Data analysis

The prescribing data were analysed for appropriateness against Australian National Therapeutic Guidelines for Respiratory Tract Infections [33] and Analgesics [34].

Australian National Therapeutic Guidelines (ANTG) for severe community acquired-pneumonia (2000 edition)

For children older than 10 years of age, erythromycin 10mg/kg up to 0.5 to 1g intravenously, 6-hourly PLUS benzylpenicillin 30 to 60mg/kg up to 1.2g intravenously, 4- to 6-hourly PLUS gentamicin 6mg/kg intravenously, daily. For patients hypersensitive

to penicillin, substitute for benzylpenicillin and gentamicin, ceftriaxone 50mg/kg up to 1g intravenously, daily or cefotaxime 50mg/kg up to 1g intravenously, 8-hourly. For children under 10 years of age, cefotaxime 50mg/kg up to 1g intravenously, 8-hourly or ceftriaxone 50mg/kg up to 1g intravenously, daily PLUS di(flu)cloxacillin 50mg/kg up to 2g intravenously, 4-hourly. The standard recommended dose for paracetamol - 15 mg/kg/dose orally, every 4 to 6 hours, to a maximum of 90 mg/kg/day

5.2.6 Statistical Evaluations

Populations were matched for demographics and the influence of the intervention by χ^2 analysis. Differences in parametric data were tested using Student's t-test. Based on α=0.05 and β=0.2 and a 20% change in drug prescribing and dose prescribing required a minimum sample of 80 patients in each group to achieve statistical significance.

5.2.7 Intervention

An intervention strategy involved a verbal presentation on appropriate drug treatment and provision of written drug information to the prescribers in the hospital. The weight of each patient was also provided. The results of the pre-intervention study were discussed with the pediatricians and specific guidelines were provided regarding appropriate choices and doses. A dosing chart was provided to the prescribers with dosing schedules according to weight.

5.2.8 Definitions

According to this study, an appropriate dose was classified as one prescribed within ±25% of the recommended dose. The designated dosage error of ±25% was based on the common variability allowed in dosage forms and bio-equivalency studies. An

inappropriate choice of the drugs / combination of drugs were those prescribed other than those recommended in the guidelines.

5.2.9 Ethical Issues

As this study involved an analysis of patient's prescription data, ethical issues relate to confidentiality and release of data. A unique non-patient identifiable code was allocated to each prescription to enable re-identification if necessary since the hospital holds a duplicate copy of the prescription. Any coded data to leave the hospital was kept secure in accord with National Health and Medical Research Council {Grandis JR, 1992 #148} guidelines and only group data released from the research. Informed consent was not required, because the study was classified as a quality control audit and the treatment was within standard of care for SCAP and prescribed independently of the study. The Curtin University of Technology Ethics Committee approved this study.

5.3 Results

The diagnosis of SCAP was made by the pediatrician and indicated on the prescription. Although hospitalisation is common with SCAP, it is not affordable for many in rural populations in India. It is therefore common to receive treatment as an outpatient.

The total study population was 301 patients of which 146 were in Group 1 and 155 in Group 2 (Table 5.4). There was no significant difference between genders (p value = 0.841) of the patients who participated in the study. The mean age of patients in Group 1 was 2.4 years and in Group 2 was 3.6 years with a statistically significant difference between the two groups ($p < 0.001$) (Table 5.5).

The prescribing of the drugs for the groups is summarized in the Table 5.6. Dexamethasone was prescribed (200-500 μg/kg/per day) for each patient given ceftriaxone and cefotaxime in Group 1 and none of the prescriptions in the Group 2 ordered dexamethasone following the intervention, showing a significant improvement ($p < 0.001$).

Table 5. 4 Profile of patient groups

Group	Group 1			Group 2		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Neonate	1	-	1	3	2	5
Infant	25	21	46	40	25	65
Toddler	17	19	36	10	11	21
Children	41	21	62	31	24	55
Teenager	1	-	1	8	1	9
Total	84	61	146	92	63	155

Table 5. 5 Influence of pharmacist intervention (Group 2) compared with usual care (Group 1) for rural pediatricians drug prescribing

Category	Group 1	Group 2	P value
Number	146	155	0.372
Gender	61F, 84M	63F, 92M	0.841
Mean age (years)	2.4	3.6	<0.001
Appropriate dose prescribed (ceftriaxone)	3/144	17/155	0.180
Appropriate dose prescribed (paracetamol)	61/135	137/152	<0.001
Dexamethasone prescribing	146	None	<0.001

Table 5. 6 Drug prescribing pattern for SCAP

Drugs prescribed	Number of patients
Group 1	
Ceftriaxone with dexamethasone and paracetamol	134
Ceftriaxone with dexamethasone	10
Cefotaxime with dexamethasone and paracetamol	1
Cefotaxime with dexamethasone	1
Total	146
Group 2	
Ceftriaxone and paracetamol	152
Ceftriaxone alone	3
Total	155

Of the total 144 patients on ceftriaxone in Group 1; 3 were prescribed an appropriate dose, 136 were 26-50% below the recommended dose, and 5 were on 51-75% below the recommended dose. In Group 2, 155 patients were prescribed ceftriaxone, of these 17 were on an appropriate dose and 14 were on a dose 26-50% below the recommended dose, 121 on 51-75% below the recommended dose and 3 on 76-100% below the recommended dose. There was no significant improvement in appropriate dosage prescribing in Group 2 compared to Group 1 ($p = 0.180$). Cefotaxime was prescribed only in Group 1. Of these, one patient was on an appropriate dose and the other on 26-50% below the recommended dose.

Of 137 patients on paracetamol for pyrexia in Group 1, 61 were on an appropriate dose, 9 were on 26-50% below the recommended dose, one on 51-75% below the recommended dose and the remaining 66 were on doses ranging from 26-50% to 126-150% above the

recommended dose. In Group 2, 137 patients were on an appropriate dose, 14 were on 26-50% below the recommended dose and one patient was on 51-75% above the recommended dose with an overall significant improvement ($p < 0.001$).

5.4 Discussion

This study has shown that there was an improvement in the treatment regimen and antipyretic dosages prescribed in SCAP patients following an educational intervention in a rural pediatric hospital in India. Even though there was a significant difference in the mean age of patients between the two groups, it is small and unlikely to have exerted any impact on the prescribing and data analysis. There was a slight increase in the number of appropriate doses of ceftriaxone in Group 2 compared to Group 1, but the improvement was not statistically significant. Sub-optimal dosing of antibiotics has two potential consequences: therapy failure and the possible emergence of resistance. In the western world antibiotic use is often strictly controlled, but on the whole a more judicious use of antibiotics has preserved the value of many of the traditional agents. In developing countries the widespread misuse of antibiotics, in combination with the spread of antibiotic resistance, has rendered several conventional antibiotics virtually useless.[36]

Most of the patients diagnosed as SCAP were treated as outpatients. The reason is that most parents cannot afford in-patient treatment due to high hospital costs and most of the parents have to work on a daily basis. If one/both of the parents stays with their child for in-patient treatment they will lose income and they usually cannot afford to pay the hospital bill. Most parents are from small villages surrounding the hospital, and visit for a consultation and medicines only. The hospital cannot accommodate every sick child due to a limited number of beds available.

In Group 1 98% of the patients and 89% in Group 2 on antibiotics were prescribed dosages below the recommended dose. The clinician has the responsibility to optimise the delivery of an appropriate antimicrobial agent to the site of an infection in concentrations that exceed those needed to inhibit the growth of the pathogen involved. An adequate level of a chemotherapeutic agent is particularly important for curing a infection in pediatric patients.[37]

Possible reasons for inappropriate dosage prescribing include (i) high antibiotic costs (ii) low monthly incomes of rural population (iii) poverty (iv) no medical insurance (vii) no government subsidised medications. For example, the cost of antibiotic treatment for a patient weighing 25kg and less than 10 years of age, diagnosed with SCAP would be as follows: cost of 1g dose of ceftriaxone is Rs 165 ($AUD 6.60) (the prices are drawn from the CIMS of India, 2000 edition). The mean duration of treatment for SCAP is 7-10 days. It therefore costs Rs 1155 ($AUD 46.20) – Rs 1650 ($AUD 66) per course for antibiotic treatment. In comparison to the antibiotic costs, the prescriber consultation fees, cost of paracetamol and other indirect costs are very low.

According to the recent survey by the National Sample Survey Organization{Grandis JR, 1992 #149}**,** there was 11.05% of the rural population below the poverty line. The per captia annual consumption expenditure was Rs 6606.36 ($AUD 264.25) in the state of Andhra Pradesh. Most patients cannot afford the total treatment costs; they buy medications for a reduced number of days than the prescribed number. In order to enhance patient compliance over the total duration of the course, pediatricians are prescribing low antibiotic dosages. This provides reasons for no improvement in the prescribing of appropriate dosages of ceftriaxone following the intervention. This was not the case with paracetamol, since paracetamol is affordable; prescribing dosages are not based on cost. Since, the prescribers did not know the weight of the patient, they guessed the weight and prescribe a dose as occurred in Group 1. Once a dosing chart and the weights of the patients were provided, there was a significant improvement in the

appropriate dosage prescribing of paracetamol in Group 2. Although the intervention period was relatively short it still demonstrates that pharmacists can have a positive impact on prescribing.

