

School of Pharmacy

**Influence of Penicillin Allergy on Antibiotic Prescribing
Patterns and Costs**

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“Terima kasih atas dukungan dan doa dari papa dan mama.”

Declaration

I certify that 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 acknowledgment has been made.

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Abstract

The first part of this research was undertaken to assess the impact of documented penicillin allergy on the choice of antibiotics and the clinical and financial consequences of changes in prescribing patterns in an Australian teaching hospital. The medical records of all patients aged ≥ 18 years admitted with community-acquired pneumonia (CAP) to Sir Charles Gairdner Hospital (SGGH) over a 15-week period were reviewed prospectively. The severity of patients' penicillin allergies was assessed using a structured questionnaire. The antibiotic cost was calculated using acquisition, delivery (labour and equipment) and laboratory monitoring costs. The appropriateness of antibiotic prescribing was assessed using the Therapeutic Guidelines: Antibiotic (TG:A).¹ The antimicrobial selections and costs were then compared for those patients with (Group A) and without (Group B) penicillin allergy. 155 patients were reviewed (males 71, females 84) with an average age of 68 ± 18 years. Of these, 27 (17.4%) had documented penicillin allergies; of which 12 were classified as Severity I (e.g. anaphylaxis, urticaria), 12 as Severity II (e.g. rash, itch) and three as intolerance (e.g. GI upset). The current TG:A recommends cephalothin or cephazolin as the drugs of choice for mild to moderate CAP patients with a history of penicillin allergy. However, combinations of cephalothin intravenously and azithromycin orally were the most commonly prescribed antimicrobials for such patients. The TG:A recommends erythromycin plus cefotaxime or ceftriaxone as the first-line therapy for severe CAP patients with a documented penicillin allergy. Yet, combinations of intravenous cephalothin, erythromycin and gentamicin were the most frequently prescribed antimicrobials for such patients. A history of penicillin allergy significantly ($p < 0.05$) increased the cost of antibiotic treatment and total cost of admission as shown below:

	Severity of pneumonia	Number of patients (%)	Average AB cost (A\$)	Average LOS (day)	Average TCA* (A\$)
Group A	MM	23 (85.2)	194.37	5.0	3 961.49
	Severe	4 (14.8)	1 118.08	12.5	10 662.84
Group B	MM	110 (85.9)	164.89	5.0	3 916.97
	Severe	16 (12.5)	467.96	8.0	6 853.75
	Aspiration	2 (1.6)	181.58	8.0	6 181.58

Group A = patients with a documented of penicillin allergy

Group B = patients without a documented of penicillin allergy

MM = mild to moderate; AB = antibiotic

LOS = length of stay; TCA = total cost of admission

** TCA = total antibiotic cost + accommodation cost (bed charge × LOS)*

p values were calculated using the t tests and they refer to comparisons between mild to moderate and severe CAP patients (Aspiration pneumonia patients were not included to the tests due to small sample size)

The adherence of antibiotic prescribing to the TG:A for patients with penicillin allergies is variable. Patients with labelled penicillin allergies had greater antibiotic costs and total cost of admission. Identifying patients with intolerance rather than allergies would reduce the total inpatient costs at SCGH by A\$ 463.01 a year for mild to moderate CAP patients and A\$ 39 614.54 a year for severe CAP patients.

The second part of the project was a prospective study of patients admitted to SCGH who had a history of penicillin allergy, but were not suffering from CAP. This study was conducted in order to ensure that the pattern of penicillin allergies of patients admitted to the hospital could be adequately characterised. Over a 5-week period, all adult patients admitted without CAP to SCGH who claimed to have a history of penicillin allergy were interviewed with regard to their penicillin allergies. The standard of allergy documentation was also assessed for each patient. Of the 140 patients assessed (males 63, females 77, average age 61 ± 17 years), 108 (77.1%) were classified as allergic: 61 (56.5%) as Severity I and 47 (43.5%) as Severity II, 26 (18.6%) as intolerant and the remaining six (4.3%) as not substantiated. The standard documentation of the patients' penicillin allergies was poor – only 40 (38.6%) of either medical records or drug charts had the type of reaction and only five (3.6%) had the date of reaction. In general, penicillin allergies were poorly documented in both patients'

medical records and on drug charts. Inadequate detail of reported reactions often made it difficult to assess their clinical significance. These findings prompted a recommendation that pharmacists should help to ensure accurate allergy documentation by evaluating patients and educating both patients and health care professionals.

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List of Abbreviations

AB	Antibiotic
ADR	Adverse Drug Reaction
ANOVA	Analysis of Variance
BP	Blood Pressure
CAP	Community-Acquired Pneumonia
CI	Confidence Interval
COA	Classification of Allergy
COPD	Chronic Obstructive Pulmonary Disease
CPI	Consumer Price Index
DCS	Drug Cost Saving
GLM	General Linear Model
Group A	Patients with a Documented of Penicillin Allergy
Group B	Patients without a Documented of Penicillin Allergy
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
IgE	Immunoglobulin E
IV	Intravenously
LOS	Length of Stay
MAR	Medication Administration Record
MM	Mild to moderate
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NS	Not Substantiated
O	Orally
OR	Odds Ratio
p	Probability
$p\text{CO}_2$	Partial Pressure of Oxygen
$p\text{O}_2$	Partial Pressure of Carbon Dioxide
PSI	Pneumonia Severity Index
RR	Respiratory Rate
SaO ₂	Oxygen Saturation
SC	Subcutaneously
SCGH	Sir Charles Gairdner Hospital

SD	Standard Deviation
SPSS	Statistical Package for the Social Science
TCA	Total Cost of Admission
TCS	Total Cost Saving
UK	United Kingdom
US	United States
VRE	Vancomycin-resistant Enterococci
VRSA	Vancomycin-resistant <i>Staphylococcus aureus</i>
WCC	White Blood Cell Count
χ^2	Chi-square

1. Introduction

1.1. Background

Penicillin, a β -lactam antibiotic, and its semisynthetic chemical derivatives (such as amoxycillin and ampicillin) are the most frequently prescribed class of antibiotics.²⁻⁵ They are effective, inexpensive antimicrobials, and therefore remain the drugs of choice for numerous infections commonly seen in clinical practice. Additionally, infections for which penicillin is indicated as the primary antibiotic (e.g. otitis media, acute bacterial sinusitis, community-acquired pneumonia, cellulitis) are common and may be increasing in incidence.^{2, 4, 6}

These agents, however, are the most common cause of allergic drug reactions, with estimates ranging from 1% to 10% for those taking the drugs.^{2, 7-10} It has also been reported that the lower incidence applies to an ambulatory population¹¹ and the higher figure applies to a population hospitalised with acute infections.^{12, 13}

Penicillin allergies can range from mild skin reactions such as a maculopapular rash to life threatening anaphylaxis. Skin rash, the most common adverse drug reaction (ADR) associated with penicillin, occurs in up to 10% of exposed patients.¹⁴ Life threatening problems are much rarer, with anaphylactic reactions occurring in about one to five per 10 000 treated patients^{3, 8, 9} and a fatal outcome in about one to two per 100 000 treated patients.^{7, 8, 15}

Penicillin hypersensitivity can be classified into three categories:

- a. Immediate reactions (Type I reactions, IgE-mediated reactions). These are often associated with the systemic manifestations of anaphylaxis such as diffuse erythema, pruritus, urticaria, angioedema, bronchospasm, laryngeal oedema, hyperperistalsis, hypotension or cardiac arrhythmias, either alone or in combination. Most reactions occur within an hour of administration of penicillin. Nevertheless, some reactions occur between one and 72 hours after administration, and are

termed as “accelerated manifestations”. Type I reactions are much more likely with parenteral administration than oral administration.^{3, 16, 17}

- b. Late reactions (Type II, III, IV, non IgE-mediated reactions). These reactions occur after 72 hours of penicillin exposure. The most common reactions are increased clearance of red blood cells and platelets by lymphoreticular system (Type II reactions, IgG-mediated reactions); serum sickness and tissue injury (Type III reactions, IgG or IgM immune complexes-mediated reactions); and contact dermatitis (Type IV reactions).^{3, 16, 17}
- c. Other reactions (idiopathic). These reactions usually occur after 72 hours of penicillin administration. Clinical signs include maculopapular or morbilliform rashes and these occur in 1% to 4% of all patients receiving penicillin.^{3, 16-18}

The patient history is often the only tool available for making the diagnosis of penicillin allergy since penicillin skin testing is often omitted if the patient’s history is not suggestive of anaphylaxis.¹⁹ In fact, approximately 5% to 20% of patients consider themselves to be allergic to penicillin and many clinicians may simply accept the diagnosis of the allergy without obtaining a detailed history of the reaction.^{3, 19} Other factors contributing to misdiagnosis of penicillin allergy include (i) faulty recall by patients, (ii) naturally declining hypersensitivity, (iii) misinterpreting non-allergic intolerance as allergy, (iv) past problems with contaminated preparations and (v) the past practice of ‘defensive medicine’ whereby an adverse effect was assumed to be drug-related, and in many cases patients were told that they should never receive that medication again.^{20, 21}

In the hospital setting, inadequate documentation of a patient’s penicillin allergy may result in the subsequent use of suboptimal or more expensive therapeutic agents. Hence, it is essential that an accurate penicillin allergy history be obtained and documented correctly in the patient’s medical record and drug chart with the date and type of reaction.^{20, 22}

A common problem in clinical practice is determining which antibiotics to use to treat infections in a patient who has been labelled as being allergic to an antibiotic, specifically penicillin.^{19, 21} In many cases, clinicians' concerns about cross-reactivity, which can occur in 2% to 10% of patients,⁹ the ease of using alternative antimicrobials, and the issue of patient safety and professional liability, often lead to avoidance of all penicillins and occasionally cephalosporins and carbapenems for such patients. This results in altered antibiotic prescribing practices.^{2, 4, 23-25} Alternate agents such as macrolides, glycopeptides and quinolones may be effective, nevertheless, all may be associated with adverse outcomes. They have potentially serious adverse effects associated with their use and increase the risk of superinfection.^{2, 9, 23, 24, 26} Furthermore, they may negatively alter the patient outcome and hospital cost by contributing to (i) greater drug costs, (ii) a longer duration of therapy required due to suboptimal treatment, (iii) an increased length of hospital stay as a result of adverse reactions or complications, and/or (iv) the development of antibiotic resistance such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), which has become one of the most severe health problems.^{24, 27-29}

Several strategies can be used to (i) minimise the selection of microorganisms resistant to antimicrobials and (ii) promote effective and economical prescribing. Firstly, producing guidelines, which review scientific evidence and issue advice on appropriate therapy. Such guidelines for antibiotic prescribing have been issued nationally on several occasions in Australia.^{1, 30, 31} Secondly, formulary restrictions limiting the availability of specific agents. Thirdly, education programs which increase clinicians' knowledge of judicious prescribing practices. Lastly, streamlining which involves having an expert review patients' antimicrobial regimens and make recommendations to their providers about stopping or narrowing therapy.²⁶

To assess the appropriateness or quality of prescribing, specifically for patients with a history of penicillin allergy, drug use needs to be compared with standards or criteria, as in the Therapeutic Guidelines: Antibiotic (TG:A).¹

Community-acquired pneumonia (CAP) has become a major health problem throughout the world.³²⁻³⁵ In the United States (US), it affects more than four million adults and results in 600 000 hospital admissions each year.^{36, 37} Mortality rates range from 15% to 30% in hospitalised patients and from 1% to 5% in outpatients, making it the sixth leading cause of death and the first cause of death from infection in the US.^{32-35, 38} In the US, the estimated cost of treating CAP including direct patient-care costs and lost wages is more than US\$ 20 billion a year, whereas in the United Kingdom (UK), it is estimated to be £ 440.7 million a year, with hospitalised patients accounting for as much as 96% of this cost.^{39, 40} Since CAP is a condition with a significant mortality and a major cost to the health services of all countries, this illness should be efficiently managed and treatment should be as effective as possible.

MacLaughlin et al² reviewed 660 medical records of ambulatory patients who received an antibiotic for either an upper respiratory tract infection, otitis media, sinusitis (acute or chronic), and/or a urinary tract infection to examine selection and cost of antimicrobial agents for patients with and without a documented β -lactam allergy. The results demonstrated that the presence of an allergy appeared to significantly affect antimicrobial prescribing and medication costs. On average, patients with a β -lactam allergy had 37% higher antibiotic costs (US\$ 26.81 vs US\$ 16.28, $p=0.004$) and were more likely to receive a broader spectrum antibiotic than those without a β -lactam allergy.

The aim of the current study was to assess the impact of documented penicillin allergy on the choice of antibiotics and the clinical and financial consequences of changes in prescribing patterns in an Australian teaching hospital.

1.2. Objectives

The objectives of the study were as follows:

- a. To determine the pattern of antibiotic prescribing in adult patients with a history of penicillin allergy.

- b. To assess the adherence of antibiotic prescribing to the TG:A for patients with penicillin allergies.
- c. To evaluate the economic impact of documented penicillin allergies.
- d. To evaluate the accuracy and consistency of penicillin allergy documentation in Sir Charles Gairdner Hospital (SCGH), Perth, Western Australia.

1.3. Significance

The current study was significant for three reasons. Firstly, it provided new information about the (i) pattern of antibiotic prescribing in adult patients with a history of penicillin allergy, (ii) adherence to antibiotic prescribing to the TG:A and (iii) economic impact of documented penicillin allergies in SCGH. Secondly, it evaluated the accuracy and consistency of penicillin allergy documentation in SCGH.

1.4 Definition of Terms

- a. Allergy is a state of hypersensitivity induced by exposure to a particular antigen (allergen) resulting in harmful immunologic reactions on subsequent exposures. In the current study, the term referred to hypersensitivity to an environment antigen (atopic allergy or contact dermatitis) or to drug allergy.⁴¹
- b. Intolerance is defined as a lowered threshold to the normal pharmacologic action of the drug and most commonly resulting in gastrointestinal adverse effects.⁹
- c. The World Health Organisation defines an ADR as a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.⁴²
- d. Antibiotics are usually restricted to substances that are produced by the growth of one species of microorganism.⁴³ Another similar term, antimicrobial, is defined as an agent that destroys or prevents the development of microorganisms.⁴⁴ Its broader definition is a natural or

synthetic substance that destroys microorganisms or inhibits their growth.⁴⁴

- e. CAP is commonly defined as an acute infection of the lower respiratory tract occurring in individuals who are not in hospital or have been in hospital for less than 48 hours, not institutionalised and not significantly immunocompromised.¹ In the current study, CAP referred to pneumonia caused by a pathogen acquired in the community with an onset of pneumonia less than 72 hours following hospitalisation.⁴⁵
- f. Pneumonia is defined as inflammation of the lung parenchyma (alveoli rather than bronchi) of infective origin and characterised by consolidation, which is a pathological process in which the alveoli are filled with a mixture of inflammatory exudate, bacteria and white cells.⁶
- g. Length of stay (LOS) is calculated by subtracting the admission date from the discharge date or the equivalent across months.⁴⁶ In the current study, LOS was calculated by subtracting the admission date from the discharge date plus one.

1.5. Research Hypotheses

The hypotheses of the study were as follows:

- a. Antibiotic prescribing practices for patients with a history of penicillin allergy are different from those without a history of penicillin allergy.
- b. The adherence of antibiotic prescribing to the TG:A for patients with penicillin allergies is variable.
- c. Patients with a documented of penicillin allergy have greater antibiotic costs compared to those without a reported penicillin allergy.
- d. Penicillin allergies are poorly documented in patients' medical records and on drug charts.

2. Literature Review

This review provides a context of the research conducted and shows why the research is important and timely. Furthermore, it will clarify the relationship between the current study and previous work, including the worth of this research.

2.1. β -Lactam Antibiotics

β -lactam antibiotics, which are named for the β -lactam ring in their chemical structure, include penicillins, cephalosporins, carbapenems and monobactams. They are structurally related and share bactericidal activity primarily directed at the bacterial cell wall.⁴⁷⁻⁴⁹ These agents are amongst the most useful antibiotics in clinical practice, except in those patients hypersensitive to them.¹ The combination of β -lactams with an inhibitor of β -lactamase also have important applications.^{1, 50}

2.1.1. *Penicillins*

Penicillins constitute one of the largest and most important classes of antibiotics. Although numerous other antimicrobial agents have been produced since the first penicillin became available, these still are widely used, major antibiotics, and new derivatives of the basic penicillin nucleus still are being produced. Details of the various types of penicillin according to their spectrum of antimicrobial activity are given in Table 2.1. Many of these have unique advantages, such that members of this group of antibiotics are presently the drugs of choice for a large number of infectious diseases.^{4, 47, 48} A list of clinical uses is shown in Table 2.2.

Table 2.1 Classification of penicillins and their antimicrobial activity^{47, 48}

Type of penicillin	Useful antimicrobial spectrum
Benzylpenicillin and congeners <ul style="list-style-type: none"> • Benzylpenicillin (penicillin G) • Phenoxymethylpenicillin (penicillin V) 	<i>Streptococcus</i> species, <i>N. meningitidis</i> , many anaerobes, spirochetes, others
β -lactamase-resistant penicillins <ul style="list-style-type: none"> • Cloxacillin • Dicloxacillin • Flucloxacillin 	<i>Staph. aureus</i>
Broad-spectrum penicillins <ul style="list-style-type: none"> • Amoxycillin • Ampicillin 	<i>L. monocytogenes</i> , <i>P. mirabilis</i> , <i>E. coli</i>
Extended-spectrum penicillins <ul style="list-style-type: none"> • Piperacillin • Ticarcillin 	<i>Pseudomonas</i> species, <i>Enterobacter</i> species, <i>Proteus</i> species, <i>Klebsiella</i>

Table 2.2 Clinical uses of the penicillins^{47, 48}

Important uses	Penicillin
• Bacterial meningitis (e.g. due to <i>N. meningitidis</i> , <i>Strep. pneumoniae</i>)	Benzylpenicillin IV
• Bone and joint infections (e.g. with <i>Staph. aureus</i>)	Flucloxacillin IV
• Bronchitis in patients with chronic obstructive airways disease	Amoxycillin O
• CAP, not severely ill (e.g. with <i>Strep. pneumoniae</i>)	Amoxycillin O
• Endocarditis (e.g. with <i>Strep. viridans</i> or <i>E. faecalis</i>)	Benzylpenicillin IV plus an aminoglycoside
• Gonorrhoea	Amoxycillin plus probenecid O plus other antibiotics
• Otitis media (organisms commonly include <i>Strep. pyogenes</i> , <i>H. influenzae</i>)	Amoxycillin O
• Pharyngitis (from <i>Strep. pyogenes</i>)	Phenoxymethylpenicillin O
• Syphilis	Procaine penicillin IV
• Serious infections with <i>Ps. aeruginosa</i>	Piperacillin IV
• Urinary tract infection (e.g. with <i>E. coli</i>)	Amoxycillin O

IV = intravenously; O = orally

2.1.2. Penicillin and β -Lactamase Inhibitor Combinations

The β -lactamase inhibitors clavulanate, sulbactam and tazobactam inhibit the enzymes produced by *Staph. aureus* and *B. fragilis*, and also the ubiquitous β -lactamase enzymes found in *E. coli*, *Klebsiella* species, *N. gonorrhoeae* and *H. influenzae*. These three drugs possess little inherent antibacterial activity, but when given with amoxicillin, ticarcillin or piperacillin, significantly extend their spectra of activity.^{47, 48} The combination of amoxicillin and potassium clavulanate (Augmentin[®]), for instance, can be used for the treatment of otitis media, sinusitis, bronchitis, urinary tract infections as well as skin and soft tissue infections. Nonetheless, these agents are more expensive than the β -lactam antimicrobials alone.^{1, 50}

2.1.3. Cephalosporins

Cephalosporin antibiotics are classified by generation based on their spectrum of antimicrobial activity, with the first generation agents having Gram-positive and modest Gram-negative activity; the second generation having somewhat better activity against Gram-negatives and including some agents with antianaerobe activity; the third generation with less activity against Gram-positive organisms, but much more activity against the *Enterobacteriaceae*, with a subset active against *Ps. aeruginosa*; and the fourth generation with a spectrum similar to the third, but having increased stability to hydrolysis by β -lactamases (Table 2.3).⁴⁷⁻⁴⁹

Table 2.3 Classification of cephalosporins and their antimicrobial activity^{47, 48}

Generation	Examples	Spectrum of activity
First	Cephalexin Cephalothin Cephazolin	<i>Streptococci, Staph. aureus</i>
Second	Cefaclor Cefotetan Cefoxitin Cefuroxime Cephmandole	<i>H. influenzae, Proteus, E.coli, Klebsiella, M. catarrhalis</i>
Third	Cefotaxime Cefpodoxime Ceftazidime Ceftriazone	<i>Enterobacteriaceae, Serratia, N. gonorrhoeae, Ps. aeruginosa</i>
Fourth	Cefepime Cefpirome	<i>Staph. aureus, Streptococci, Strep. pneumoniae, Enterococci, Ps. aeruginosa</i>

Clinical studies have shown cephalosporins to be effective as both therapeutic and prophylactic agents. They still are useful as alternatives to penicillins for a variety of infections in patients who cannot tolerate penicillins. These include streptococcal and staphylococcal infections.^{47, 48} Some clinical uses of the cephalosporins are listed in Table 2.4.

Table 2.4 Clinical uses of the cephalosporins^{6, 47, 48}

Clinical uses	Cephalosporin
• Meningitis	Ceftriaxone, cefotaxime IV
• Otitis media	Cefaclor, cefuroxime O
• Pelvic inflammatory disease	Cefoxitin, cefotetan IV
• Pneumonia due to susceptible organisms	Ceftriaxone, cefotaxime IV
• Septicaemia	Cefuroxime, cefotaxime IV
• Sinusitis	Cefadroxil O
• Surgical prophylaxis	Cephalothin, cephalazolin IV
• Urinary tract infections	Cephalexin O

IV = intravenously; O = orally

2.1.4. Carbapenems

Carbapenems, which include imipenem and meropenem, have the broadest antimicrobial spectrum of any antibiotic. They have good activity against Gram-positive, Gram-negative organisms and anaerobes. Nevertheless, they are inactive against MRSA and *E. faecium*.^{1, 47, 48}

Due to inactivation by a renal dipeptidase, imipenem is formulated in combination with the dipeptidase inhibitor, cilastatin, whilst meropenem is more resistant to renal dipeptidase, and can therefore be given alone. Carbapenems are particularly useful when single agent treatment is required for complex mixed infections; otherwise combinations of less expensive drugs provide similar antimicrobial cover and clinical efficacy.^{1, 48}

2.1.5. Monobactams

The main monobactam is aztreonam, in which the antimicrobial activity differs from those of other β -lactam antibiotics and more closely resembles that of an aminoglycoside. This agent is highly active against the majority of aerobic Gram-negative bacteria including β -lactamase producing *H. influenzae*, enteric Gram-negative rods and *Pseudomonas* species. Yet, it is inactive against Gram-positive organisms and anaerobes.^{1, 47, 48}

The indications of aztreonam are as follows:^{47, 48}

- a. Reserved for the treatment of infections where the person is allergic to other antimicrobials or when other agents are ineffective.
- b. An alternative to aminoglycosides and broad spectrum cephalosporins for infections caused by Gram-negative aerobes.
- c. Alternative agent for septicaemia, intra-abdominal and gynaecological infections, urinary tract infections and lower respiratory tract infections (including cystic fibrosis).

2.2. Drug Allergies

An allergic or hypersensitivity reaction to a drug may be defined broadly as any immunologic response to a drug or its metabolites that results in an adverse reaction.^{41, 51} Most allergic reactions occur after sensitisation by previous drug exposure. Thus, allergic reactions usually do not occur on first exposure to a drug although they may occur with prolonged administration. Some individuals may be allergic to all drugs of the same or similar class on the basis of an immunologic response to shared antigenic determinants among the drugs.⁵¹

2.2.1. Epidemiology and Incidence of Drug Allergies

Allergic and other immunologic drug reactions cause 6% to 10% of observed ADRs in a primarily inpatient population.⁵¹ Reports suggest that the risk of an allergic reaction for most drugs is 1% to 3%.⁵² In hospital surveys, fatalities occur in one of 10 000 allergic drug reactions. Drug-associated fatalities are reported in 0.01% of surgical inpatients and 0.1% of medical inpatients.⁵³ Fatal adverse reactions often have allergic features.⁵¹

2.2.2. Risk Factors for Drug Allergies

There are two specific factors influencing drug allergy susceptibility – drug factors and patient factors.⁵¹

2.2.2.1. Drug Factors

- a. Characteristics of the drug^{51, 54}
- b. Variations in metabolism^{51, 54}
- c. Drug exposure (route, dose, duration and frequency of drug administration)

Sensitisation may occur by any route of drug administration, however, the topical and oral routes of administration generally have the greatest and least risks, respectively. Topical application of drug favours the induction of a delayed hypersensitivity reaction.^{19, 51, 54, 55} Parenterally administered medications such as β -lactam antibiotics are more likely to cause anaphylaxis than orally administered medications.⁵⁶ Single prophylactic doses of an antibiotic are less likely to sensitise than high

dose, prolonged parenteral therapy. Frequent courses of therapy are more likely to result in allergic reaction than courses of therapy separated by several years.⁵¹

2.2.2.2. Patient Factors

a. Age

Drug allergy appears to be less common and less severe in infants and in the aged, perhaps due to immaturity or involution of the immune system, respectively.^{19, 55}

b. Gender

Women have a 35% higher incidence of adverse cutaneous reactions to drugs than men, and may have a risk more than 20-fold greater than men for anaphylactic reactions associated with radiocontrast media.^{57, 58}

c. Genetic and constitutional factors

The genetic ability to recognise antigenic determinants is another potentially important factor in drug allergy.⁵¹ Attaway *et al*⁵⁹ reported that children of parents who were allergic to an antibiotic had a 15-fold greater relative risk for allergic reactions to antibiotics than children without such histories, but no attempt was made to verify these allergies. Often, children appear to be allergic to different drugs than are their parents.

Some patients are more likely to be at risk for allergic reactions to multiple drugs. The multiple drug allergy syndrome, reported to occur primarily with antimicrobial agents, may reflect a general tendency to respond immunologically to haptens rather than to react to specific classes of drugs.⁶⁰

d. Concurrent illnesses and therapies

Concurrent disease and therapy may influence the risk for ADRs and perhaps drug allergy.⁵¹ A study by Battegay *et al*⁶¹ demonstrated that patients with concurrent Epstein-Barr virus or human immunodeficiency virus infection (HIV) or with chronic lymphatic leukaemia had increased frequency of occurrence of ampicillin and

amoxicillin-associated rashes. Another study by Becker *et al*⁶² reported that patients with systemic lupus erythematosus might have an increased prevalence of allergic drug reactions, but it was not clear whether this was related to the underlying immunologic abnormality or to more frequent exposure to drugs.

Co-administration of β -blocker drugs has been reported to be associated with an increased risk if a severe anaphylactic reaction occurs since it reduces the effect of adrenaline as immediate treatment for anaphylactic shock.⁵⁴

e. History of atopy

A history of atopy (allergic rhinitis, asthma or atopic dermatitis) does not seem to be an independent risk factor for the development of an allergy to β -lactam antibiotics although atopic persons, especially those with asthma, may be predisposed to severe and fatal reactions should anaphylaxis occur.^{8, 63, 64}

f. Previous drug exposure

A patient with a history of allergy to antibiotic, specifically penicillin, is at least six times more likely to develop a reaction than a non-allergic patient on subsequent exposure.⁸

g. History of other drug allergy

Shepherd⁶⁵ found that patients with a history of reacting to an unrelated drug were three times more likely to react to penicillin, suggesting a subset of patients who are prone to multiple drug allergies.