In India, health care is subsidised by the government and free medical care including medicines is available in government-sponsored hospitals. According to the annual report in 1998-1999 from the Govt. of India, there were 14,000 full-fledged hospitals, 810,538 hospital beds, 22,243 primary health care centers and 131,471 sub-primary health centers of which all are government owned in which 503,900 doctors are providing services to patients.{Grandis JR, 1992 #150;Grandis JR, 1992 #151} These numbers are low when the size of the population is considered and is below WHO recommendations.

India produces 20,000 diploma and 11,000 degree and 1000 postgraduates in pharmacy each year, which is more than any other developing country in the world. In most hospitals, the hospital pharmacy section is often consigned to a mediocre location and facilities are often outdated, antiquated and nonfunctional. Unlike the west, the role of the pharmacist in hospitals in India has until now not been fully utilized. Several training courses in hospital and clinical pharmacy have occurred since 1999 in India with the help of international bodies, but these developments are insignificant considering the size of the country.[41]

Ceftriaxone is a 3rd-generation cephalosporin with a prolonged half-life, a broad spectrum, and excellent bioavailability when administered intramuscularly, allowing effective once daily intramuscular treatment for pneumonia and many other severe community-acquired infections. It is also effective against many bacterial infections.[42-45]

In a study by Dagan et al[45], children and infants with community-acquired serious infections were safely and effectively treated as outpatients using a regimen of once daily ceftriaxone given intramuscularly. A retrospective study by Powell & Mawhorter[46], showed that ceftriaxone was efficacious for the completion of therapy on an outpatient basis after the drug had been initiated during hospitalisation for infants and children with serious infections.

Dagan et al[45] have also shown that there was a saving of 376 days of hospitalisation for the 72 successfully treated patients. The only cost during their treatment was for ceftriaxone and the daily clinic visits. This represents a considerable financial saving compared with the cost of inpatient management for those conditions. Furthermore all successfully treated patients and their parents resumed normal activity within 3 days after initiation of treatment.

In SHSC, dexamethasone was prescribed with every dose of parenteral antibiotic to prevent any anaphylactic reaction due to antibiotic administration. ANTG does not recommend any steroid administration with the parenteral antibiotic. Steroids in pharmacological doses depress cell-mediated immunity more than humoral immunity, leading to an impairment of monocyte/macrophage killing, antigen processing, and cytokine release. They may potentiate infection with intracellular pathogens due to suppression of release of γ-interferon, interleukin-1, and interleukin-2 from T-lymphocytes.[47] Stuck et al reported that, the overall rate of infection in patients receiving systemic corticosteroids was 13%.[48] It is noted that dexamethasone was prescribed in all patients in Group 1 and none in Group 2 following the intervention. It was found that none of the patients were readmitted to the hospital due to any anaphylactic reaction from antibiotic administration during the three-week study.

Children pose unique challenges to the system for ordering, dispensing, administering, and monitoring medications. For instance, since weight-based dosing is needed for most drugs in pediatrics, ordering medications typically involves calculations and therefore more potential errors than for adults.[49]

Paracetamol is an antipyretic, widely used in children, which does not induce nausea and vomiting. It has a good reputation for safety within the recommended dosage range. The antipyretic effect of paracetamol is directly related to its plasma concentration.[50] Patients on low anti-pyretic dosage suffer high temperatures, severe complications, longer duration of hospital stay and increased costs and patients on high dosage may suffer from hepatotoxicity. However, toxicity has been reported rarely with therapeutic doses when administered over several days in children who have concurrent illnesses such as fever, vomiting, and diarrhoea.[51]

In this study 55% of the children in Group 1 received doses above that recommended. Of particular concern were 8 children being prescribed more than 100% of the recommended dose. In addition to the immediate concern, medically prescribed dosages of medicines that are easily purchased subsequently such as paracetamol may lead to these dosages being continued when purchased elsewhere.

5.5 Conclusion

Severe community-acquired pneumonia presents challenges in the management of children, since its morbidity is significant, its diagnosis is intangible and the treatment choices are not always clear. Following the intervention there was no significant impact on the level of appropriate dosage prescribing of ceftriaxone and pediatricians have continued prescribing low doses of antibiotics to enhance patient compliance. Cost considerations were found to be a major contributing factor to the above problem.

Significant improvement was achieved in the level of appropriate dosage prescribing of paracetamol and following the intervention none of the patients were prescribed dexamethasone. There are social and economic factors influencing the prescribing of expensive drugs in the rural India.

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Chapter six

Evaluation of antibiotic and analgesic prescribing in Adenoidectomy, Tonsillectomy and Adenotonsillectomy procedures in pediatric patients

6.1 Introduction

Tonsillectomy (TON), adenoidectomy (ADD) and adenotonsillectomy (ADT) are the most common major surgical procedures performed by otolaryngologists in children younger than 15 years of age [1-3]. Although the frequency of those procedures has decreased from the peak levels of the 1960s, an estimated 140,000 US children underwent ADD, and 286,000 underwent ADT procedures in 1994 [2, 4, 5].

Times have changed dramatically since Cornelius Celsus performed the first known tonsillectomy almost 2000 years ago[5]. As surgical techniques have improved through the years, complications associated with TON have decreased. However, many patients experience pain and nausea postoperatively. These effects may limit their activity level and oral fluid intake, leading to dehydration and a prolonged hospital stay. Many otolaryngologists prescribe antibiotics for patients who undergo TON [6].

Prolonged adenoidal upper airway obstruction may result in obstructive sleep apnea or cardiorespiratory syndrome requiring prompt surgical intervention. Adenoidal hypertrophy which obstructs the nasal airway in children is associated with multiple symptoms, including snoring, nasal congestion and chronic mouth breathing [7]. Chronic sinusitis, recurrent otitis media associated with pediatric adenoidal hypertrophy are the common indications for surgical removal of the adenoids [8].

The purpose of this study was to evaluate the prescribing pattern of antibiotics and analgesics in ADD, TON and ADT procedures in children at a pediatric teaching hospital in Western Australia.

6.2 Methods

6.2.1 Setting and patient population

A retrospective study was conducted at Princess Margaret Hospital for Children, Subiaco, Western Australia, a 250-bed pediatric teaching hospital. All patients admitted for ADT, ADD and TON surgery were eligible to be included in this study. Drug prescribing for the above procedures was obtained retrospectively for all cases coded for each procedure over the period June to November 1999. The records were obtained from the Patient Information Management Services Department. Patient consent and ethics approval was not required since it was classified as a quality assurance audit.

Data was collected on the prescribing of antibiotics and analgesics for both prophylaxis and treatment and entered from the medical records onto a coded form. Patient details included age, weight, sex, date of admission, date of discharge, clinical details such as principal diagnosis and principal procedure and medication details including drug name, dose, frequency, route and number of doses administered. Prophylactic antibiotics prescribed were sourced from the operation drug sheet; drugs prescribed in the ward were obtained from the inpatient medication sheet and discharge medications from discharge medication sheet. The collected data were evaluated against the Australian Therapeutic Guidelines for Antibiotics [9] and Analgesics [10].

6.2.2 Australian Therapeutic Guidelines for Antibiotics and Analgesics

Pre-operative prophylaxis: According to the guidelines, prophylaxis should be considered for clean contaminated head and neck procedures that involve an incision through the oral, nasal, pharyngeal or oesophageal regions. The preferred regimen is cephalothin 25 mg/kg up to 2g or cephazolin 25 mg/kg up to 1g intravenously, at the time of induction.
Post-operative antibiotics: For post-operative treatment, amoxicillin 15mg/kg up to 500mg, PO q8h or cefaclor 10mg/kg up to 250mg PO q8h for seven days.
Post-operative analgesics: The standard recommended dose for paracetamol is 20 mg/kg/6hrly or 15 mg/kg/4hrly when required to a maximum of 100 mg/kg/24hrs. Ibuprofen, an alternative, should be given as a 5-10 mg/kg/dose, 6-8 hourly.

For this study, an appropriate dose was classified as one prescribed within ±25% of the recommended dose and an appropriate choice of the drugs / combination of drugs were those recommended in the guidelines. The designated dosage error of ±25% was based on the common variability allowed in dosage forms and bio-equivalency studies. Statistical evaluations were performed using $\chi 2$ analysis for non-parametric and differences in parametric data were tested using Student's t-test.

6.3 Results

A total of 221 patients' medical records comprising 115 males and 106 females were analysed. Of these patients, one infant (1 month to 1 year), 10 toddlers (1-2 years), 187 children (3-12 years) and 23 teenagers (13-17 years). Of 221 patients, 170 underwent ADT, 42 ADD, and 9 TON.

The mean age of the patients was 6.63 years. No significant difference occurred between the mean of age of patients for the procedures ADT & ADD but a statistically significant difference was found between ADT & TON and ADD & TON (Table 1).