2.3. Frequency and Nature of β -Lactam Allergies

β -lactam antibiotics are the most common causes of drug-induced hypersensitivity.⁶⁶ Of all the β -lactams, penicillin is the most common cause of allergic drug reactions and anaphylaxis. The estimated prevalence of penicillin allergy is 2%, but the reported incidence varies widely between 1% and 10% of patients treated. The different reaction rates are probably related to numerous factors including the (i) history of exposure, (ii) route of

administration, (iii) duration of treatment, (iv) elapsed time between the reaction and diagnostic testing or exposure, (v) nature of the initial reaction and (vi) difficulty in attributing reactions particularly when several drugs are being administered simultaneously.^{51, 67}

Numerous studies, nevertheless, have shown that only a minority of patients (<20%) who claimed to have penicillin allergy had convincing evidence of their allergy, as indicated by the results of skin testing and oral challenge.^{63, 67-69} Some of these patients may have lost their sensitivity to a drug over time. Many patients have experienced predictable adverse reactions (i.e. drug-related side effects) rather than true allergic reaction, while others may experience a coincidental symptom. Often, the suspected allergy event was due to infectious agent rather than a drug. One complicating factor is that some infections seem to create an inflammatory milieu that increases the chance that a drug will activate T cells and initiate an immunologic reaction in a patient who would otherwise not react to that drug. An example of this is the rash that commonly occurs when amoxicillin is given to patients with Epstein-Barr virus infection.¹⁹

2.3.1. Proof of β -Lactam Allergy

Patient history and skin tests are the two most important elements in the evaluation of an individual for the presence or absence of β -lactam hypersensitivity. Other diagnostic tools (measurement of drug-specific antibodies, lymphocyte transformation tests, etc) remain investigational. Standardised and widely applied protocols for skin testing exist solely for the penicillins and only allow assessment of IgE-mediated hypersensitivity.¹⁸

2.3.1.1. Patient History

Patient history is worthwhile in determining the probability of a true β -lactam allergy and in determining which individuals should not be tested or ever rechallenged. The main goal is to establish whether the patient had an IgE-mediated reaction to a β -lactam antibiotic which could manifest as urticaria, pruritus, angioedema, hyperperistalsis, bronchospasm, hypotension, and/or arrhythmias.¹⁹

Hence, the medical history of patients with reactions to antibiotics should include (i) a detailed description of the symptoms (e.g. urticaria, pruritus, angioedema or respiratory difficulties) and severity (e.g. mild or life threatening), (ii) the time course of the reaction to help determine whether the event was a drug reaction and (iii) a list of all the medications the patient was taking at the time of the event to help determine whether the symptoms were caused by a reaction to the antibiotic or to another drug.^{3, 70}

Several studies, nonetheless, found that inaccuracy in patient reporting of drug allergies was common and a description of allergic reactions was poorly documented in patients' medical records. Preston *et al*⁹ interviewed 117 adult inpatients with a reported penicillin allergy. The aims were to (i) determine the consistency of penicillin allergy documentation of penicillin allergy documentation in the patient chart and medication administration record (MAR) for patients with a reported penicillin allergy and (ii) determine the correctness of the documentation by patient interview. The results showed that of 117 patients, 97 (82.9%) were classified as allergic: 67 (69.1%) as Severity I (e.g. anaphylaxis, angioedema) and 30 (30.9%) as Severity II (e.g. rash, itch). While the remaining 20 patients (17.1%) were classified as intolerant (e.g. GI upset). The allergy was documented in 98.7% of patient charts and 96.7% of MARs. But, the symptoms of the allergic reaction were described in the chart for only 34% of patients. In comparison, Armour *et al*¹⁰ found that of 79 patients reporting penicillin allergy, 68 (86.1%) were classified as having a 'true' allergic reaction and 11 (13.9%) as having a 'questionable allergy'. Wyer²⁰ investigated the penicillin allergy histories of adult inpatients and assessed the standard of documentation of those reactions in medical records and on drug charts. This study also found a poor result in the standard of documentation of the patients' penicillin allergies with just 35% (21/60) of medical records having the type of reaction and only 10% (6/60) having the date of reaction documented.

On the contrary, Tripp *et al*¹¹ found that the penicillin allergy label could be removed from 13% of patients' charts based solely on information obtained from the history. They further supported the removal of the allergy labels by following those patients who went on to receive a penicillin or a

cephalosporin without a skin test result. Two percent of the patients were rechallenged and did not react.

2.3.1.2. Skin Tests

Penicillin skin testing is a safe, reliable and valid method to detect the presence or absence of penicillin-specific IgE antibodies.⁷² Importantly, when performed with both major and minor determinants, it has a very high negative predictive value of greater than 99% for immediate-type reactions.^{27, 73}

It has been shown that patients who have a convincing history of penicillin allergy are more likely to have a positive penicillin skin test than those who have a vague history.²⁷ In a recent review of the literature, however, it was found that in history positive patients who have positive penicillin skin tests, one-third of these individuals had vague histories of penicillin allergy.⁷⁴ Furthermore, it has been reported that the history of penicillin allergy, including potential IgE-mediated reactions such as anaphylaxis and hives, does not correlate with skin test positivity, the closest test to a criterion standard for allergy. Mild, possibly nonallergic reactions such as delayed-onset rashes do not increase the probability of a negative skin test and a history of anaphylaxis does not increase the odds of a positive test.⁷⁵ These findings indicate that one cannot rely on history alone to confirm the presence or absence of penicillin-specific IgE since a significant number of skin test positive patients report a vague drug allergy history.²⁷

Positive penicillin skin tests decrease by 10% annually after a penicillin allergic reaction⁷⁶ and 78% of penicillin allergic patients have negative skin tests after 10 years of avoidance.⁷⁷ Also, a study revealing 52% of penicillin-allergic patients and 92% of amoxicillin allergic patients had negative skin testing after five years demonstrated that the type of penicillin may affect duration of sensitivity.⁷⁶⁻⁷⁸

For patients who have a history of allergy to penicillin but who have a negative skin test result when major and minor determinants are used, studies show that the chance of having any reaction to a subsequent dose of penicillin ranges up to 9.1%, with an average incidence of approximately

3%.⁶³ Nevertheless, only nearly 1% of such patients develop a reaction that appears to be IgE-mediated and the only serious reaction ever described was in an anaesthetised patient who had also received other drugs.⁷⁹ Penicillin-induced anaphylaxis has never been reported following a negative penicillin skin test result. Therefore, patients who have a negative skin test result may be able to use a penicillin compound, which could reduce the unnecessary use of broad-spectrum antibiotics and decrease the emergence of resistant microorganisms.¹²

Penicillin skin testing should be performed when the patient is well and not in need of antibiotic treatment. Because a single penicillin skin test is predictive not only for immediate administration but also for future courses with the antibiotic, skin testing may not need to be repeated each time a patient with a history of penicillin allergy requires treatment.⁸⁰

2.3.2. Cross-reactivity of β -Lactam Antibiotics

If a patient has an allergy to penicillin and it is IgE-mediated, the patient is likely to have a similar reaction to ampicillin, amoxycillin, cloxacillin and piperacillin because these agents all share the same β -lactam ring.⁴⁷ However, sometimes the patient has had an IgE-mediated reaction to the side chain of penicillin and will tolerate other penicillins.⁴⁸

The incidence of allergic reactions to cephalosporins in patients hypersensitive to penicillin is approximately 8.2%, whilst the incidence of allergic reactions to cephalosporins in patients not hypersensitive to penicillin is around 1.7%.¹⁴ According to the TG:A, between 3% and 6% patients hypersensitive to penicillin experience cross-reactivity to cephalosporin. The use of a cephalosporin is contraindicated in patients with a history of immediate reactions, while a history of later reactions (non IgE-mediated reactions) is not contraindicated, but cephalosporins should be given with caution.¹

It is suggested that imipenem should not be administered to patients with a history of immediate reaction to penicillin or those with a positive penicillin skin test.³ McConnel *et al*⁸¹ conducted a retrospective study of patients experiencing imipenem/cilastatin and penicillin allergy. The aim was to

assess cross-sensitivity in patients with documented history of penicillin allergy, and the results showed that there was 9.5% (6/63) incidence of cross-reactivity. The limitation of the study was the retrospective nature of study in which there were no skin tests performed to determine the incidence of both penicillin and imipenem/cilastatin reactions. The incidence of allergy depends solely on interpretation of the documented data in patient's medical records. In comparison, Saxon *et al*⁸² found that there was a 47% (9/19) cross-sensitivity between imipenem/cilastatin and penicillin in patients with a positive skin test to penicillin. In both positive and negative skin tests to penicillin, the incidence of cross-reactivity was 25% (10/40). The hypersensitivity of both imipenem/cilastatin and penicillin were determined entirely by skin test and no systemic therapy was given, and this was the limitation of the study. A prospective study assessing cross-sensitivity between penicillin and imipenem would be beneficial.

It has been indicated that aztreonam could be administered safely to most patients with a history of immediate reactions to penicillin.^{1, 3} There is a lack of data on cross-sensitivity between penicillins and monobactams, and no studies have been identified from a recent search of Medline.

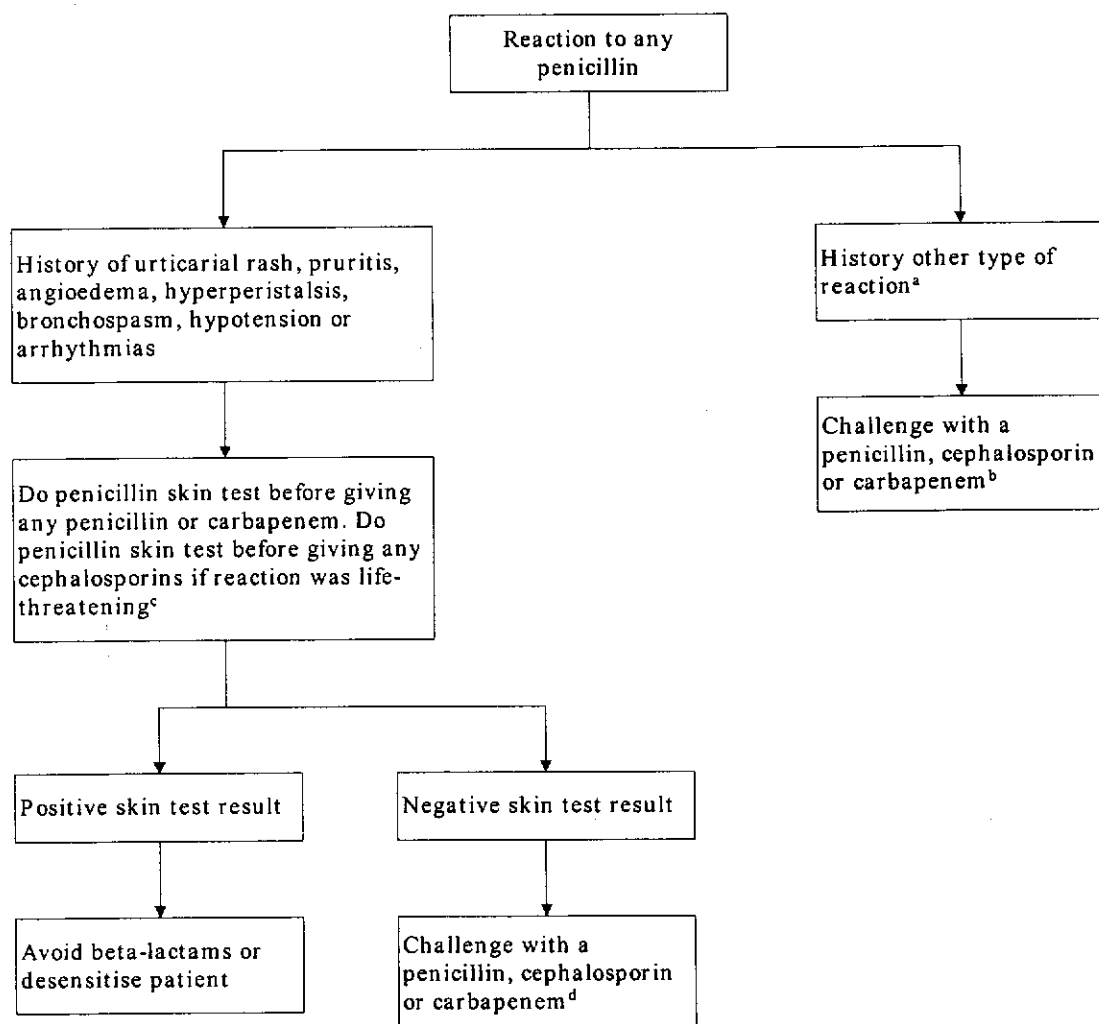
2.4. Treatment of Patients with β -Lactam Allergy

Robinson *et al*¹⁹ recommended steps that should be taken if a patient is thought to have had a reaction to a β -lactam antibiotic (Figure 2.1 and 2.2). If a patient has weak evidence of a β -lactam allergy and is likely to require that antibiotic in the future, rechallenge may be appropriate. This rechallenge should be performed in a setting where anaphylaxis can be treated, if the physician thinks the previous reaction could have been IgE-mediated or if the patient remains anxious about taking the drug. Rechallenge can be performed when the patient is assessed or it can be delayed until the patient requires the antibiotic.¹⁹

For patients with a possible IgE-mediated reaction to a β -lactam antibiotic that they require, desensitisation is a safer option than rechallenge, but it needs to be repeated each time they require the antibiotic and after any

missed doses. If a β -lactam is clearly the drug of choice and there is a convincing history of allergy to that antibiotic or a positive skin test result, desensitisation should be considered. Desensitisation is thought to be effective either because IgE is neutralised by the increasing dose of antigen or because the mast cells are slowly degranulated.^{19, 83}

Figure 2.1 Approach for patients with a suspected allergic reaction to a penicillin¹⁹