In ADT, 6 different types of drug regimens and 2 in ADD were considered appropriate perioperative antibiotics (Tables 6.2 and 6.3). In TON procedures, 2 of 5 drug regimens were considered appropriate antibiotic choices (Table 6.4). All the discharge antibiotic regimens used in ADT, ADD and TON were considered appropriate (Tables 6.5-6.7). 110 out of 170 in ADT, 6 of 42 in ADD and 8 of 9 patients in TON were on peri-operative antibiotics and 112 of 170 in ADT, 7 of 42 in ADD and 7 of 9 in TON were on discharge antibiotics.

Table 6. 1 Comparison of mean age (years) between procedures

Type of surgery	Number of patients	Mean age	Standard deviation	P value
Adenotonsillectomy	170	6.33	3.13	0.966
Adenoidectomy	42	6.35	3.83	
Adenotonsillectomy	170	6.33	3.13	0.000
Tonsillectomy	9	13.6	3.3	
Adenoidectomy	42	6.35	3.83	0.000
Tonsillectomy	9	13.6	3.3	

Table 6. 2 Profile of antibiotic/s prescribed post-operatively in adenotonsillectomy

Drug/s prescribed	Number of patients
Amoxycillin	104
Amoxycillin + ceftriaxone	1
Augmentin	1
Cefaclor	2
Amoxycillin + cefotaxime	1
Cefaclor + gentamicin	1
No antibiotics	60
Total	**170**

Table 6. 3 Profile of antibiotics prescribed post-operatively in adenoidectomy

Drug/s prescribed	Number of patients
Amoxycillin	5
Augmentin	1
No antibiotics	36
Total	42

Table 6. 4 Profile of antibiotics prescribed in tonsillectomy

Drug/s prescribed	Number of patients
Amoxycillin	4
Benzyl penicillin + metronidazole	1
Benzyl penicillin	1
Flucloxacillin	1
Cefaclor	1
No antibiotics	1
Total	**9**

Table 6. 5 Profile of discharge antibiotics prescribed in adenotonsillectomy

Drug/s prescribed	Number of patients
Amoxycillin	111
Augmentin®	1
Cefaclor	1
No antibiotics	57
Total	**170**

Table 6. 6 Profile of discharge antibiotics prescribed in adenoidectomy

Drug/s prescribed	Number of patients
Amoxycillin	5
Augmentin®	1
Cefaclor	1
No antibiotics	35
Total	**42**

Table 6. 7 Profile of discharge antibiotics prescribed tonsillectomy

Drug/s prescribed	Number of patients
Amoxycillin	5
Augmentin®	1
Cefaclor	1
No antibiotics	2
Total	**9**

32 of 116 on amoxycillin prescribed peri-operatively and 30 of 121 on amoxicillin and 1 of 3 on cefaclor prescribed as discharge antibiotics are on appropriate dosages. 147 of 201 on Liquigesic, 101 of 123 on paracetamol, 7 of 7 on Panadeine, 21 of 27 on Panadeine forte and 10 of 10 on Ibuprofen are also considered as on appropriate dosage (Table 8-11).

Table 6. 8 Profile of drug dosage prescribing in adenotonsillectomy

Drug name	No of patients (doses) below the recommended dose		No of patients (doses) above the recommended dose	No of patients (doses) on appropriate doses	Total no of patients (doses)
	26-50% below	51-75% below	26-50% above		
Amoxycillin	66 (121)	14 (28)		26 (65)	106 (214)
Augmentin	1 (1)				1 (1)
Cefaclor		1 (2)	2 (18)		3 (20)
Cefotaxime				1 (12)	1 (12)
Ceftriaxone				1 (1)	1 (10
Gentamicin				1 (1)	1 (1)
Ibuprofen				8 (15)	8 (15)
Liquigesic	44 (119)	2 (2)		125 (281)	171 (402)
Paracetamol	13 (22)	1 (2)	4 (8)	78 (119)	96 (120)
Panadeine				4 (5)	4 (5)
Panadeine forte	5 (11)			14 (27)	19 (38)

Table 6. 9 Profile of drug dosage prescribing in adenoidectomy

Drug name	No of patients (doses) below the recommended dose		No of patients (doses) above the recommended dose	No of patients (doses) on appropriate doses	Total no of patients (doses)
	26-50% below	51-75% below	26-50% above		
Amoxycillin	2 (2)	1 (1)		2 (3)	5 (6)
Augmentin		1 (2)			1 (2)
Ibuprofen				1 (1)	1 (1)
Liquigesic	8 (12)			19 (23)	27 (35)
Paracetamol	2 (2)		2 (2)	17 (20)	21 (24)
Panadeine				2 (5)	2 (5)
Panadeine forte	1 (1)			2 (8)	3 (9)

Table 6. 10 Profile of drug dosage prescribing in tonsillectomy

Drug name	No of patients (doses) below the recommended dose	No of patients (doses) on appropriate doses	Total no of patients (doses)
	26-50% below		
Amoxycillin		4 (8)	4 (8)
Benzyl penicillin	2 (4)	1 (7)	3 (11)
Cefaclor		1 (1)	1 (1)
Flucloxacillin	1 (2)		1 (2)
Metronidazole		1 (4)	1 (4)
Ibuprofen		1 (1)	1 (1)
Liquigesic		3 (7)	3 (7)
Paracetamol		6 (6)	6 (6)
Panadeine		1 (2)	1 (2)
Panadeine forte		5 (12)	5 (12)

Table 6. 11 Profile of discharge drug dosage prescribing

Drug name	No of patients (doses) below the recommended dose		No of patients (doses) above the recommended dose	No of patients (doses) on appropriate doses	Total no of patients (doses)
	26-50% below	51-75% below	26-50% above		
Adenotonsillectomy					
Amoxycillin	74 (1554)	12 (252)		25 (525)	111 (2331)
Augmentin®	1 (7)				1 (7)
Cefaclor			1 (7)		1 (7)
Liquigesic®				1 (5)	1 (5)
Adenoidectomy					
Amoxycillin	4 (84)			1 (21)	5 (105)
Augmentin®	1 (21)				1 (21)
Cefaclor				1 (21)	1 (21)
Tonsillectomy					
Amoxycillin	1 (21)			4 (84)	5 (105)
Augmentin	1 (21)				1 (21)
Cefaclor		1 (21)			1 (21)

All the patients having TON & ADT procedures were prescribed one or more than one analgesic peri-operatively but in ADD 40 of 42 were only on analgesics. Paracetamol has been prescribed for 10%, paracetamol/codeine preparations for 52%, paracetamol and paracetamol/codeine preparations together prescribed for 33%, ibuprofen and paracetamol for 1.4%, paracetamol, paracetamol/codeine and ibuprofen for 0.9% and paracetamol/codeine and ibuprofen for 2.3% of the patients of the total analgesics (Table 12).

Table 6. 12 Profile of analgesics usage

Analgesics prescribed	Adenotonsillectomy	Adenoidectomy	Tonsillectomy
Paracetamol alone	9	12	1
Paracetamol/codeine preparations only	89	22	3
Paracetamol + paracetamol/codeine preparations	64	5	4
Ibuprofen + paracetamol	3	-	-
Paracetamol/codeine + ibuprofen	3	1	1
Paracetamol+ paracetamol/codeine + ibuprofen	2	-	-
Total number of patients on analgesics in the total	170/170	40/42	9/9

The total mean length of stay was 1.98 days. There was an increase in the mean length of stay in ADT and TON compared to total mean length of stay. Significant differences in the mean length of stay between ADT & ADD and ADD & TON but not between ADT & TON was found (Table 6.13).

No significant difference in the mean length of stay between patients received and not received antibiotics post-operatively in ADT and TON (Table 6.14). There was an increase in the mean length of stay between patients received antibiotics to patients not received antibiotics with a significant difference of p value equal to 0.001 (Table 6.15).

Table 6. 13 Comparison of mean length of stay between procedures

Type of surgery	Number of patients	Mean length of stay in days	Standard deviation	P value
Adenotonsillectomy	170	2.12	0.82	0.000
Adenoidectomy	42	1.35	0.48	
Adenotonsillectomy	170	2.12	0.82	0.724
Tonsillectomy	9	2.22	0.66	
Adenoidectomy	42	1.35	0.48	0.000
Tonsillectomy	9	2.22	0.66	

Table 6. 14 Comparison of mean length of stay between patients received and not received antibiotics

Category	Number of patients	Mean length of stay	Standard deviation	P value
Adenotonsillectomy				
Antibiotics	109	2.14	0.95	0.624
No antibiotics	60	2.08	0.52	
Adenoidectomy				
Antibiotics	4	2.0	0.000	0.002
No antibiotics	36	1.26	0.44	
Tonsillectomy				
Antibiotics	8	2.25	0.70	0.749
No antibiotics	1	2.0	-	

Table 6. 15 Comparison of mean length of stay of patients received and not received antibiotics

Category	Number of patients	Mean stay in days	Standard deviation	P value
Antibiotics	124	2.14	0.91	0.001
No antibiotics	97	1.77	0.63	

There was no significant difference in the mean length of stay found between patients received antibiotics between ADT & ADD, ADT & TON and ADD & TON and patients received appropriate and inappropriate antibiotic dosages in ADT &ADD (Table 6.16 to 6.17). And a statistically significant difference found between patients not received antibiotics between ADT & ADD (Table 6.18).

Table 6. 16 Comparison of mean length of stay between patients received antibiotics

Type of surgery	Number of patients	Mean length of stay in days	Standard deviation	P value
Adenotonsillectomy	109	2.14	0.95	0.759
Adenoidectomy	4	2.0	0.000	
Adenotonsillectomy	109	2.14	0.95	0.764
Tonsillectomy	8	2.25	0.70	
Adenoidectomy	4	2.0	0.000	0.506
Tonsillectomy	8	2.25	0.70	

Table 6. 17 Comparison of mean length of stay between patients received appropriate and inappropriate antibiotic dosages

Type of surgery	Number of patients	Mean length of stay in days	Standard deviation	P value
Appropriate (ADT)	28	2.4	1.1	0.138
Inappropriate (ADT)	84	2.1	0.9	
Appropriate (ADD)	2	2.0	0.000	0.541
Inappropriate (ADD)	4	1.75	0.5	
Appropriate (TON)	7	2.5	0.97	0.356
Inappropriate (TON)	3	2.0	0.000	

Table 6. 18 Comparison of mean length of stay in days between patients not received antibiotics between ADT & ADD

Category	Number of patients	Mean length of stay	Standard deviation	P value
ADT	60	2.08	0.52	<0.001
ADD	36	1.26	0.44	

6.4 Discussion

Tonsillectomy, adenoidectomy and adenotonsillectomy are still common procedures performed in the pediatric age group and are reportedly associated with significant

morbidity [11]. More than 200 patients underwent ADT, ADD and TON procedures at PMH in approximately six months. Most patients underwent an ADT procedure.

Streptococcus pyogenes was the pathogen responsible in 90% of cases of chronic tonsillitis in the 1990's, however there is increasing evidence that Haemophilus influenzae and Staphylococcus aureus may now play significant roles. Both of these organisms are β-lactamase producers and are characterised by multi-resistance to antibiotics. In the Colreavy study, patients were treated post-tonsillectomy with an antibiotic which provided cover against these organisms who were identified as chronic carriers [5]. Antibiotics administered intra-operatively and for 7 days after surgery showed in patients decreased pharyngeal pain and dramatically lessened duration of pain [12].

In 1956, Orzac noted the use of pre-operative and post-operative antibiotics to relieve pain [5]. In 1980's Telian et al [13] demonstrated that the use of pre-operative antibiotics decreased post-operative fever and pain, leading to improved oral intake of liquids. None of the patients in this study received any antibiotics pre-operatively.

Morbidity that children experience subsequent to surgery includes intermittent fever, throat pain, odynophagia with poor oral intake, weight loss, and a foul odour from the mouth following adenotonsillectomy procedures. Many surgeons attempt to prevent or minimise these symptoms by treatment with antibiotics in the postoperative period [13]. In this study, 121 of 218 (55%) patients were prescribed post-operative antibiotics and analgesics and the remaining patients were only given analgesics.

Grandis et al found a statistically significant improvement in postoperative morbidity in adult patients who received amoxycillin and clavulanic acid after tonsillectomy[14]. This

study identified 115 patients prescribed amoxycillin and two patients given amoxycillin/clavulanic acid as post-operative antibiotics.

The mean length of stay of patients who received antibiotics was higher than those on no antibiotics. A possible explanation is that patients whose procedure had warranted antibiotics may have been considered a greater risk so there was an increased length of stay. In general this only amounted to a few hours.

According to Jones et al, there was no significant difference between cefaclor and amoxycillin treated groups post-operatively for a period of seven days. They concluded that cefaclor should be reserved for the child who demonstrates a protracted or difficult recovery following the surgery [15]. In this study, 58% (127 of 218) of the patients received post-operative antibiotics for a period of seven days. Of these, 1% (3) patients received cefaclor and the remainder received amoxycillin as a discharge medication.

Underdosing in relation to the guidelines was identified in this study with 68% (83/121) of the patients on antibiotics and 22% (82/368) of prescriptions for analgesics having doses considered to be below the recommended minimum dose. Examples were: (i) 68/114 patients on amoxycillin (ward) and (ii) 79/121 patients on amoxycillin (discharge) were on 26-50% below the recommended dose. Suboptimal dosing of antibiotics has two potential consequences: those of therapy failure and the possible emergence of antibiotic resistance [8].

The ideal postoperative pain medication should provide adequate analgesia while minimizing side effects. Two of the most commonly used pain medications after pediatric ADT, ADD & TON were paracetamol and paracetamol with codeine [16].

Paracetamol is an analgesic widely used in children and does not induce nausea and vomiting. It has a good reputation for safety within the recommended dosage. The analgesic effect of paracetamol is directly related to its plasma concentration [17]. In this study, 73/359 prescriptions for paracetamol/paracetamol with codeine products were prescribed at 26-50% below the recommended dose, hence their full analgesic effectiveness may not be achieved. Low dosages of paracetamol might lead to preventable suffering of pain and a longer length of stay in the hospital.

The addition of codeine gives the theoretical advantage of two analgesics with different mechanisms of action combined to enhance analgesia [16]. In a meta-analysis of 19 trials, De Craen et al [18] found that the addition of codeine to paracetamol produced a 5% increase in analgesic effect. According to Harley and Dattolo [19] paracetamol with codeine appeared to be a more efficacious agent in the treatment of early post-tonsillectomy/adenotonsillectomy pain in children. They found that children treated with paracetamol with codeine appeared to resume normal night time sleeping patterns and return to a regular diet earlier than those treated with paracetamol alone.

NSAIDs are an attractive option for the relief of post tonsillectomy/adenotonsillectomy pain because of the neutralization of prostaglandin-induced inflammation and oedema. In children with severe airway obstruction, the potential for central nervous system depression, as would be seen with opiates, is averted [19]. Forbes et al. noted ibuprofen and ketorolac to be more effective analgesics, with fewer side effects than paracetamol with codeine. Ibuprofen was as effective as paracetamol with codeine in postoperative analgesia. Ibuprofen and paracetamol with codeine were equal in their effect on postoperative temperature control and bleeding. Furthermore, ibuprofen patients had much less nausea than paracetamol with codeine patients. Therefore ibuprofen appears to be a very useful alternative to paracetamol with codeine for these patients [12].

Besides evaluating antibiotic and analgesic usage in TON, ADT and ADD procedures in children, this study has in addition evaluated the dosage prescribing appropriateness in the same subjects. With respect to the latter it has identified dosages that warrant further review by clinicians.

Review is an essential element of drug policies in hospitals, but as far as antibiotic agents are concerned such a review should include a reconciliation of the guidelines and usage with antibiotic resistance and cost. The application of antibiotic policies will resulted in improved practices and reduced costs [20].

Providing feedback to clinicians regarding their own prescribing practices has been a successful technique for achieving behaviour change. Feedback can entail comparisons with peers or with a standard. As with practice guidelines, feedback may be most effective when the system is developed with local input, where clinicians accept the measures as important, fair, and relevant to their own practices [21].

Ideally, the pharmacist should be involved in pursuing the above objectives through continually monitoring prescribing, providing information to new doctors and nurses and maintaining the process of drug use review.

6.5 Conclusion

In the study subjects, the major finding was that the dosages prescribed for post-operative and discharge antibiotic and analgesics were somewhat lower than those recommended in the current guidelines. None of the patients received prophylactic antibiotics and many patients did not receive post-operative and discharge antibiotics. When prescribed most

of the patients received a recommended post-operative antibiotic regimen and a small number of patients were administered both the recommended choice and dosage of antibiotics.

6.6 Reference

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Chapter seven

General Discussion

7.1 Discussion

This thesis has considered major areas of drug usage in pediatric settings. It has identified that the interventions used can have an impact on prescribing including the dosage levels. Different intervention strategies were used in each study to alter the prescribing behaviour. Different studies have shown varied levels of change in the prescribing behaviour according to the type of intervention implemented.

This thesis has investigated quality use of medicines in a range of pediatric settings including some limited but important studies in developing countries. In terms of the evaluations in pediatric hospitals an overall approach to understanding usage was initially studied. Drilling down from that broad evaluation then occurred to investigate in depth specific treatments in selected disease states. These were selected based on usage patterns e.g. ceftriaxone where there was potential for the usage to be modified where other antibiotics were recommended in Australian or local guidelines. In the pediatric setting dosage is a much greater factor since it varies with respect to age, weight or surface area. Dosage being less variable in adults except in a small number of drugs with a narrow therapeutic range is often less important. In previous studies in pediatric settings involving rational drug usage dosages have received a low priority.

To have any influence on drug usage there has to be the ability to communicate and achieve a consensus. The availability or development of national or local policies against which usage can be evaluated frequently creates circumstances where changes can be implemented[1].