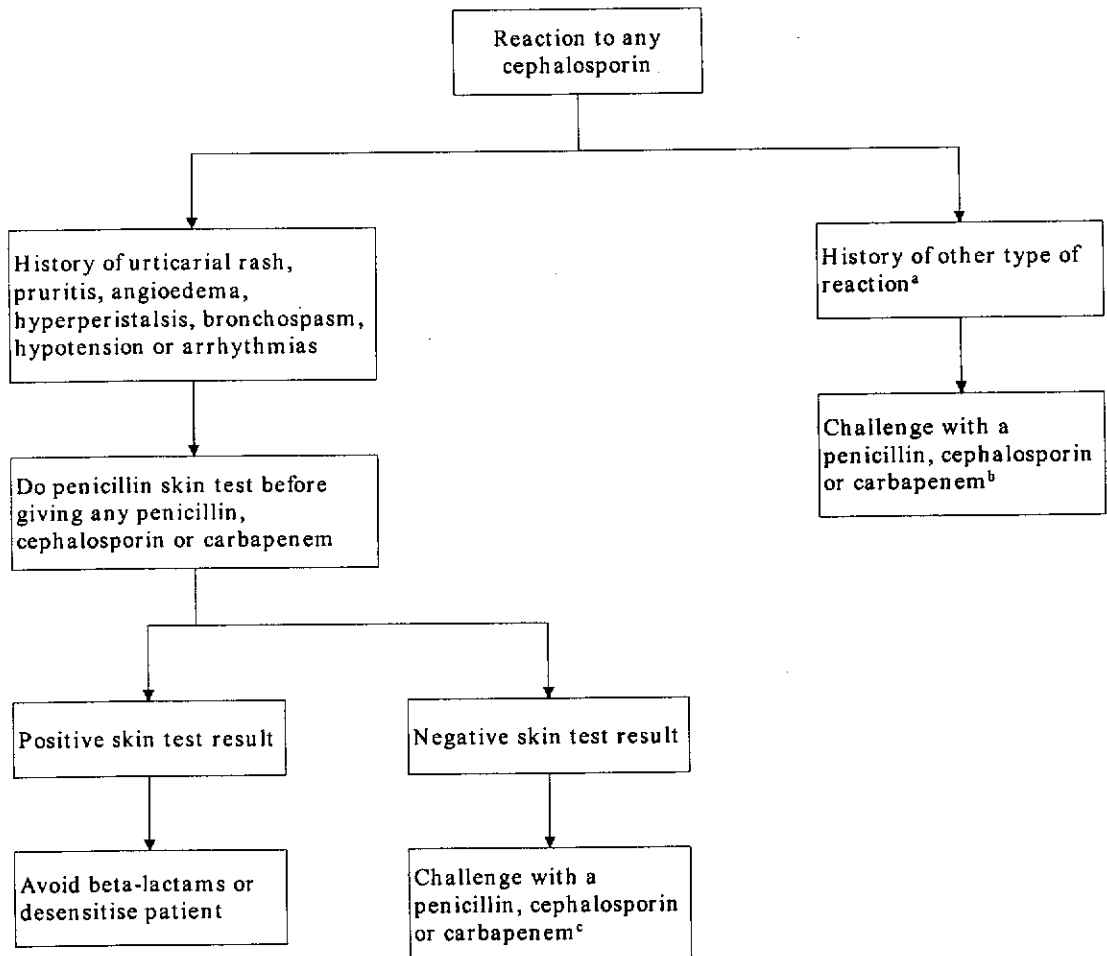
^a It is often difficult to obtain an accurate history of a rash. If there is any doubt, assume it could have been urticarial.

^b Avoid use of first-generation cephalosporins and cephmandole. If the suspected drug reaction was Stevens-Johnson syndrome or toxic epidermal necrolysis, skin testing should not be performed and use of penicillins should be avoided.

^c Skin tests with amoxicillin are sometimes performed if the reaction was to amoxicillin, but the incidence of false-negative skin test results is not known.

^d If the reaction was serious, challenge in a supervised setting, and use a graded challenge: start with a small dose in an orally administered formulation, if that is practical, then increase the dose, then try an intravenous formulation, if it is required. This is most relevant if the reaction was to a penicillin other than natural penicillin (such as cloxacillin or ampicillin), in case the reaction was to a side chain and cannot be detected by a penicillin skin test. Avoid use of first-generation cephalosporins and cephmandole.

Figure 2.2 Approach for patients with a suspected allergic reaction to a cephalosporin¹⁹



^a It is often difficult to obtain an accurate history of a rash. If there is any doubt, assume it could have been urticarial.

^b Use a cephalosporin of a different generation than the one associated with the reaction. If the suspected drug reaction was Stevens-Johnson syndrome or toxic epidermal necrolysis, skin testing should not be performed and use of cephalosporins should be avoided.

^c The negative penicillin skin test result means that, if the previous reaction was IgE-mediated, the antigen was likely a cephalosporin side chain rather than the β -lactam ring. Therefore, use a cephalosporin of a different generation than the one that was associated with the reaction. If the reaction was serious, challenge in a supervised setting and use an orally administered formulation first, if possible.

Treatment for anaphylactic reactions due to penicillin allergy is similar to other anaphylactic reactions. Some main lines of treatment include:^{84, 85}

- a. Adrenaline, the primary drug therapy for the treatment of anaphylaxis.
The dose for mild reaction is 0.3-0.5 mg SC, whereas the dose for severe reactions is in the order of 5-10 µg/minute by IV infusion.
- b. Inhaled β₂-agonists (e.g. salbutamol 2.5-5 mg 1-2 hourly as needed)
- c. Antihistamines (diphenhydramine 25-50 mg IV over one minute)
- d. Corticosteroids (equivalent of hydrocortisone 200-3 000 mg IV)
- e. Vasopressors (noradrenaline)

2.5. Impact of β-Lactam Allergy on Antibiotic Prescribing

The clinician today has several therapeutic options when managing the adult patient who has a history of β-lactam allergy. These options include (i) skin testing to determine if penicillin-specific IgE exists, (ii) desensitisation if the antibiotic is the drug of choice and the skin test is positive or not available, and (iii) choosing an alternative non β-lactam antibiotic.²⁷ In patients with neurosyphilis, for which penicillin is the drug of choice, skin testing and desensitisation are widely accepted and performed, but these procedures are generally avoided in other patients.²³ Most physicians continue to try to avoid prescribing the antibiotic and use alternative antimicrobials to treat infection in such patients which results in altered antibiotic prescribing practices.^{5, 23}

Solensky *et al*²⁷ surveyed various physician groups to determine how they would manage penicillin allergic patients who present with an infectious process for which penicillin is the drug of choice. The results showed that for those patients who present with a vague history of penicillin allergy, 58% and 59% of the physicians surveyed stated that they would choose cephalosporins for individuals with mild and moderate diseases, respectively. In contrast, in the vague penicillin history or severe disease scenario, physicians were split between choosing cephalosporins (42%) and vancomycin (40%). For those patients who present with a convincing history of penicillin allergy, 55% of the physicians chose erythromycin for individuals with mild disease, 44% chose quinolones for individuals with

moderate disease and 63% chose vancomycin for individuals with severe disease.

Puchner *et al*⁵ found that 61% of all responders (community and academic physicians, medical students, residents and allergists) chose an alternative antibiotic for patients with a history of penicillin allergy. These results indicated that community physicians favoured macrolides and academic physicians preferred trimethoprim-sulfamethoxazole as alternative.

MacLaughlin *et al*² also found that patients with β -lactam allergies noted in medical record were more likely to have received a cephalosporin, macrolide or other antibiotic (e.g. quinolones, tetracycline or nitrofurantoin) than those who did not have an allergy documented in the medical record.

The unnecessary use of broad-spectrum antibiotics presents a multitude of problems in clinical medicine. Many of these antibiotics are expensive and may have a toxic side effect profile such as vancomycin.²⁷ Another significant problem that is largely due to the unnecessary use of broad-spectrum antibiotics is the increasing prevalence of multiple drug resistant bacteria such as VRE and vancomycin-resistant *Staphylococcus aureus* (VRSA). These strains represent a major public threat because they are resistant to all clinically available antibiotics. In addition, VRE can potentially transmit their antibiotic resistance to other bacteria.⁸⁶

2.6. Community-Acquired Pneumonia

CAP is one of the most common infections encountered in clinical practice. It remains a common cause of morbidity throughout the world, with an estimated incidence of 12 cases per 1 000 population per year.⁴⁰ Since CAP is a condition with a significant mortality and a major cost to the health services of all countries, this illness should be efficiently managed and treatment should be as effective as possible.

Based on the large number of antimicrobial agents available, it is not surprising that four recent surveys have demonstrated substantial variation in physicians' antimicrobial prescribing patterns for patients with CAP.^{36, 87-89} Although this finding is potentially important from a clinical and health-

service perspective, these studies were limited in their design and scope. One survey was restricted to a particular time of year, disregarding the potential relationship between seasonal pneumonia aetiology and the selection of antimicrobial therapy,⁸⁷ one relied on physician reports of antimicrobial therapy that may have differed from actual practice,⁸⁸ one failed to distinguish the treatment of CAP and hospital-required pneumonia,⁸⁹ and one evaluated the relationship between antimicrobial use and costs of antimicrobial therapy.³⁶ None evaluated the antimicrobial selection and cost effect of reported penicillin allergies in hospital. Hence, this study was designed to evaluate CAP treatment in patients with penicillin allergy, both from clinical and economic perspectives.

2.6.1. Severity Criteria Assessment

Niederman *et al*⁹⁰ defined severe CAP as the clinical syndrome of severe ill patients with pneumonia requiring intensive care unit (ICU), whilst other authors defined severe CAP as the presence of one or more of the following not attributable to another cause (Table 2.5).

Table 2.5 Severity criteria for severe community-acquired pneumonia^{1, 6, 91}

-
- Altered mental state
 - Respiratory rate >30 per minute *
 - pO_2 <60 mmHg or SaO_2 <90% on room air
 - pCO_2 >50 mmHg on room air
 - Blood pressure <90/60 mmHg*
 - White blood cell count <4 or >30×10⁹/L
 - Serum urea >7 mmol/L*
 - Bilateral or multilobe radiographic shadowing
 - Increase the size of infiltrates by ≥50% within 48 hours
 - Need for mechanical ventilation or inspired oxygen >35% to maintain SaO_2 >90%
-

pO_2 = partial pressure of oxygen; SaO_2 = oxygen saturation

pCO_2 = partial pressure of carbon dioxide

* The presence of two or more of these is associated with a 21-fold increase risk of mortality

In the absence of any of the above, a high risk of poor prognosis exists in any patient with two or more of the following significant co-morbidities as shown in Table 2.6.^{6, 92}

Table 2.6 Significant co-morbidities associated with severe community-acquired pneumonia^{87, 93, 94}

-
- Age >50 years
 - Coexisting illnesses
 - Alcoholism
 - Asthma
 - Cerebrovascular disease
 - Congestive heart failure
 - Chronic obstructive pulmonary disease
 - Dementia
 - Diabetes mellitus
 - Liver disease
 - Neoplastic disease
 - Renal failure
 - Immunosuppression (neoplasias, HIV infection, corticosteroid treatment)
 - Indigenous background
 - Institutionalisation
 - Smoking
 - Temperature <35°C or ≥40°C
 - Admission to hospital in the previous year with pneumonia
-

HIV = Human Immunodeficiency Virus

In the US, a prospectively validated severity prediction score is increasingly used – the Pneumonia Severity Index (PSI).⁹³ Fine *et al*⁸⁷ developed a PSI score as part of the Pneumonia Patient Outcome Research Team Study. The 20 items included three demographic variables, five co-morbid conditions, five physical examination findings and seven laboratory or imaging results. For each variable present, points are added to the score, and this final score is then broken into five risk classes. Those patients in risk classes I-III are at low risk and can be managed as outpatients, with a mortality rate less than 1%. However, those patients with risk classification IV had a 9.3% mortality rate, and class V patients had a 27% mortality rate. The study suggested that patients in classes IV and V should require hospitalisation.

Although the study did not specifically evaluate the need for ICU admission, patients in class V were more likely to require ICU admission.

The severity assessment criteria are important in helping physicians identify patients who need hospitalisation or ICU admission, but they are not meant to remove physicians' clinical judgement in the decision-making process.

2.7. Antimicrobial Treatment

Treatment guidelines have been developed by several professional organisations to standardise therapy for CAP. During the past year, the American Thoracic Society, the Canadian Infectious Diseases Society and the Canadian Thoracic Society, the Infectious Disease Society of America, and the Centers for Disease Control and Prevention published updated, extensive guidelines that reflect the evolution of opinion regarding CAP management in adults. All of these guidelines support the idea that the treatment of patients with CAP should be focus on the possible associated etiological agents.⁹⁵

It is necessary to develop local guidelines for antibiotic usage because the guidelines have to be based on, other than universal principals of use of antibiotics, local epidemiological data, potential pathogens, patterns of antimicrobial susceptibility and local clinical experience.^{1, 96} Thus, empirical antibiotic guidelines for CAP in Australia have been developed nationally on several occasions.¹

The choice of empirical therapy must take into account the (i) range of pathogens potentially causing the infection, (ii) severity of the infection, (iii) known susceptibility patterns for the respiratory pathogens and (iv) effect of any antibiotics on the bystander organisms.⁹² The current TG:A recommends the following antibiotics for adult patients with CAP (Table 2.7).