A range of methodologies has been employed in these studies. The random controlled trial (RCT) is considered the gold standard for providing a high level of scientific validity. The normal methodology for a RCT is not directly applicable to drug usage studies involving interventions since the intervention cannot usually be contained or blinded to one group of prescribers. Hence the pre-post design is the most common approach adopted. The weakness in this design is that change may have occurred as a result of external factors (e.g. a recently published paper). This design is strengthened by the use of a control group and time series analyses with respect to the intervention.

The above methodology was adopted for these studies as the most appropriate for this type of investigation. Data collection can be retrospective or prospective. In this study both were used but in the main study retrospective collections were performed. The advantages of retrospective studies are the lack of influences on prescribers. It is advantageous to adopt standard methodologies to eliminate bias in data collection. The major issue in retrospective collections is insufficient or deficient data recorded. This was not a significant factor in these studies.

Several studies have evaluated drug usage in children[2-7], and in pediatric appendectomy[8-10], but none of the studies considered dosage prescribing appropriateness in children. Our study has identified that pharmacist intervention influences drug dosage-prescribing appropriateness of pediatricians in pediatric settings.

In this study the term appropriateness related to the prescribing of dosage or drug or both in accordance with the guidelines used in this study. The term appropriateness has been defined differently in different studies. In a French study by Talon et al.[11] which evaluated surgical antimicrobial prophylaxis, used the terms acceptable and unacceptable in their study. A multi-centre study by Bailly et al.[12] on surgical antibiotic prophylaxis in eighteen hospitals used the terms justified and not-justified. Tunger et al.[7] used the terms

rational and irrational use for antibiotics. The terms defined in other studies have a similar meaning to this study where we have used appropriate and inappropriate.

7.2 Practice guidelines

Practice guidelines have been developed in many countries and become well recognized[13]. The value of using guidelines as the underlying arbiter in this study is the view that they are independent, involve multidisciplinary groups either local national or international in their development and the information is clearly defined[14].

Often guidelines provide recommendations based on cost-effectiveness as part of their decision-making, although the main aim is to reduce inappropriate practices. The literature includes methodological approaches for the development of guidelines[13, 14].

This study has commonly employed the Australian Therapeutic Guidelines. Initial studies have shown that despite popularity there was only limited antibiotic prescribing that complied with the recommendations[15]. Many studies have identified the value of guidelines as an acceptable basis for clinical practice[16]. Poor acceptance usually arises from a lack of ownership or where there is difficulty in application at the clinical interface[16, 17]. This study had built on the general acceptance of national and local guidelines being accepted bases for quality prescribing. This has not been questioned in areas of the studies carried out.

7.3 Therapeutic guidelines and studies on surgical prophylaxis and antibiotic usage

The Therapeutic Guidelines indicated that for abdominal surgery adequate concentrations of antimicrobial must be present prior to surgery. A single dose is usually sufficient unless the procedure is longer than 3 hours. Several alternatives are available however

cefetotan is recommended as a single agent at the time of anaesthetic indication{Grandis JR, 1992 #54}.

This recommendation was adopted within the hospital following appropriate consultation. The second-generation cephalosporins are used widely in surgical prophylaxis and are a current recommendation for appendectomy procedures[19-21]. In a review, which has evaluated the literature, cefotetan (n = 389) had a low rate in infection failure at 8.4%, lower than most other commonly used regimes. The adverse event rate for cefotetan was slightly higher than some other regimes however the range is less marked. An overall assessment of cefotetan selected for this study was as good or better than combination therapy with respect to overall efficacy[22]. The major advantage was the simplicity of a single dose. This allows it to be used in a similar way to ceftriaxone, as this is an inappropriate choice because of its potential for producing resistance.

Emil et al.[23] evaluated the current therapeutic recommendations for appendicitis in children in pediatric surgery department. In their study, gentamicin (2mg/kg) and clindamycin (10mg/kg) were given as prophylactic antibiotics to all the patients. For simple or normal appendectomy, no further antibiotics were administered post-operatively.

In this appendectomy study, for routine prophylaxis including patients with 'non-anaphylactic' penicillin allergy, cefotetan 50mg/kg IV (maximum dose of 1g) as a single dose was given at the time of induction of anaesthesia. Patients with a history of penicillin allergy, clindamycin 10mg/kg IV (maximum dose 600mg) and gentamicin 7mg/kg IV, was given as a single dose at the time of induction. To determine whether the appendix was normal or not, was based on the pathology report irrespective of the surgeons diagnosis. Generally the pathology report was sent to the surgeon two days after the surgery. In the mean time, surgeons might have given antibiotics post-operatively. In

this study, patients with a normal appendix also received post-operative antibiotics. Even though different prophylactic regimens were used in the Emil et al. study, they worked effectively. But the outcomes were different from our study. Their infection rate was higher 88/648 (13.6%) than ours 2/207 (0.9%), length of stay was lower, and the number of patients that did not receive prophylactic antibiotics was 21/648 (3.2%) lower than our study 18/102 (18%). It is difficult to reconcile these to antibiotic solution or other circumstances.

In the study by Bailly et al. 112/117 (95.7%) patients received an antibiotic with a broader spectrum of activity than that recommended; mostly third generation cephalosporins or quinolones instead of first or second-generation cephalosporins or co-amoxiclav. In a study in Thailand[24], second or third generation cephalosporins were given when cefazolin would have been equally effective, which was classified as an inappropriate choice of antibiotics for surgical prophylaxis. In their study, they concluded that third-generation cephalosporins should not be prescribed for surgical prophylaxis, as the use of these broad-spectrum agents leads to unacceptable increases in hospital costs and the emergence of resistant bacteria and superinfections. In our study, 58% (59/102) of the patients were on third generation cephalosporins in the pre-intervention study, which was decreased to 6% (6/105) following the implementation of multi-faceted educational intervention program. Knowledge of diagnostics and therapeutics is believed to play a role in inappropriate prescribing of antibiotics. Doctors in their desire to use 'potent' medicines, tend to use newer, broad-spectrum, more expensive agents, as opposed to cost effective, proven, well-established and documented antimicrobial agents[25].

Van Houten et al.[6] analysed the utilisation of antibiotics in a pediatric hospital over three consecutive years, with special regard to antibiotic prescription attitudes and patterns. They found that children admitted to intensive care units and young children are especially at risk of receiving multiple courses of antibiotics. A total of 1120 patients

were admitted during the study period in their study, of which a mean of 36% received at least one course of antibiotics during their hospitalisation. During the study period a shift to the use of more expensive and broader spectrum antibiotics was noticed for all groups. In the initial broad study of drug usage reported in this thesis 25.5% of patients were prescribed antibiotics.

7.4 Intervention studies

In our study, 0% of patients were on an appropriate prophylactic antibiotic regimen, which was increased to 68% and appropriateness of total antibiotic dosages from 0% to 57% following the implementation of treatment guidelines developed by the pharmacy department in conjunction with microbiology and surgical services divisions through a multifaceted educational intervention program. In community-acquired pneumonia where data was collected for two weeks before and after the implementation of the intervention by giving feedback of the pre-intervention study results. An educational intervention program carried out in Thailand[24] has a similar methodology as the community-acquired pneumonia study and guideline development in the appendectomy study. They found that a 22% reduction in the prevalence of antibiotic use for in-patients, and a 23% for out-patients occurred after the intervention. The cost of antibiotics was decreased by 20%. In a pediatric department, the prevalence of antibiotic use in in-patients decreased from 59% to 50% and 54% to 36% in the out-patient setting. In their study, the guidelines for the appropriate use of antibiotics was developed by an antibiotic use committee with support from clinical, pharmacology, microbiology and finally approved by the medical department. The intervention was implemented by providing training sessions for individual groups of prescribers separately. Feedback was given two weeks following the intervention and the impact was then evaluated for a week after the intervention. However the intervention was a single workshop and followed for only one week. Its long-term impact is therefore unknown.

Gorecki et al[26] compared the efficacy of Surgical Infection Society (SIS) guidelines versus common practice for antibiotic usage in pediatric surgery patients. They defined appropriate prophylactic administration, which was adopted from SIS guidelines but failed to define the acceptable dosage error in the study. There was no pre-intervention study to compare the impact of the guidelines.

The study was divided into two groups, Group A prescribers were SIS guideline supporters and Group B common practice supporters. The mean duration of antibiotic treatment was 3.9 days in Group A and 7.1 days in Group B, antibiotic usage appropriateness was 77% and 36% and excessive duration of treatment received was in 31% and 54% of patients. Their effort to follow the SIS guidelines resulted in significantly better antibiotic usage than in the comparative group B.

They stated that the inability of the clinician to distinguish between inflammation, contamination, and infection and the failure to stratify its severity were the main reasons for the excessive administration of antibiotics. Consequently, courses of treatment were continued for periods much longer than needed. The current pediatric surgery environment demands the provision of quality health care at an affordable cost. Both payers and regulators are committed to lowering cost through initiation of best practice strategies that include practice guidelines, clinical pathways, and standards of care[26].

In our study, we evaluated the dosage of inappropriately administered antibiotics to evaluate the ability of surgeons to prescribe recommended antibiotic dosages appropriately. This gives information about surgeon's ability to prescribe other drug treatments also. The definition of dosage and acceptable dosage error was clearly defined in our study. In a study by Talon et al.[11] both indication and choice of antibiotic were considered inappropriate, dosage was not evaluated. How was the dosage evaluated and the definition for the appropriate dosage was not mentioned in their study. The

percentage of patients on appropriate dosage of antibiotic was higher than in our study since adults were given fixed dosage units, the chances of prescribing an inappropriate dosage is therefore lower.

Emil et al. in their study on appendicitis in children, dosage appropriateness was not defined and also not evaluated[23]. In a multi-centre study by Bailly et al., dosage evaluation was considered but not defined what was the acceptable appropriate dosage error in the study[12]. Tunger et al. collected data related to dosage of antibiotics, but never considered their appropriateness[7].

A recent French study[11] in adult patients in four surgical departments evaluated the surgical antimicrobial prophylaxis in various procedures before and after the implementation of local guidelines, found that 75/101 (74%) of patients were on appropriate antibiotic choice which changed to 124/129 (96%) following the intervention. The number of patients on appropriate dosage was 72/77 (96%) improved to 123/124 (99%). The total appropriateness in their study was 45/145 (31%), which increased to 114/139 (82%) following the intervention with a significant difference. The success of their intervention was due to the development of guidelines by anaesthetists in collaboration with surgeons, who are the main antibiotic prescribers in the theatre and surgical department. In our study, clinical pharmacists in conjunction with clinical microbiologists and the division of surgical services developed the guidelines. We also achieved a statistically significant improvement in the total appropriateness of antibiotic prescribing in appendectomy procedures following the implementation of local treatment guidelines.

Dean et al.[27] evaluated the impact of their intervention following the implemented treatment guidelines for community-acquired pneumonia. In their study, they implemented the guidelines by giving formal presentations, academic detailing, letters,

reminders by pharmaceutical representatives, pre-printed outpatient and admission order sheets, and reporting of outcome data to providers[26]. This is similar to our multi-faceted educational intervention program implemented in appendectomy study. In our study, we released a newsletter, gave presentations, held formal discussions, posted guideline posters in ward and theatre and reminded by clinical pharmacists in the wards.

The limitations of their study were data related to specific antibiotic use and severity of the pneumonia patients were not evaluated. However, among all patients admitted to the Intermountain Health Care hospitals during the study period, the percentage that were treated with a guidelines-recommended antibiotic regimen increased from 677/2350 (28.1%) to 1386/2462 (56.3%) before and after the implementation of the guidelines[27]. Although a significant improvement, the extensive nature of the intervention has had only a moderate effect.

Berbatis et al.[28] evaluated the effect of drug bulletin on prescribing of oral analgesics before and after the release of drug bulletin. They found a marked improvement in prescribing but the effect was short-lived. Drug bulletins can be used to create an awareness of specific prescribing problems and achieve a temporary change in prescribing patterns.

Dobrzanski et al.[29] evaluated the impact of guideline introduction on peri-operative antibiotic prescribing of surgeons in a district general hospital. They found a decrease in the number of antibiotic doses, total cost per patient, and increase in the number of patients on appropriate therapy. In their study they did not mentioned how the intervention was implemented or guidelines developed. A major financial impact was shown with the mean antibiotic cost per patient. The pharmacist interaction program with verbal consultation between pharmacists and physicians was effective in improving overall compliance compared to newsletter intervention and control groups[30].

Davis et al.[31] reviewed 50 randomised controlled trials to assess the impact of diverse continuing medical education interventions on physician performance and health outcomes and they showed that the methods of continuing medication education were very important in changing the behaviour of clinicians. The method of disseminating information alone produced mostly negative or inconclusive results whereas the methods of dissemination of information plus the measure facilitating the desired change in the practice site or reinforcing via reminders or feedback consistently improved physician performance and in some instances, health outcomes. In the area of prescribing antibiotics, it has been shown that antibiotic guidelines or mailed brochures alone were unlikely to be effective[32, 33], although some of the studies found a minimal effect[29]. However, when other interventions such as problem-oriented training sessions, face-to-face information via pharmacist or physician visits, reminders, or information campaigns were used or combined in the educational program, they were likely to be effective in improving antibiotic use[34, 35].

In this drug utilisation evaluation study, a change of appropriateness of dosage prescribing of ceftriaxone from 58% to 89% ($p<0.001$), flucloxacillin from 68% to 90% ($p<0.001$) and Liquigesic Co® from 73.8% to 73.9% ($p>0.05$) was noticed following the release of dosage guidelines in the form of a newsletter and given formal presentation by chief pharmacist. The intervention had an impact on the dosage prescribing of ceftriaxone and flucloxacillin. Liquigesic Co® dosage appropriateness did not show any significant improvement following the intervention. This shows that the intervention, which was the same methodology as for antibiotics, showed success for antibiotics and had no effect on analgesic prescribing. On further investigation it was found that prescribers were using a monograph, which is not endorsed by the hospital and also did not match the current guidelines for dosages of analgesics. When newsletters were used alone, without clinical pharmacist involvement they are not capable of affecting a large-scale change in the

short-term particularly if the motivation to change is low. If the degree of resistance is high, this intervention program should begin well in advance of the change.

The percentage of patients on total antibiotic dosage in the appendectomy study was 31%, 75% in drug utilisation evaluation study, 7% in community-acquired pneumonia study and 17% in tonsillectomy study and 67% of anti-pyretic dosage in liquid medication dosing errors study were identified as appropriate. Using antibiotics at an inappropriate dosage can led to resistant strains. Guillemot et al[36]. found that children treated with low daily doses of oral β-lactams had an increased risk of penicillin resistant streptococcus pneumococci carriage compared with children who did not. Patients on low anti-pyretic dosages suffer high temperatures, severe complications, longer duration of hospital stay and increased costs and patients on high dosage may suffer from hepatotoxicity. Following the implementation of the educational intervention program and introducing guidelines in appendectomy, providing feedback of the pre-intervention study results compared against national guidelines along with the treatment guidelines reinforced in all studies except in tonsillectomy, achieved a statistically significant improvement.

Table 7. 1 Summary of dosage appropriateness in all studies

Study	Category	Pre-intervention	Post-intervention	P value
DUE	Ceftriaxone	50/86 (58%)	68/76 (89%)	<0.001
	Flucloxacillin	108/157 (68%)	87/96 (90%)	<0.001
APP	Total antibiotic	0/102	60/105 (57%)	<0.001
	Total analgesic	159/222 (71%)	244 /260 (94%)	<0.001
LMDE	Paracetamol (overall)	76/175 (43%)	160/162 (99%)	<0.001
CAP	Ceftriaxone	3/144 (2%)	17/155 (4.5%)	0.180
TON	Total antibiotic (post-operative)	38/218 (17%)	-	-

Different studies in this thesis have shown varied levels of inappropriateness in the prescribing of medications by pediatricians. But, the common basis of inappropriateness was the dosage prescribing. Prescribing inappropriate dosages was evident in both Australian and Indian studies reported in this thesis. Pharmacist educational intervention both initially and reminders had significantly improved appropriate dosage prescribing in the Australian studies. In Indian studies, the improvement was only seen in low cost drugs due to lower income patients who cannot afford expensive antibiotics. Hence the social context was clearly important in achieving change. In the Indian setting a more appropriate antibiotic, which would provide a similar outcome to ceftriaxone but is cheaper and at the first or second generation level needs to be identified.

7.5 Pneumonia studies

In community-acquired pneumonia study, the impact of intervention was seen in areas where there is no increase in cost of drug treatment to the patient. High antibiotic costs, low monthly incomes, poverty, no medical insurance and finally no government subsidies for prescription medications are the reasons led to the inappropriate dosage prescribing of antibiotics by pediatricians in that settings. Even though prescribers were aware of the appropriate dosage, intentionally they are prescribing low dosage to enhance patient compliance of taking medicines by reducing the cost of drug treatment. In this type of situation, if the pediatrician was to prescribe appropriate dosages, the patient cannot afford to buy the medicines, and the patient might shop around to find a cheaper drug treatment for their condition. Henceforth, the government should take an initiative to provide subsidies for essential drugs for at least people below poverty in India.

In SHSC, dexamethasone was prescribed with every dose of parenteral antibiotic to prevent any drug reaction. Since there exits no system for reporting a suspected reaction,

and there is no official mechanism for alerting doctors of possible adverse reactions, the doctors are taking precautions to avoid any adverse events. Drugs are prescribed based on their familiarity rather than their efficacy and safety in pediatric patients in India. Following the intervention, the dexamethasone prescribing was stopped and no patient was re-admitted due to any adverse event.

In developing nations bacterial infectious diseases are among the major clinical problems that the medical practitioner should be expected to manage with a high degree of skill and expertise. Therefore, the medical education system is obligated to prepare physicians to understand the key elements of medical microbiology and the fundamentals of pathogenesis, diagnosis, natural history, immunization, and chemotherapy of infectious diseases. It should be emphasised in the curriculum that the ultimate objective of this training is the welfare of the patient and that effective therapy can be accomplished best when the physician also understands the patients social, cultural, and economic background[37].