Table 2.7 Treatment of community-acquired pneumonia¹

Severity of pneumonia	First-line therapy	Second-line therapy
Group 1. mild to moderate	amoxicillin OR doxycycline OR roxithromycin OR benzylpenicillin OR procaine penicillin	cephalothin OR cephazolin
Group 2. severe (non-tropical Australia)	erythromycin PLUS benzylpenicillin PLUS gentamicin	erythromycin PLUS cefotaxime OR ceftriaxone
Group 3. aspiration and/or lung abscess	benzylpenicillin PLUS metronidazole	clindamycin OR ticarcillin + clavulanate OR piperacillin + tazobactam
Group 4. staphylococcal	di(flu)cloxacillin OR cephalothin	vancomycin
Group 5. severe (tropical Australia)	gentamicin PLUS EITHER ticarcillin + clavulanate OR ceftriaxone	gentamicin PLUS EITHER imipenem OR meropenem OR ciprofloxacin

Duration of antibiotic treatment for bacterial CAP depends on the clinical response, but usually 5 to 10 days, with longer treatment advised for mycoplasma or chlamydial infections (14 days) and legionella infections (21 days). Severe or complicated cases may need prolonged treatment.^{1, 90}

Antimicrobial treatment failures are usually underestimated. The most common causes include:^{1, 97}

- a. Incorrect diagnosis (e.g. pulmonary embolism, pulmonary oedema)
- b. Microbial resistance to the initial antimicrobial regimen
- c. Development of a complication (e.g. empyema, lung abscess)
- d. Inadequate dose or route of administration
- e. Underlying disease (e.g. lung cancer, heart failure, immunodeficiency)
- f. The presence of nosocomial pneumonia

After the initial clinical improvement, hospitalised patients should be switched from intravenous antibiotic therapy to oral therapy, while continuing similar antimicrobial coverage that provides similar tissue concentrations as the parenteral counterpart. Criteria for determining when the patient can make the transition to oral antibiotics include:^{90, 98-102}

- a. No clinical indication for continuing intravenous therapy
- b. The ability to tolerate antibiotics by mouth
- c. A functioning gastrointestinal tract
- d. Stable blood pressure
- e. A decreasing white blood cell count
- f. A decreasing C-reactive protein levels
- g. Improving or resolving signs and symptoms of infection (cough, dyspnea, fevers, respiratory distress)

A meta-analysis by Rhew *et al*⁹⁹ evaluated early switch and early discharge strategies in patients with CAP, with a significant and safe reduction of the mean length of stay.

2.8. Assessment of Antibiotic Costs and Antibiotic Treatment Costs

Antibiotics are the major component of a hospital's drug expenditure, consuming 15% to 30% of the total spent on pharmaceuticals. A high priority is therefore placed on containing antibiotic use.²⁸ Certainly, it is important to be concerned about the purchase price of drugs and it is appropriate that hospitals try to obtain pharmaceutical products at the lowest possible price through means such as bulk purchasing and multi-

hospital systems, as well as by purchasing the least expensive of equivalent agents. However, paying attention to the purchase price (acquisition cost) only part of its economic impact on the hospital.¹⁰³

In addition to the cost of buying drugs, there are a number of other economic implications of pharmaceutical products. Whilst pharmacy costs themselves may present 5% to 10% of the operating expenditure of a major hospital, a number of other expenses are related to (i) administering drugs, (ii) monitoring for their side effects, (iii) treating the adverse effects of the drugs and (iv) providing nursing and medical care to patients receiving these pharmaceutical products. In fact, these hidden costs of a drug are several-fold the purchase price.^{103, 104}

Plumridge²⁸ studied the cost of preparing and administering several intravenous antibiotics in an Australian teaching hospital. The costs were calculated using acquisition cost of the drugs, cost associated with drug delivery (administration system, ancillary equipment, labour) and laboratory monitoring for potential toxicity. Standard regimens based on the TG:A were used to compile the daily total cost. The results indicated that these components affected the daily total cost of individual antibiotics in different ways. Acquisition cost was often a poor predictor of total cost, which ranged from 1.2 times to almost eight times the acquisition cost. Less frequent administration reduced total costs substantially, as did slow injection compared with infusion. Laboratory monitoring costs constituted between 3.6% and 23% of the daily total cost and were most pronounced with antibiotics that had low acquisition costs.

Gilbert *et al*³⁶ assessed the costs of antimicrobial therapy in patients with CAP. The total antimicrobial costs were estimated by summing drug costs, using average wholesale price for oral agents and institutional acquisition prices for parenteral agents, plus the costs associated with preparation and administration of parenteral therapy. The results demonstrated that the overall median cost of antimicrobial therapy was US\$ 12.90 for outpatients and ranged from US\$ 10.80 to US\$ 58.90 among treatment sites ($p < 0.0001$). While the overall median cost of antimicrobial therapy was US\$

228.70 for inpatients and ranged from US\$ 183.70 to US\$ 315.60 among sites ($p < 0.0001$).

Niederman *et al*¹⁰⁵ conducted a retrospective analysis based on national incidence data and paid claims data for patients treated for CAP to assess the frequency of services rendered and costs to the health-care system. The results showed that a total cost of US\$ 4.8 billion for treating patients aged ≥ 65 years and US\$ 3.6 billion for treating patients aged < 65 years. These calculations were based on the following: 1.1 million hospital discharges resulting in inpatient costs of US\$ 4.4 billion (52.4% of the US\$ 8.4 billion) for the 0.6 million patients aged ≥ 65 years and US\$ 3.1 billion (36.9% of the US\$ 8.4 billion) for the 0.5 million patients aged < 65 year. The average hospital length of stay was 7.8 days with an average cost of US\$ 7 166 for patients aged ≥ 65 years and 5.8 days with an average cost of US\$ 6 042 for younger patients. Room and board represented the largest percentage cost of the average hospital bill for patients with CAP.

3. Methodology

The current study comprised two parts. The first part was a prospective audit of antibiotic prescribing involving adult patients for treatment of CAP to SCGH. This was undertaken to assess the impact of documented penicillin allergy on the choice of antibiotics and the clinical and financial consequences of changes in prescribing patterns in an Australian teaching hospital. The second part was a prospective study of patients admitted to SCGH who had a history of penicillin allergy, but were not suffering from CAP. This was conducted in order to ensure that the pattern of penicillin allergies of patients admitted to the hospital could be adequately characterised.

3.1. Part One

3.1.1. *Study Design*

The study was a prospective, observational, case-control study involving adult patients admitted with CAP to SCGH over a 15-week period.

3.1.2. *Ethics Approval, Informed Consent and Confidentiality*

This study was carried out in a manner conforming to the principles set out by the “National Statement on Ethics in Research Involving Humans” and according to the Good Clinical Practice Guidelines and the International Conference of Harmonisation. Both the Curtin University of Technology Human Research Ethics Committee (HREC) (Appendix 1) and the SCGH HREC (Appendix 2) reviewed and approved the study.

After the study had been explained to the patients in detail (Appendix 3 and 4), those patients providing written informed consent (Appendix 5 and 6) were entered into the study.

The study records were kept in the School of Pharmacy during the study and will be stored in a locked archive for five years from the time the study is closed and will be destroyed at that time. Only the investigators of the study are able to access the study records. Personal data, which may be

sensitive, (e.g. name, date of birth) were collected and processed but only for research purposes in connection with this study. All the data was de-identified by removal of personal information on the completion of data collection. To ensure patients anonymity in the database, patient codes were kept separately during data entry and data analysis.

3.1.3. Study Population

To be included in the study, patients had to be at least 18 years of age, be admitted with a clinical diagnosis of CAP and commenced on a course of antibiotics. Patients were excluded from entry to the study if they were admitted directly to the ICU or oncology ward, had communication difficulties (mental/physical disabilities), did not speak English or were unwilling to participate in the study. Patients who were admitted directly to the ICU and oncology ward were excluded because they might use more expensive drugs or alternative drugs, require longer duration of therapy and LOS than those who were not admitted directly to the general medical wards.

3.1.4. Sample Size

A sample size of 130 patients was chosen as it would allow the detection of A\$ 6.57 difference in the cost of antibiotic therapy per dose at the 95% confidence interval. This would give the study on 80% power.

3.1.5. Study Conduct

On entry to the study, procedures included verification of inclusion and exclusion criteria as well as obtaining informed consent. Patients were then divided into two groups based on documented of penicillin allergy – Group A – those patients with a documented of penicillin allergy (Target patients) and Group B – those patients without a documented of penicillin allergy (Control patients). The groups were compared on the basis of patient demographics (age, gender), markers of severity of pneumonia (Table 3.1) and presence of significant risk factors (Table 3.2) to assess whether or not the groups were adequately matched.

Table 3.1 Severity of pneumonia¹

Severity of pneumonia was classified into five groups:

Group 1. Mild to moderate community-acquired pneumonia

Group 2. Severe community-acquired pneumonia

Group 3. Aspiration pneumonia and lung abscess from aspiration

Group 4. Staphylococcal pneumonia

Group 5. Severe community-acquired pneumonia (tropical Australia)

Severe pneumonia was defined by the presence of one or more of the following not attributable to another cause.

Respiratory failure:

- Respiratory rate >30 per minute
- pO_2 <60 mmHg or SaO_2 <90% on room air
- pCO_2 >50 mmHg on room air
- Chest X-ray evidence of bilateral involvement or involvement of multiple lobes
- Increase in the size of chest X-ray opacity by 50% or more within 48 hours of admission
- Requirement for mechanical ventilation or inspired oxygen >35% to maintain SaO_2 >90%

Haemodynamic compromise:

- Systolic blood pressure <90 mmHg
- Diastolic blood pressure <60 mmHg
- Recent deterioration in renal failure (urea >7 mmol/L)
- White blood cell count <4 or >30x10⁹/L

pO_2 = partial pressure of oxygen; SaO_2 = oxygen saturation

pCO_2 = partial pressure of carbon dioxide

Table 3.2 Significant risk factor of community-acquired pneumonia⁹³

Age over 50 years	Immunosuppression
Alcoholism	Indigenous background
Asthma	Institutionalisation
Chronic obstructive pulmonary disease	Seizure disorders
Dementia	Smoking
Heart failure	Stroke

Data collected included patient demographics (age, gender, weight, ethnicity), history of drug allergies or adverse effects, history of presenting complaint, clinical diagnosis on admission, past medical history, social history, relevant biochemical tests (Table 3.1), chest X-ray findings, antibiotics prescribed – [drug(s), dosage and duration], therapeutic drug monitoring, antibiotic on discharge, treatment outcomes determined by discharge status (i.e. discharged home, returned to institution or died) and LOS. All data were obtained by reviewing the patients' medical records and drug charts. Data were recorded on a standardised data collection form (Appendix 7).

Patients in Group A were interviewed regarding their penicillin allergies using a structured questionnaire (Appendix 8). The questionnaire gathered information on history of the patient's penicillin allergy – what drug was implicated, when did the reaction occur, what type of reaction occurred, how was the drug administered, how soon did it occur after commencing the drug, how was the reaction treated, who told the patient that he/she had suffered a reaction, was advice given to avoid the drug or related drugs in the future, had the patient been exposed to the same drug or related antibiotics since the reaction, and whether any skin test had ever been done to confirm the allergy.

Patients were considered to have a penicillin reaction based on self-reporting of an adverse event or the presence of a Drug Alert sticker in either their medical records or on drug charts. Patients were not required to have undergone allergy testing to be considered penicillin allergic.

Patients with documented penicillin reactions were classified as penicillin allergic, intolerant or not substantiated based on data obtained from the interviews, and predetermined criteria as follows:

- a. Allergy: one or more symptoms including difficulty in breathing, swelling, rash, itch, anaphylaxis, loss of consciousness, seizures, skin sloughing (Stevens-Johnson syndrome), rapid heartbeat and congestion involving mucous membranes of the eyes, nose and mouth.¹⁰⁶⁻¹⁰⁸

- b. Intolerance: one or more gastrointestinal symptoms including nausea, vomiting, diarrhoea, crampy abdominal pain and the combination of gastrointestinal effects and feeling faints.¹⁰⁶⁻¹⁰⁸
- c. Not substantiated: patients could not recall the incident of the allergic reaction and the corresponding symptoms, denied the allergy or reported no penicillin allergy at the time of the interviews.

If the patient met at least one criterion for allergy, the patient was classified as allergic, regardless of any intolerant also reported. The patients classified as allergic were sub-classified into one of two reaction severities: Severity I (more serious) and Severity II (less serious). Severity I symptoms included anaphylaxis, difficulty in breathing, swelling, rapid heartbeat, loss of consciousness, skin sloughing and seizures. Severity II symptoms included rash and itch.

3.1.6. Economic Evaluations

The cost of antibiotic therapy was based on the actual cost of administering antibiotics. It provided a comprehensive analysis of three components of antibiotic administration to patients – acquisition cost, delivery costs (labour and equipment) and laboratory monitoring costs. Each of the three components was costed as follows:

- a. Acquisition cost was based on the costs to public hospitals in Western Australia derived from the State Tender for Drugs and Ethical Preparations and Disinfectants and Antiseptics, 2002 or the wholesale price to public hospitals from manufacturers or pharmaceutical wholesaling agents, 2002. No account was made for purchasing overheads.
- b. Delivery costs comprised the cost to prepare and administer the antibiotic in a form suitable for intravenous administration. These included the cost of a delivery system, being either a syringe for slow intravenous injection, or a minibag of compatible sterile solution and an administration set for intravenous infusion; the cost of ancillary equipment including needles, syringes and compatible diluent for

reconstituting antibiotic powders; and the cost of labour required for the preparation and administration of each dose by a nurse. Labour costs were based on the salary of a seventh year, level one registered nurse in Western Australia, with allowance made for penalty rates. No account was made for personnel overheads. All of the delivery costs were based on the work undertaken by Plumridge.²⁸ The following drugs have the same delivery costs per dose since they have the same methods of administering antibiotics: amoxycillin and cephalothin; cefepime, ceftriaxone, erythromycin, and ticarcillin/potassium clavulanate; clindamycin and gentamicin. The delivery costs were then adjusted to the current costs using the Australia Customer Price Index (CPI), weighted average of eight capital cities.¹⁰⁹

- c. Laboratory monitoring costs were related to assays required for therapeutic drug monitoring of narrow therapeutic indices (e.g. aminoglycosides). These costs were obtained from the Department of Microbiology, SCGH. As biochemical test are performed routinely for most patients requiring antibiotics intravenously, the cost of these tests was not included.

The length of each patient's stay was also incorporated in the cost evaluations. The hospital running cost was obtained from the Health Department, Western Australia. The total cost, therefore, was calculated by adding the accommodation cost (hospital running cost x LOS) to the total drug costs.

The calculation of potential cost savings was achieved through identification of patients without penicillin allergies and avoidance of use of more expensive antibiotic alternatives. The antibiotic cost savings of the study period was computed as follows:

$$AB\text{savings} = [AC_A - AC_B] \times N \quad \text{Equation 3.1}$$

where

ABsavings = total antibiotic cost savings for the study period

AC_A = average antibiotic cost for patients with penicillin allergy

AC_B = average antibiotic cost for patients without penicillin allergy

N = number of patients with intolerant of penicillin

The antibiotic cost savings per year was obtained by extrapolating the total antibiotic cost savings of the study period.

3.1.7. Data Entry and Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) for MS Windows version 11.0[®] was utilised for data entry and data analysis. All data were coded as necessary and entered through SPSS. The data entry to SPSS was double-checked for randomly selected patients and questionnaires.

The adherence to antibiotic prescribing was assessed using the TG:A. The antimicrobial selections and costs were then compared between Group A and Group B. The accuracy and consistency of penicillin allergy reporting in SCGH was also evaluated.

Patients were categorised into one of four age groups: young adults (18-30 years), adults (31-50 years), older adults (51-64 years) and elderly (≥ 65 years). Appropriate summary statistics including means, medians and percentages were presented to describe the sample. Comparisons between groups were conducted using the Student t-test for continuous variables, and Chi-square (χ^2) statistics and odds ratios (ORs) for categorical data. Continuous variables were assessed for Normality. If they found to be skewed, natural logarithm transformations were then applied. In some instances where transformations did not achieve Normality, non-parametric tests were used. Two-way Analysis of Variance (ANOVA) or Univariate General Linear Model (GLM) were also used to find association between one dependent variable and more than one independent variables, and to investigate of the interactions between them. Differences were considered statistically significant at $p < 0.05$.

3.2. Part Two

3.2.1. Study Design

Due to the lower than expected accrual rate for patients with CAP, a second prospective study of penicillin allergy was conducted at SCGH over a 5-week period in order to ensure that the pattern of penicillin allergies of patients admitted to the hospital could be adequately characterised. Data from this study were used in calculating possible cost saving through better documenting of patients' adverse reactions to penicillins.

3.2.2. Ethics Approval, Informed Consent and Confidentiality

This study was carried out in a manner conforming to the principles set out by the "National Statement on Ethics in Research Involving Humans" and according to the Good Clinical Practice Guidelines and the International Conference of Harmonisation. Both the Curtin University of Technology HREC (Appendix 9) and the SCGH HREC (Appendix 10) reviewed and approved the study.

After the study had been explained to the patients in detail (Appendix 11), those patients providing written informed consent (Appendix 12) were entered into the study.

No personal information was recorded as part of the interview ensuring the patient's anonymity.

3.2.3. Study Population

To be included in the study, patients had to be at least 18 years of age, admitted without CAP and had documented penicillin allergy. Patients were excluded from entry to the study if they had communication difficulties (mental/physical disabilities), did not speak English or were unwilling to participate in the study.

3.2.4. Study Conduct

On entry to the study, procedures included verification of inclusion and exclusion criteria as well as obtaining of informed consent. Patients were

interviewed regard their penicillin allergies using a structured questionnaire (Appendix 13), which was basically the same as the questionnaire administered to the CAP patients in Part One of the study. Apart from the interview, age, gender and other drug allergies reported were also recorded.

Patients were considered to have a penicillin reaction based on self-reporting of an adverse event or the presence of a Drug Alert sticker in either their medical records or on drug charts. Patients were not required to have undergone allergy testing to be considered penicillin allergic.

Patients with documented penicillin reactions were classified as penicillin allergic or intolerant or not substantiated based on data obtained from the interviews, and predetermined criteria as previously described (in Part One).

If the patient met at least one criterion for allergy, the patient was classified as allergic, regardless of any intolerants also reported. The patients classified as allergic were sub-classified into one of two reaction severities: Severity I (more serious) and Severity II (less serious) as previously described (in Part One).

3.2.5. Data Entry and Statistical Analysis

The SPSS for MS Windows version 11.0[®] was utilised for data entry and data analysis. All data were coded as necessary and entered through SPSS. The data entry to SPSS was double-checked for randomly selected questionnaires.

Appropriate summary statistics, including means and percentages were presented to describe the sample. Continuous data were analysed using the Student t-test, whereas categorical data were compared with the use of χ^2 statistics. For all analyses, a two-tail $p < 0.05$ was considered to indicate statistical significance. The standard of allergy documentation was also assessed for each patient.

4. Results and Discussion

This chapter comprised three parts. The first part was the results and discussion of a prospective audit of antibiotic prescribing involving adult patients admitted for treatment of CAP to SCGH. The second part was the results and discussion of a prospective study of patients admitted to SCGH who had a history of penicillin allergy, but were not suffering from CAP. Whilst the third part was the combined data and discussion of patients with documented of penicillin allergy in the current study.

4.1. Part One (Community-Acquired Pneumonia Patients with Penicillin Allergy)

4.1.1. Patient Demographics

4.1.1.1. Number of Patients Recruited

During the 15-week study period, the medical records of 233 patients admitted with CAP to SCGH were reviewed. Of these, 78 were deemed ineligible for the study for the following reasons: 10 (12.8%) were admitted directly to the ICU ward, 56 (71.8%) had communication difficulties (mental/physical disabilities), nine (11.6%) did not speak English and three (3.8%) were unwilling to participate in the study. Therefore, in total of 155 (66.5%) patients were included in the study after giving informed consent. Of these, 27 (17.4%) had documented penicillin allergies in their medical records or on drug charts (Group A) and 128 (82.6%) were assigned to be the control group (Group B). These two groups were not significantly different ($p>0.05$) based on the basis of patient demographics, markers of severity of pneumonia and presence of significant risk factors as shown in Tables 4.1 – 4.3.

Table 4.1 Patient demographics

Characteristic	Group A (n=27)	Group B (n=128)	p value
Age, mean (\pm SD)	69 \pm 14	67 \pm 18	0.666 ^a
Female, No. (%)	16 (59.3)	68 (53.1)	0.561 ^b

Group A = patients with a documented of penicillin allergy

Group B = patients without a documented of penicillin allergy

^a Significance was determined using the t test

^b Significance was determined using the χ^2 test

Table 4.2 Markers of pneumonia severity¹ comparing the penicillin (Group A) and non-penicillin (Group B) groups

Markers of pneumonia severity	Group A (n=27)	Group B (n=128)	p value ^a
	n (%)		
RR >30 per minute	1 (3.7)	12 (9.4)	0.334
pO ₂	2 (33.3)	4 (12.5)	0.199
pCO ₂	3 (15.0)	16 (15.1)	0.991
SaO ₂	2 (33.3)	5 (15.6)	^b
Bilateral/multilobe radiographic shadowing	4 (14.8)	17 (13.3)	0.695
Systolic BP <90mmHg	0 (0)	0 (0)	^b
Diastolic BP <60mmHg	1 (3.7)	1 (0.8)	^b
Urea >7mmol/L	16 (59.3)	53 (41.4)	0.090
WCC <4 or >30x10 ⁹	1 (3.7)	1 (0.8)	^b

Group A = patients with a documented of penicillin allergy

Group B = patients without a documented of penicillin allergy

RR = respiratory rate

pO₂ = partial pressure of oxygen

pCO₂ = partial pressure of carbon dioxide

SaO₂ = oxygen saturation

BP = blood pressure

WCC = white blood cell count

^a Significance was determined using the χ^2 test

^b No test was conducted due to small sample size

Table 4.3 Significant risk factors of community acquired pneumonia⁹³ comparing the penicillin (Group A) and non-penicillin (Group B) groups

Characteristic	Group A	Group B	p value *
	(n=27)	(n=128)	
	n(%)		
Age >50	24 (88.9)	105 (82.0)	0.386
Alcohol intake ^a	18 (66.7)	90 (70.3)	0.708
Smoking	9 (33.3)	43 (33.6)	0.979
Institutionalisation ^b	3 (11.1)	26 (20.3)	0.265
Indigenous background	0 (0)	6 (4.7)	#
Asthma	14 (51.9)	64 (50.0)	0.861
COPD ^c	11 (40.7)	38 (29.7)	0.262
Dementia	0 (0)	13 (10.2)	0.084
Heart failure	2 (7.4)	9 (7.0)	0.945
Immunosuppression ^d	14 (51.9)	59 (46.1)	0.586
Seizure disorders	1 (3.7)	11 (8.6)	0.388
Stroke	4 (14.8)	9 (7.0)	0.185

Group A = patients with a documented of penicillin allergy

Group B = patients without a documented of penicillin allergy

^a Alcohol intake was defined as harmful alcohol use (≥ 5 standard drinks a week)

^b Institutionalisation was defined as nursing home residents, hostel residents and retirement village residents

^c COPD (Chronic Obstructive Pulmonary Disease) was defined as chronic bronchitis, chronic airflow limitation and emphysema

^d Immunosuppression was defined as use of systemic corticosteroids (10 mg/day of prednisolone or its equivalent)

* Significance was determined using the χ^2 test

No test was conducted due to small sample size

4.1.1.2. Frequency of Penicillin Allergy Reported

The 17.4% of patients reported as penicillin allergic was higher than reported in other studies,^{9, 110} but similar to that recently reported in a Queensland hospital,²⁰ two Sydney hospitals¹⁰ and a Chicago hospital.¹⁵ When the patients were interviewed for the details of their allergy, 88.9% (24/27) were classified as having a true allergic reaction. Based on this result, the actual proportion of patients with true penicillin allergy in the current study was calculated to be 15.5%, which is still higher than reported previously.^{9, 15, 110}

4.1.1.3. Age of Patients

Age, which is a continuous variable, was tested using the t test and found to be normally distributed. The ages of the patients with and without documented penicillin allergies ranged from 55 to 83 years, and 49 to 85 years, respectively (Table 4.1).

4.1.1.4. Gender of Patients

As shown in Table 4.1, 16 patients (59.3%) in Group A and 68 (53.1%) in the Group B were females ($p=0.561$). This result indicates that there is no significant association between the presence of penicillin allergy and gender. In contrast, several previous studies found that females were more likely to have allergic reactions to drugs than males.^{10, 54, 57, 58}

4.1.2. Accuracy of Penicillin Allergy Reporting

Appropriate documentation of the incidence of penicillin allergy is important to (i) prevent patients from being rechallenged, (ii) decrease the risk for a potential life-threatening reaction and (iii) avoid the unnecessary use of potentially more toxic, less effective or more expensive drugs.^{9, 22}

4.1.2.1. Documentation of Penicillin Allergy

At SCGH, any ADRs including drug allergy must be documented in the medical record and on the front cover as well as inside cover of the drug chart. Drug Alert stickers should be attached to the front cover and inside cover of the drug chart. These alerts are important to immediately remind health professionals of any ADRs experienced by the patient. Furthermore, labelling on the outside of the chart can make the allergy more obvious to the prescriber and decrease the chance of inappropriate orders being written.⁹

In the current study, the penicillin allergy was documented in the patient's medical record and on drug chart in 26 (96.3%) and 25 (92.6%) cases, respectively. Drug Alert stickers were attached in 85.2% (23/27) of cases to the front cover of drug charts and 70.4% (19/27) to the drug charts' inside cover. Nevertheless, brief information regarding the allergic reactions (e.g. drug name, type of reactions involved) was only present for one-third of the

patients (33.3%). Furthermore, none of either the medical records or drug charts had the date of the reaction documented. This is consistent with findings of previous studies,^{9, 111} in which approximately 35% of patients had a description of their allergy in the drug charts and none of the patients' records had a note as to when the initial reactions occurred or what dosage forms were involved.

These results suggest that the standard of documentation of the patients' penicillin allergies is poor and does not comply with the SCGH policy for the documentation of ADRs. Without a detailed description of the allergy in the patients' medical records and on the drug charts, it is difficult to judge the nature of the allergy or to ascertain the appropriateness of subsequent β -lactam therapy.⁹ It is possible that the health care professionals were more likely to read the front part of the drug charts than the front and inside cover of medical records to find any relevant history of allergy. But, as the principal source of information, the medical record should have completed documentation of allergic reactions. A prime example of the positive outcomes of adequate documentation is the patient in the current study who was successfully rechallenged with amoxicillin after the doctor was notified about the details of the patient's penicillin allergy history.

4.1.2.2. Characteristics of Penicillin Allergies Reported

In the current study, it was possible to conduct a further interview with all patients with documented penicillin allergy. The results of the patient interviews are presented in Table 4.4.

Table 4.4 Responses to interviews with patients labelled as having penicillin allergy

Question and Response	No. (%)
Aware of allergy?	
Yes	27 (100.0)
No	0 (0)
Penicillin causing allergy?	
Amoxicillin	14 (51.9)
Augmentin® (amoxicillin and potassium clavulanate)	2 (7.4)
Do not remember	11 (40.7)
First occurrence of penicillin allergy? (no. yr ago)	
0-5	4 (14.8)
6-10	1 (3.7)
11-20	8 (29.7)
21-30	2 (7.4)
>30	12 (44.4)
Do not remember	0 (0)
Route of administration when reaction occurred?	
Oral	12 (44.4)
Injection	15 (55.6)
Do not remember	0 (0)
Onset of allergy?	
Immediately (within few minutes)	4 (14.8)
≤72 hours	13 (48.2)
>72 hours	5 (18.5)
Do not remember	5 (18.5)
Treatment of allergy?	
Penicillin was ceased	22 (81.5)
Penicillin was ceased and unknown drugs given	3 (11.1)
Do not remember	2 (7.4)
Patient told of allergy by whom?	
Doctor	20 (74.1)
Nurse	2 (7.4)
Parents	1 (3.7)
Self ^a	4 (14.8)
Told not to receive drug again?	
Yes	24 (88.9)
No	3 (11.1)
Told not to receive related compounds again?	
Yes	3 (11.1)
No	23 (85.2)

Do not remember	1 (3.7)
Subsequently received a penicillin again?	
Yes, and a reaction occurred	1 (3.7)
Yes, and no reaction occurred	3 (11.1)
No	23 (85.2)
Subsequently received a related compound again?	
Yes, and a reaction occurred	2 (7.4)
Yes, and no reaction occurred	16 (59.3)
No	6 (22.2)
Do not remember	3 (11.1)
Was skin testing ever done?	
Yes	1 (3.7) ^b
No	26 (96.3)

^a Patient self-diagnosed the allergy

^b Result was positive

4.1.2.2.1. Penicillin Causing Allergy and Time Since Allergic Reaction

Approximately 60% of the interviewed patients in the current study could recall what type of penicillin they were allergic to – 51.9% (14/27) were allergic to amoxicillin and 7.4% (2/27) were allergic to Augmentin®. While the remaining 11 patients (40.7%) had difficulty remembering the penicillin causing their allergy.