7.6 Parental education studies

In our liquid medication dosing errors study, we evaluated the ability of parents to measure the liquid medication correctly pre-post educational intervention by demonstrating how to measure a dose along with a marked syringe by a pharmacist. A significant improvement in the measurement of liquid medication by parents was achieved irrespective of their educational status with a simple educational intervention program implemented by a qualified pharmacist in India. This finding is similar to a study by Taylor et al.[38] conducted a randomised controlled trial to determine whether "Your Child and Antibiotics", accompanied by a short videotape message reinforcing the key points in the pamphlet, would be effective in improving parental attitudes about the judicious use of antibiotics. The effect of the intervention was similar in parents of differing educational levels on antibiotic usage.

Parents in the intervention group had significantly different attitude scores about antibiotic use in their children from those in the control group. Parents who received the antibiotic education materials were statistically less likely to agree that antibiotics are necessary when a child's nasal discharge turns to green in colour, that it is worth trying an antibiotic in their children when upper respiratory infections (URI) symptoms persist for 5 days, that antibiotics are useful in treating colds, that giving antibiotics to a child with a URI can prevent a bacterial infection, and that antibiotics help URI symptoms clear up more quickly than parents who did not receive these materials[38].

Trepka et al.[39] assessed the impact of a multifaceted community-wide effort to reduce the inappropriate use of antibiotics. The intervention consisted of distribution of the pamphlet "Your Child and Antibiotics" and presentations to groups of parents and providers. Parents of young children who resided in the intervention and a control community were surveyed before and after the educational effort. Parents who lived in the exposed community had a significantly greater increase in awareness about antibiotic resistance than those in the control community. In addition, the reduction in the number of viral respiratory illness diagnoses for which parents thought antibiotics were indicated was greater in the intervention community.

In a study of similar design to Taylor et al., Bauchner et al conducted a randomised controlled trial of the effectiveness of an educational 20-minute videotape and accompanying brochure in modifying parental knowledge and attitudes about antibiotics. Parents who were randomised to the intervention group received the educational materials, whereas those in the control group did not get any materials. After responses on the initial questionnaires were compared with the pre-intervention group, there were few differences found between parents in the intervention and control groups on the second questionnaire[40].

In our study on liquid medication dosing errors following the implementation of pharmacist educational intervention to the prescriber on appropriate dosage prescribing and to parents on measuring a correct liquid medication dosage, shown a significant improvement from 76/175 (43%) to 160/162 (99%). Pharmacists also could be involved in developing education programs and drug therapy protocols. Limited published data are available regarding the role of the clinical pharmacist in reducing medication errors in children. Fortescue et al.[41] found that a clinical pharmacist's monitoring ordering might have prevented 58% of all medication errors and 72% of potentially harmful errors related to dosing. Pharmacists monitoring transcribing might have prevented an additional 20% of all errors and 13% of potentially harmful errors. Pharmacist intervention involving parental and pediatrician education can be very effective in improving the administration of medication and prescribing of appropriate dosage to the pediatric patient.

Since cost is not a factor in paracetamol prescribing, the pediatricians are willing to prescribe appropriate dosage according to the recommended guidelines provided and parents are administering correct liquid medication dosage according to the recommendation made by the pediatrician with the help of pharmacist consultation in India.

After the release of a report by Institute of Medicine entitled " To Err Is Human[42]" by the committee on quality of health care in America in 1999, many studies have assessed medication errors in children and adults in USA. None of the studies evaluated the combined effect of prescribing and administration error to a pediatric patient. In this study, we evaluated the affect of pharmacist intervention on parents' measurement and pediatrician prescribing appropriateness and also evaluated the combination error, which

led to inappropriate dose, was incorrectly measured to overall result in appropriate dose in pediatric settings. This study of its kind is first to be carried out in India or elsewhere.

In our studies, we demonstrated that establishing a formal policy to govern antibiotic use and giving feedback of the prescribing to physicians might help to rationalise questionable prescribing and with improved patient care. The most immediately apparent impact of the guidelines was that fewer doses of antibiotics and unnecessary antibiotics and appropriate prophylactic antibiotics were given in appendectomy study, reduced inappropriate antibiotic dosage prescribing in drug utilisation study, increased adherence to guidelines on the choice of drugs and non-prescription of dexamethasone following the intervention in community-acquired pneumonia, improvement in the prescribing of anti-pyretic doses and measurement of correct liquid medication doses in liquid medication dosing errors and identification of errors in prescribing doses and omission of prophylactic antibiotics in tonsillectomy study was reported. It might be argued that patients in our studies gained benefit in not receiving unnecessary drugs, and there was, in turn, a reduced workload for medical and nursing staff in terms of drug administration. The reduction in the inappropriate antibiotic and analgesic dosage was achieved in our studies was therefore a reduced likelihood of the emergence of bacterial antibiotic resistance and unnecessary patient sufferings.

Drug utilisation studies need to perform regularly by pharmacists in order to improve physicians prescribing and implement policies and procedures in the hospitals in conjunction with other departments. While doing so increased patient care can be achieved and probably reduced financial burden on the government. More studies needs to be performed on children since they pose unique challenges to the system for ordering, dispensing, administering, and monitoring medications.

7.7 Conclusions

The study has achieved through pharmacist educational interventions implemented in this thesis:

- Improvement in the prescribing of appropriate dosages of ceftriaxone and flucloxacillin across the hospital
- The choice and dosage of pre-and post-operative antibiotics and analgesics were significantly improved in appendectomy patients
- Improvement in the prescribing and measurement of correct liquid medication dosages were achieved in out-patients in a rural hospital setting in India
- Prescribing of dexamethasone along with every antibiotic was ceased in community acquired pneumonia in a rural hospital in India

The following outcomes were identified in studies carried out in this thesis

- Evaluation of drug usage and implementation of local guidelines along with feedback of the pre-intervention results has resulted in improved practices
- Locally developed guidelines are more likely to be accepted and followed than those developed nationally without local input and promotion
- Ability of parents from rural areas of a developing country to measure a correct liquid medication dosage can be improved by pharmacist intervention
- Cost considerations were found to be a major contributing factor to the prescription of low dosage of ceftriaxone in India
- None of the patients received prophylactic antibiotics and many patients did not receive post-operative or discharge antibiotics in tonsillectomy procedures
- The dosages prescribed for post-operative and discharge antibiotics and analgesics were often significantly higher or lower than those recommended in current guidelines

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Appendix 8. 1 Publications and Presentations

Publications

Publication 1

Liquid Medication Dosing Errors: a pre-post time series in India

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International Journal of Pharmacy Practice. 2003, 11; 105-110

Abstract

Objective To evaluate the influence of pharmacist intervention on the level of parental dosing measurement errors and pediatrician dosage prescribing in a clinic in India.

Design and setting The study was conducted at Srujan Hospital for Sick Children, India. The design involved 175 children prescribed paracetamol and assigned to a standard treatment (Group 1). Following an educational intervention including feedback on dosages prescribed for Group 1 and promotion of a dosing chart for prescribers and individual dosing education for parents, 162 patients were admitted to the intervention group (Group 2). Patients in Group 1 received paracetamol suspension and verbal instructions from hospital staff (standard care). Parents in Group 2 were provided with a syringe with a line marking the prescribed dose and its use demonstrated to them by the pharmacist. Data on the dosages prescribed and measurement accuracy by parents were obtained for both groups.

Main outcome measures (i) improvement in the measurement of correct dosages by parents (ii) improvement in the prescribing of appropriate dosages by prescribers

Results In Group 1 85 of 175 (48.9%) correctly measured (±0.5ml) doses and pediatricians prescribed 67 of 175 (38.2%) appropriate dosages. In Group 2, 160 of 162 (98.7%) parents measured the correct dose and physicians prescribed 160 of 162 (98.7%) appropriate dosages showing statistically significant improvements in both indicators ($p<0.001$). When the impact of prescribing and dosing correctness was combined on an

individual patient basis, 76 of 175 (43.4%) were appropriate in Group 1, whereas 160 of 162 (98.7%) were appropriate in Group 2. There was a statistically significant improvement ($p<0.001$) in appropriate dosing outcome between the two groups.

Conclusion Pharmacist intervention through patient education including the use of a syringe significantly improved parents dosing accuracy and physicians prescribing errors in a country where currently pharmacist involvement is minimal.

Presentations

Presentation 1

Treatment of Community-Acquired Pneumonia at a Rural Indian Pediatric Hospital

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This study is presented at the following conferences:
American Society of Health System of Pharmacists, Baltimore, USA, 2002
The Mark Liveris Health Sciences Research Student Seminar, Perth, Australia, 2002
Australasian Pharmaceutical Science Association, Melbourne, Australia 2001
Pharmaceutical International Federation, Singapore, 2001

Objective. This study was to evaluated drug therapy provided to pediatric patients diagnosed with community-acquired pneumonia (CAP) at a pediatric hospital, India in order to compare prescribed drug therapy in relation to Australian National Therapeutic Guidelines (ANTG) and evaluate the impact of an intervention on prescribing trends in drug management.