The mean period since the patients' first penicillin allergic reaction was 29 years (range: 0 to 53 years ago) – 51.9% (14/27) of patients had their first penicillin allergic reaction more than 20 years ago. Interestingly, the current study found that the first occurrence of penicillin allergy did not influence the penicillin causing allergy (Table 4.5).

Table 4.5 Association between first occurrence of penicillin allergy and penicillin causing allergy

Penicillin causing Allergy	First occurrence of penicillin allergy (no. yr ago)					p value *
	0-5 (n=4)	6-10 (n=1)	11-20 (n=8)	21-30 (n=2)	>30 (n=12)	
Amoxicillin	3 (75.0)	1 (100.0)	3 (37.5)	0 (0)	7 (58.3)	0.930
Augmentin®	1 (25.0)	0 (0)	1 (12.5)	0 (0)	0 (0)	
Do not remember	0 (0)	0 (0)	4 (50.0)	2 (100.0)	5 (41.7)	

* Significance was determined using the χ^2 test (Amoxicillin and Augmentin® (amoxicillin and potassium clavulanate) were combined so as the time period from 0-5 years ago up to 21-30 years ago to meet the assumptions of the test)

As can be seen in Table 4.5, around 45% (12/27) of the patients with documented penicillin allergy had their initial exposure in 1970s or earlier. Of these, seven (58.3%) claimed that they were allergic to amoxicillin, while the remaining five patients (41.7%) could not recall what type of penicillin they were allergic to. Nonetheless, it is possible that some of them were allergic to ampicillin rather than amoxicillin since amoxicillin was released onto the market in 1970s. Moreover, ampicillin was more commonly used 30 years ago.¹¹²

4.1.2.2.2. Route of Administration

Surprisingly, all of the 27 patients in the current study could recall the route of administration when penicillin reaction occurred – 44.4% of the reactions occurred following parenteral administration and the remaining 55.6% following oral administration. This finding differs from a recent Australian study by Wyer,²⁰ in which of the 60 patients claimed to have a history of penicillin allergy, 41 (68.3%) reported that the drug was administered by injection, 13 (21.7%) by oral and six (10.0%) by an unknown route.

4.1.2.2.3. Time to Onset of Allergy

The majority of patients experienced symptoms of their allergy within 72 hours of the drug being administered, with 14.8% (4/27) experiencing symptoms immediately (within few minutes). This is consistent with a previous findings of Wyer,²⁰ that is of the 60 patients with a reported penicillin allergy, 17% experienced symptoms of their allergy immediately.

4.1.2.2.4. Reported Symptoms

The mean (\pm SD) number of symptoms reported by patients during the interview was 3.1 ± 1.6 (range: 1-7). Similar to a previous findings by Preston *et al*,⁹ rash was the most common symptom of penicillin allergic reactions, followed by itch and swelling (Table 4.6).

Table 4.6 Reported symptoms of allergic reaction to penicillin

Symptom*	No. (%)
Rash	17 (63.0)
Itch	13 (48.1)
Swelling	10 (37.0)
Nausea	3 (11.1)
Loss of consciousness	2 (7.4)
Rapid heartbeat	2 (7.4)
Difficulty breathing	2 (7.4)
Skin sloughing	2 (7.4)
Vomiting	1 (3.7)
Feeling sick	1 (3.7)
Hallucinations	1 (3.7)

* Patient could have more than one symptom

4.1.2.2.5. Classification of Penicillin Allergy

It was possible to assess whether the patient had suffered true allergic reaction or was intolerant to penicillin in all patients interviewed. Of the 27 patients assessed, 24 (88.9%) were classified as allergic: 12 (50.0%) as Severity I and 12 (50.0%) as Severity II. The number of patients classified as intolerant was relatively small (11.1%) and is similar to a figure quoted as 'intolerant' in previous reports.^{9, 10, 71} These findings indicated that most of

the patients were correctly labelled as penicillin-allergic according to the study's criteria. Some of the patients admitted that they knew that they were not 'truly' allergic to penicillin, but still did not want to be rechallenged.

In the current study, the classification of penicillin allergy depended on patient recall and there had been a long interval between many original events and the interview. So, it is possible that this affected the reliability of information received. But, in the current study, all of the penicillin-allergic patients were interviewed to obtain detailed information on the nature and severity of their penicillin allergies, whereas in other studies,^{2, 15, 20} data were collected from secondary sources such as pharmacy computer and patient records. Since this information is not always complete, it seemed more appropriate to ask the patients for detailed information.

4.1.2.2.6. Diagnosis of Penicillin Allergy

As shown in Table 4.4, the majority of the interviewed patients were told of their penicillin allergy by health care professionals. However, similar to a previous report,⁹ 14.8% (4/27) deemed themselves to be allergic to penicillin. Two of these (50.0%) were classified as allergic according to the study's criteria, whereas the other two (50.0%) were classified as intolerant. Thus, clinicians should not simply accept the diagnosis of the allergy without obtaining a detailed history of the reaction.

4.1.2.2.7. Incidence of Reactions to Multiple Drug Allergies

The current study found that 14 patients (51.9%) reported multiple drug allergies, with the mean (\pm SD) number of allergies reported per patient being 1.8 ± 1.5 (range: 1-8). Five (18.5%) reportedly penicillin-allergic patients also reported an allergy to a related compound – three (60.0%) of these were allergic to cephalosporins and the remaining two (40.0%) were allergic to cephalosporins, carbapenems and monobactam. These figures are similar to that found by Sullivan *et al*⁶⁰ In their study, 21% of patients with a history of a probable Ig-E mediated reaction to penicillin also had a history of a probable IgE-mediated reaction to another class of antibiotics. On the

contrary, another study by Khoury *et al*¹¹³ reported that the incidence of reactions to multiple antibiotics was no higher among patients with positive penicillin skin test results than among patients with negative penicillin skin test results or those with allergic rhinitis.

4.1.2.2.8. Advice for Avoiding Penicillin or Related Compounds in the Future

Of the three patients who reported that they were not told to avoid taking penicillin, two (66.7%) were classified as allergic and one (33.3%) as intolerant. On the other hand, of the 24 patients who reported that they were told to avoid taking penicillin, 22 (91.7%) were classified as allergic and two (8.3%) as intolerant. This could be because of the common practice of 'defensive medicine' whereby the doctor caring for them at the time of the reaction told them not to have penicillin again.¹¹⁴ In contrast to the above results, the majority of the patients were not advised to avoid taking the related compounds in the future.

4.1.2.2.9. Rechallenge with Penicillin Antibiotic

As shown in Table 4.4, four (14.8%) of the interviewed patients reported that they had been rechallenged with a penicillin antibiotic. One of these, who had suffered a life-threatening reaction 20 years ago, stated that the second reaction was the same as the first reaction (swelling, rash and itch). Yet, two patients (50.0%) who experienced minor rash and itch at least 30 years ago reported that they did not experience any adverse reactions when they subsequently received a penicillin again less than five years ago. This suggests that the two patients may have been mislabelled as penicillin allergic because of past problems with penicillin preparations in the 1960s.^{115, 116} In addition, they may also have lost their sensitivity to the drug over time.^{51, 117}

4.1.2.2.10. Rechallenge with Other β -Lactam Antibiotics

The current study found that 66.7% (18/27) of the penicillin-allergic patients reported that they had been rechallenged with a penicillin related compound. Of these, one (5.6%) experienced a life threatening reaction (e.g. angioedema) when cephalosporins, carbapenems and monobactam were

administered, one (5.6%) experienced minor rash and itch when cephalosporins were administered and the remaining 16 (88.8%) stated that no reactions occurred when they received other β -lactam antibiotics.

4.1.2.2.11. Penicillin Skin Tests

Surprisingly, only one of the interviewed patients (3.7%) has ever had skin testing done for her penicillin allergy. Reports in the literature indicate that the true incidence of penicillin allergy is overstated,^{77, 118-120} and many patients who report a penicillin allergy have negative skin tests and are not at risk for IgE-mediated allergic reactions.^{55, 117, 121, 122} Hence, for patients who report a history consistent with a true penicillin allergy, skin testing may be a consideration before giving any penicillin or other related compounds.¹⁹

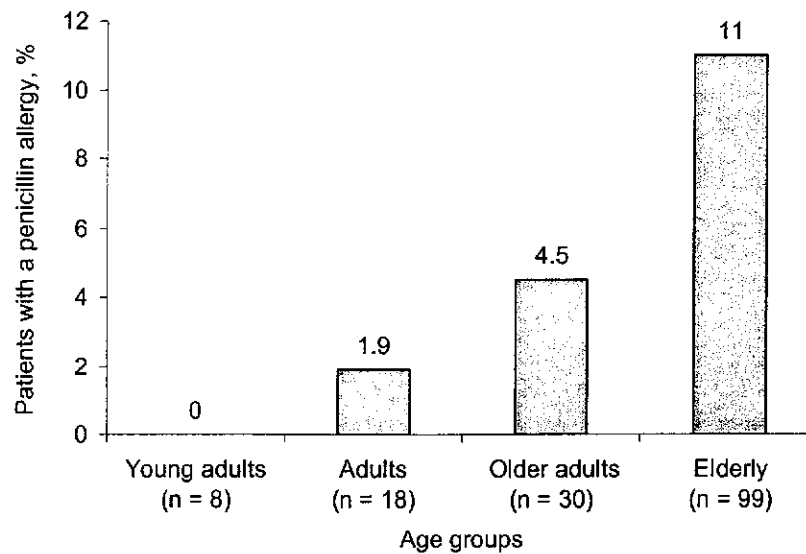
4.1.2.3. Comments for Improving Penicillin Allergy Reporting

There is a definite role for pharmacists in allergy documentation; although it was not the purpose of the current study to quantify this. Pharmacists are responsible for preventing or correcting drug-related problems, and accurately documenting allergies is one way of accomplishing this goal. Thus, pharmacists should ensure consistency of allergy documentation in the patient's medical record and on drug chart. Also, they should correct misclassifications by removing the allergy label from the patient's medical record and drug chart when the patient is not allergic.⁷¹ This must be done with care because of the potential legal repercussions if an allergic event is to occur after the label is removed. Further, the pharmacists must become actively involved in patient education, for example, by giving educational materials and discussing the patient's allergy with the patient.¹²³ Other health care providers would also benefit from allergy education by the pharmacist.^{9, 21}

4.1.3. Influence of Age on Penicillin Allergy

The percentage of patients with a reported penicillin allergy varied between each of the four age groups (Figure 4.1).

Figure 4.1 Percentage of patients with a reported penicillin allergy for each age group



Age groups include: young adults (18-30 years); adults (31-50 years); older adults (51-64 years); and elderly (≥ 65 years)

The above data demonstrated that on average, patients with a documented penicillin allergy were 30 years older. As patient age increased, the odds of a patient having a documented penicillin allergy increased. This observation is consistent with the natural history of documented drug allergies. Hypersensitivity reactions to penicillin depend on the presence of preformed antibodies.¹¹⁷ The likelihood of prior exposure to a penicillin increases with age. Therefore, older patients have a greater probability of having a documented allergy. Additionally, once an 'allergy' is documented in the medical record, it will likely remain there for the life of the patient.²

4.1.4. Influence of Penicillin Allergy on Other Drug Allergies

The current study shows that there is a significant association between the presence of penicillin allergy in other β -lactam allergies and other drug allergies, respectively (Table 4.7). Patients having history of penicillin allergy have nine times higher odds of other β -lactam allergies compared to those without a history of penicillin allergy (OR = 0.237; 95% CI = 0.024 – 0.474). A previous study by Sullivan *et al*⁶⁰ also found that patients who were

allergic to penicillin had increased risk of having other β -lactam sensitivity and it was estimated to be 10-fold.

Further, patients having history of penicillin allergy have three times higher odds of other drug allergies compared to those without a reported of penicillin allergy (OR = 0.356; 95% CI = 0.104 – 0.590). Other published studies^{55, 65} have also observed that patients experiencing penicillin hypersensitivity have an increased risk of non β -lactam antibiotic sensitivity.

Table 4.7 Association between penicillin allergy, other β -lactam allergies and other drug allergies

Characteristic	Group A	Group B	p value ^b
	(n=27)	(n=128)	
	n(%)		
Other β -lactam allergies ^a	5 (18.5)	3 ^c (2.3)	0.001
Other drug allergies	14 (51.9)	27 (21.1)	0.001

Group A = patients with a documented of penicillin allergy

Group B = patients without a documented of penicillin allergy

^a Other β -lactam allergies were defined as cephalosporins, carbapenems and monobactam allergies

^b Significance was determined using the χ^2 test

^c The n value was less than 5, which weakens the significance of the results

4.1.5. Influence of Asthma on Penicillin Allergy

Similar to popular belief, the current study found that asthma patients did not appear to be at increased risk for penicillin allergy (Table 4.8). Patients with a history of asthma, however, were found to be three times more likely to experience severe allergic reactions to penicillin compared to those without a history of asthma. These findings are similar to previous reports.^{8, 52, 63}

Table 4.8 Association between penicillin allergy and asthma

Asthma	Group A (n=27)	Group B (n=128)	p value *
	n(%)		
Yes	13 (48.1)	64 (50.0)	0.861
No	14 (51.9)	64 (50.0)	

Group A = patients with a documented of penicillin allergy

Group B = patients without a documented of penicillin allergy

* Significance was determined using the χ^2 test

4.1.6. Antimicrobial Use in Community-Acquired Pneumonia Patients without a Documented of Penicillin Allergy

4.1.6.1. Classification of Community-Acquired Pneumonia Patients

Based on the current TG:A,¹ the 128 CAP patients without a documented of penicillin allergy were classified as follows:

- 110 (85.9%) patients with mild to moderate CAP
- 16 (12.5%) patients with severe CAP
- Two (1.6%) patients with aspiration pneumonia

4.1.6.2. Antimicrobial Use Prior to Admission

Of the 128 CAP patients without a reported of penicillin allergy, 23 (18.0%) received oral antibiotics prior to admission. The most common antibiotics were macrolides (34.8%), followed by amoxicillin (21.7%), amoxicillin with potassium clavulanate (13.0%), cephalexin (8.7%) and unknown (21.8%).