Method. Prescribing data of pediatric patients with CAP treatment were collected prospectively for four weeks from outpatients in Group 1. Patient details included age, weight, sex, and medication details including drug name, dose, frequency, and number of doses administered were documented on a standardised form. These data were analysed according to the ANTG. An intervention strategy involved, presentation of results and provision of drug information to the prescriber. A post-intervention study in Group 2 was conducted after an intervention to evaluate the impact.

Result. The study evaluated 171 patients, of which 146 were diagnosed as severe CAP and 25 as mild CAP in Group 1. For severe CAP, a combination of ceftriaxone, dexamethasone and paracetamol was prescribed for most patients and for mild CAP,

ciprofloxacin and paracetamol. Of these 98% (1005/1021) of ceftriaxone, 16% (36/215) of ciprofloxacin, 54% (861/1597) of paracetamol doses were classified as inappropriate according to ANTG. The major factors influencing these data were low and high dosages and inappropriate drug choice. In Group 2, 155 patients were diagnosed as severe CAP. Of these, 152 were on ceftriaxone and paracetamol and 3 other. Inappropriate prescribing of paracetamol and ceftriaxone doses has been reduced to 9% (186/1992) and 89% (1208/1354) and none of the patients received dexamethasone in Group 2. The intervention had a statistically significant (p value=0.000) in the reduction of inappropriate prescribing of paracetamol and dexamethasone in this setting.

Conclusion. This study reveals that (i) there was an improvement in the prescribing of drugs for CAP (ii) there were social, culture and economic factors playing a role in the decision of prescribing of drugs (iii) pediatricians were prescribing less antimicrobial cover and low dose to enhance patient compliance based on the capacity to pay.

Presentation 2

Liquid Medication Dosing Errors: A pre-post time series in India

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This study is presented at American Society of Health System of Pharmacists, Baltimore, USA, 2002 and Australasian Pharmaceutical Science Association, Melbourne, Australia 2001.

Objective. To determine whether parental errors in dosing liquid medication and prescribing behaviour of a pediatrician can be improved through the pharmacist intervention by education.

Design and setting. A controlled trial was conducted at Srujan Hospital for Sick Children, India. Children of 220 uneducated and 117 educated parents treated with an analgesic suspension were assigned to standard treatment or an intervention. Group 1 patients received the prescription, analgesic suspension and verbal instructions from the hospital staff and Group 2 patients received the prescription, analgesic suspension, a syringe and a line was marked at the correct dose and was demonstrated how to measure the dose by a qualified pharmacist. The pediatrician received a dosing chart for patient Group 2.

Main outcome measure. (i) percent of patients who administer the correct dose (ii) improvement in the prescribing of appropriate dose by the pediatrician.

Result. Group 1 parents administer (±0.5 ml) 85 of 175 (48%) and physician prescribed (±25% recommended dose) 60 of 175 (30%)) of the appropriate dose. In Group 2, 160 of 162 (98%) parents administered the correct dose and physician prescribed appropriate dose (p value 0.000). When physician's prescribing and parents dosing administration combined, 31 of 175 were appropriate in Group 1, whereas 158 of 162 were appropriate in Group 2. There is a statistically significant difference (p value 0.000) between the two groups.

Conclusion. Pharmacist intervention through patient education significantly improved parents dosing and physicians prescribing errors even in a country where currently pharmacist involvement is minimal.

Presentation 3

Impact on surgeons prescribing following the implementation of treatment guidelines in pediatric appendectomy procedures

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This study is presented at the following conferences:

American Society of Health-System Pharmacists, New Orleans, USA 2004

Society of Hospital Pharmacists of Australia, Canberra, 2003

Pharmaceutical International Federation, Sydney, Australia 2003

Society of Hospital Pharmacists of Australia, Perth, 2002

Australasian Pharmaceutical Science Association, Melbourne, Australia 2002

The Mark Liveris Health Sciences Research Student Seminar, Perth, Australia, 2002

Objective To evaluate the appropriateness of antibiotic therapy for appendectomy surgery in patients at a West Australian pediatric teaching hospital pre and post an educational intervention programme.

Method Demographic, clinical and prescribing data of patients who had undergone appendectomies were reviewed retrospectively from April 2000 to August 2001 (Group 1). In the absence of in-house prescribing guidelines, prescribing data for antibiotic prophylaxis and treatment was analysed against the antibiotics for abdominal surgery as outlined in the Antibiotic Therapeutic Guidelines Version 11 2000. A multi-faceted intervention strategy was designed and undertaken and a post-intervention study was conducted from December 2001 to April 2002 (Group 2) to evaluate the impact. Group comparisons involved χ^2 and Student's t-test statistics.

Results The study evaluated 102 patients in Group 1 and 105 in Group 2. There was no significance difference between the patient populations of the two groups ($p > 0.05$). In Group 1 82% of patients were documented as receiving prophylactic antibiotics however none of these complied with the recommended standard regimen. Following the intervention programme 66% of patients received prophylactic antibiotics in accordance with the recommended regimen ($p<0.001$). The appropriateness of the prescribed dosage of prophylactic antibiotics improved from 50% of patients in Group 1 to 94% of patients in Group 2. In patients prescribed post-operative antibiotics, 48% of Group 1 patients received antibiotics in accordance with the recommended regimen. Following the intervention this increased to 85% of patients. The appropriateness of the prescribed dosage of post-operative antibiotics increased from 32% of patients in Group 1 to 87% of patients in Group 2.

Conclusion Significant improvements can be achieved in both the selection and use of antibiotics by an effective multi-faceted intervention strategy.

Presentation 4

Antibiotic and analgesic usage review in pediatric appendectomy and adenotonsillectomy procedures

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This study is presented at the following conferences:

American Society of Health-System Pharmacists, New Orleans, USA 2004

Pharmaceutical International Federation, Singapore, 2001

Australasian Pharmaceutical Science Association, New Castle, Australia 2000

Objective To review antibiotics and analgesic prescribed for appendectomy (APP) and adenotonsillectomy (ADT) procedures in pediatric patients at Princess Margaret Hospital for Children, a 250-bed pediatric teaching hospital.

Method A retrospective review of the medical records for consecutive patients who had undergone APP and ADT between April 1999 to Feb 2000 for APP and June to Nov 1999 for ADT was performed. A range of demographic, clinical and medication details were recorded in a standardised form and analysed for prescribing with respect to hospital and national policies and guidelines.

Results An 174 patients for APP and 229 patients for ADT were included in this study. For the APP procedure, metronidazole was prescribed alone for 16%, ceftriaxone alone 4.4%, a combination of metronidazole and ceftriaxone was prescribed for 52%, and metronidazole in combination with other drugs was prescribed 26% of patients. Of these 85% of metronidazole, 71% of ceftriaxone and 44% of paracetamol doses administered were classified as inappropriate. For ADT, amoxycillin was prescribed 141 times as in-patient medication and 149 times as discharge medication. Of these, 19% of in-patient medication and 20% of discharge medications were inappropriate. The dosages

prescribed were frequently well below those stated in the guidelines. For analgesia, paracetamol was prescribed 135 times and Liquigesic®(paracetamol/codeine) 191 times for the ADT procedure. Approximately half of the doses prescribed were outside of the guidelines for Liquigesic® and 27% for paracetamol.

Conclusion This study has identified problems related to the prescribing of antibiotic and analgesic for APP and ADT procedures in this hospital. The next step in the strategy is to reduce the level of inappropriate prescribing of antibiotic and analgesic by educating physicians and clinical pharmacists in the hospital.

Presentation 5

Intervention studies regarding antibiotic and analgesic prescribing in a pediatric teaching hospital

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This study is presented at the following conferences:

American Society of Health-System Pharmacists, New Orleans, USA 2004

Pharmaceutical International Federation, Singapore, 2001

Australasian Pharmaceutical Science Association, New Castle, Australia 2000

Objective To evaluate the level and impact of an intervention on the levels of inappropriate prescribing of flucloxacillin, ceftriaxone and Liquigesic Co® (paracetamol 120 mg, codeine 5 mg/ml) in a pediatric teaching hospital

Method Prescribing data for the above treatments were collected by retrospective review of 348 patient records from standard wards over five weeks. Data collected included dosage, frequency, duration, and sensitivity data (where available). These data were analysed according to hospital and national policies and guidelines. An intervention strategy involved a lecture and provision of drug information. A prospective study was carried out over five weeks evaluating all prescribing of the above treatments.

Results The study evaluated 348 patient records of which 45% of Liquigesic Co®, 43% of flucloxacillin and 51% of ceftriaxone doses were administered inappropriately. The major factor influencing these data were the prescribing of low doses (44% Liquigesic Co®, 42% flucloxacillin and 46% ceftriaxone). The intervention had a major impact with statistically significant reductions in inappropriate prescribing of flucloxacillin (25%) and ceftriaxone (25%) but an increase in Liquigesic Co® to 58%. This resulted from a shift in

the percentage of inappropriately high doses increasing from 0.4% to 54% following the intervention.

Conclusion The intervention had statistically significant effects on the prescribing of antibiotics and Liquigesic Co® although in the wrong direction for the latter. The levels of inappropriate prescribing identified warrant continued vigilance in the maintenance of the quality of use of medicines.