4.1.6.3. Antimicrobial Use During Hospitalisation

All patients without a history of penicillin allergy received antibiotics for the entire duration of hospitalisation. About 78% of patients (100/128) received their initial dose of antibiotics within eight hours of admission, while the remaining 28 patients received their initial antibiotic dose more than eight hours after presentation to the hospital. These results are consistent with other previous published studies.^{39, 124}

Overall, ten individual antimicrobial agents in six classes were prescribed for patients without a documented of penicillin allergy (Table 4.9). The current study indicated that the majority of patients with mild to moderate CAP and aspiration pneumonia received a combination of an intravenous and oral antibiotic, followed by one oral antibiotic. Whilst the majority of patients with severe CAP received three intravenous antibiotics, followed by two intravenous antibiotics, a combination of an intravenous antibiotic and oral antibiotic, and one oral antibiotic.

4.1.6.3.1. Antibiotic Therapy Prescribed for Mild to Moderate Community-Acquired Pneumonia Patients

The current TG:A recommends amoxicillin or doxycycline or roxithromycin or benzylpenicillin or procaine penicillin as the drugs of choice for mild to moderate CAP patients without a history of penicillin allergy.¹ However, combinations of amoxicillin intravenously and azithromycin orally were the most frequently prescribed antimicrobials for such patients (Table 4.9). Interestingly, none of these patients received amoxicillin intravenously alone.

4.1.6.3.2. Antibiotic Therapy Prescribed for Severe and Aspiration Community-Acquired Pneumonia Patients

As presented in Table 4.9, the most commonly prescribed antibiotic therapy for severe CAP patients was a combination of intravenous amoxicillin, gentamicin and erythromycin. Whereas the most frequently prescribed antibiotics for aspiration pneumonia patients were a combination of amoxicillin intravenously and metronidazole orally. These are consistent with the current TG:A.¹

Table 4.9 Antibiotic therapy prescribed for community-acquired pneumonia patients without a history of penicillin allergy

Severity of pneumonia	Antibiotic prescribed *	No. (%)
Mild to moderate	Amoxicillin IV	109 (38.0)
	Azithromycin O	109 (38.0)
	Augmentin [®] O	54 (18.8)
	Amoxicillin O	10 (3.5)
	Timentin [®] IV	2 (0.7)
	Cephalexin O	1 (0.4)
	Erythromycin IV	1 (0.4)
	Moxifloxacin O	1 (0.4)
Severe	Amoxicillin IV	14 (20.9)
	Gentamicin IV	13 (19.4)
	Erythromycin IV	11 (16.4)
	Azithromycin O	11 (16.4)
	Augmentin [®] O	10 (14.3)
	Timentin [®] IV	4 (6.0)
	Ceftriaxone IV	1 (1.5)
	Amoxicillin O	1 (1.5)
	Erythromycin O	1 (1.5)
	Moxifloxacin O	1 (1.5)
Aspiration	Amoxicillin IV	2 (25.0)
	Augmentin [®] O	2 (25.0)
	Metronidazole O	2 (25.0)
	Metronidazole IV	1 (12.5)
	Azithromycin O	1 (12.5)

IV = intravenously; O = orally

Augmentin[®] = amoxicillin and potassium clavulanate

Timentin[®] = ticarcillin and potassium clavulanate

* Patients could receive more than one treatment

4.1.6.4. Antimicrobial on Discharge

The antibiotics prescribed on discharge were also reported in the current study. It showed that only 10.1% of the patients (11/128) without a documented of penicillin allergy were not prescribed any antibiotics on their discharge (Table 4.10).

Table 4.10 Discharge antibiotic for community-acquired pneumonia patients without a history of penicillin allergy

Severity of pneumonia	Antibiotic prescribed *	No. (%)
Mild to moderate	Augmentin® O	63 (76.8)
	Amoxicillin O	17 (20.7)
	Cephalexin O	1 (1.2)
	Azithromycin	1 (1.2)
Severe	Augmentin® O	11 (64.7)
	Amoxicillin O	3 (17.7)
	Azithromycin O	2 (11.8)
	Erythromycin O	1 (5.9)
Aspiration	Augmentin® O	2 (66.7)
	Metronidazole O	1 (33.3)

O = orally

Augmentin® = amoxicillin and potassium clavulanate

* Patients could receive more than one treatment

4.1.7. Influence of Penicillin Allergy on Antibiotic Prescribing in Community-Acquired Pneumonia Patients

4.1.7.1. Classification of Community-Acquired Pneumonia Patients

Based on the current TG:A,¹ the 27 CAP patients with a documented of penicillin allergy were classified as follows:

- 23 (85.2%) patients with mild to moderate CAP
- Four (14.8%) patients with severe CAP

4.1.7.2. Antimicrobial Use Prior to Admission

Of these 27 patients, seven (25.9%) received oral antibiotics prior to admission. These included macrolides (28.6%), cefaclor (14.3%), cotrimoxazole (14.3%) and ciprofloxacin (14.3%). In two patients, the prior antimicrobial regimen could not be reliably assessed.

4.1.7.3. Antimicrobial Use During Hospitalisation

As reported in Section 4.1.6.3, all patients with a history of penicillin allergy also received antibiotics for the entire duration of hospitalisation. The antimicrobial treatment during the hospitalisation comprised monotherapy, dual combination therapy and triple combination therapy. Dual combination therapy was commonly prescribed in patients with mild to moderate CAP, whereas triple combination therapy was more frequent in patients with severe CAP.

4.1.7.3.1. Antibiotic Therapy Prescribed for Mild to Moderate Community-Acquired Pneumonia Patients

The current TG:A recommends cephalothin or cephazolin as the first-line therapy for mild to moderate CAP patients with a history of penicillin allergy.¹ The current study, however, found that physicians were most likely to prescribe combinations of cephalothin intravenously and azithromycin orally for those who present with mild to moderate CAP. As listed in Table 4.11, only one patient received intravenous cephalothin alone since the patient was allergic to macrolide.

4.1.7.3.2. Antibiotic Therapy Prescribed for Severe Community-Acquired Pneumonia Patients

The current study found that combinations of intravenous cephalothin, erythromycin and gentamicin were the most commonly prescribed antimicrobials for patients with severe CAP (Table 4.11). This differs from the current TG:A, in which erythromycin plus cefotaxime or ceftriaxone are the drugs of choice for such patients.¹

Table 4.11 Antibiotic therapy prescribed for community-acquired pneumonia patients with a documented of penicillin allergy

Severity of pneumonia	Antibiotic prescribed*	No. (%)
Mild to moderate	Cephalothin IV	22 (34.4)
	Azithromycin O	21 (32.8)
	Cefaclor O	7 (10.9)
	Cefepime IV	5 (7.8)
	Cephalexin O	5 (7.8)
	Doxycycline O	2 (3.1)
	Clindamycin IV	1 (1.6)
	Ciprofoxacin O	1 (1.6)
Severe	Erythromycin IV	4 (21.1)
	Cephalothin IV	3 (15.8)
	Cefaclor O	3 (15.8)
	Gentamicin IV	3 (15.8)
	Azithromycin O	2 (10.5)
	Erythromycin O	2 (10.5)
	Clindamycin IV	1 (5.3)
	Clindamycin O	1 (5.3)

IV = intravenously; O = orally

** Patients could receive more than one treatment*

4.1.7.4. Antimicrobial on Discharge

The current study showed that the majority of patients with a history of penicillin allergy still received antibiotics when they were discharged. Only 18.5% of the patients (5/27) were not prescribed any antibiotics on their discharge. The oral therapy consisted predominantly of cefaclor followed by cephalexin and doxycycline (Table 4.12).

Table 4.12 Discharge antibiotic for community-acquired pneumonia patients with a history of penicillin allergy

Severity of pneumonia	Antibiotic prescribed	No. (%)
Mild to moderate	Cefaclor O	13 (72.2)
	Cephalexin O	3 (16.7)
	Doxycycline O	2 (11.1)
Severe	Cefaclor O	3 (100.0)

O = orally

4.1.7.5. Concern for Cross-Reactivity between Penicillin and Other β -Lactam Antibiotics

Patients with a penicillin allergy are more likely to have similar allergies to cephalosporins.¹²⁵ Although this cross-reactivity is relatively low, it often translates into empirically avoiding the use of cephalosporins in patients with β -lactam allergy.² Nevertheless, the current study suggests that this may not be true as patients were more likely to receive a cephalosporin if they were allergic to penicillin. Of the six patients who stated that they had not received a penicillin-related compound since their allergic reaction, two (33.3%) had also received a cephalosporin during the current hospitalisation without any adverse effects. From these data, it is reasonable to conclude that most of the prescribers are not concerned about potential cross-reactivity between penicillin and cephalosporins.

The extent of immunologic cross-reactivity between penicillin and cephalosporins that may lead to immediate allergic reactions is still not known.²⁷ Some authors have reported the incidence of allergic reactions in penicillin allergic patients who receive cephalosporins to be no higher than the incidence in the general population,^{117, 126, 127} whereas, other data suggests that penicillin-allergic patients may have a four to eight-fold increased risk of an immediate reaction to cephalosporins.¹²⁸⁻¹³⁰

4.1.7.6. Comments on Penicillin Skin Tests

Another interesting and surprising findings of the current study is that only one patient has ever had skin testing done to confirm the allergy. This supports the belief that prescribing an alternative antibiotic is more convenient than pursuing penicillin skin testing.

Penicillin skin testing can play an important and valuable role in decreasing the unnecessary use of broad-spectrum antibiotics in those patients labelled "penicillin allergic" and in turn, helping contain the spread of drug resistant bacteria. Hence, allergist would need to make primary care physicians aware of the option of penicillin skin testing, educate them when penicillin skin testing is clinically indicated and outline the risks, benefits and limitations of this type of testing, and therefore are denied access to these antibiotics needlessly.^{5, 27}

4.1.8. Treatment Outcomes (Discharge Status)

All of the 155 CAP patients entered into the study were discharged alive from the index hospitalisation. As shown in Table 4.13, there is no significant association between the presence of penicillin allergy and discharge disposition.

Table 4.13 Treatment outcomes

Discharge disposition	Group A (n=27)	Group B (n=128)	p value ^b
	n(%)		
Home	24 (88.9)	88 (68.8)	0.069
Returned to institution ^a	3 (11.1)	21 (16.4)	
Transferred to another hospital	0 (0)	19 (14.8)	

Group A = patients with a documented of penicillin allergy

Group B = patients without a documented of penicillin allergy

^a Institution was defined as nursing homes, hostels and retirement villages

^b Significance was determined using the χ^2 test

4.1.9. Costs Comparison of Intravenous Antibiotic Administration for Community-Acquired Pneumonia

The spreadsheet of acquisition, delivery and laboratory monitoring costs of antibiotic therapy for CAP is shown in Table 4.14.

Table 4.14 Costs of antibiotic therapy for community-acquired pneumonia

Antibiotic	Route	Average dose (mg)	Average doses per day	Acquisition cost per dose (A\$)	Delivery cost per dose (A\$)	Laboratory cost per dose (A\$)	Total cost per dose (A\$)	Total cost per day (A\$)
Penicillins								
• Amoxicillin	IV	1000	4	1.65	7.30	-	8.95	35.80
• Amoxicillin	O	1000	4	0.20	-	-	0.20	0.80
• Augmentin®	O	875/125	2	1.04	-	-	1.04	2.08
• Timentin®	IV	3100	4	10.50	14.00	-	24.50	98.08
Cephalosporins								
• Cephalothin	IV	1000	4	2.19	7.30	-	9.49	37.96
• Cephalixin	O	500	4	0.11	-	-	0.11	0.44
• Cefaclor	O	375	2	0.84	-	-	0.84	1.68
• Ceftriaxone	IV	2000	1	11.66	14.00	-	25.66	25.66
• Cefepime	IV	1000	2	15.40	14.00	-	29.40	58.80
Macrolides								
• Azithromycin	O	500	1	7.23	-	-	7.23	7.23
• Erythromycin	IV	500	4	5.16	14.00	-	19.16	76.64
• Erythromycin	O	250	4	0.09	-	-	0.09	0.36
Aminoglycoside								
• Gentamicin	IV	280	1	1.24*	12.70	18.00	31.94	31.94
Tetracycline								
• Doxycycline	O	100	2	0.08	-	-	0.08	0.16
Lincosamides								
• Clindamycin	IV	600	3	23.70	12.70	-	36.40	109.20
• Clindamycin	O	300	4	0.86	-	-	0.86	3.44

Nitroimidazoles	IV	500	2	2.08	7.64	-	9.72	19.44
• Metronidazole	O	400	3	0.06	-	-	0.06	0.18
• Metronidazole								
Quinolones								
• Ciprofloxacin	O	750	2	5.00	-	-	5.00	5.00
• Moxifloxacin	O	400	1	8.44	-	-	8.44	8.44

IV = intravenously; O = orally

Augmentin® = amoxicillin and potassium clavulanate

Timentin® = ticarcillin and potassium clavulanate

* Costing of 280 mg dose of gentamicin assumes that four 80 mg ampoules are used to obtain the dosage required. This is normal practice in SCGH and results in wastage of 40 mg of the fourth ampoule used

4.1.9.1. Acquisition Cost

From the above results can be seen that acquisition cost is often a poor predictor of the total daily cost of administering an antibiotic. This applies particularly to antibiotics with low acquisition costs. As Table 4.14 shows, the total daily cost of gentamicin therapy is 26 times the acquisition cost of each dose. This finding is similar to the Plumridge study²⁸ although gentamicin is provided in a 50 mL minibag and administered once a day in the current study.

4.1.9.2. Delivery Costs

The different delivery costs per dose relate to the four methods of preparation and administration as shown in Table 4.15.

Table 4.15 Methods of antibiotic administration

Methods	Drugs
<ul style="list-style-type: none"> • Slow intravenous injection over 3-5 minutes of an antibiotic reconstituted from powder form 	Amoxicillin, cephalothin
<ul style="list-style-type: none"> • Infusion administration of 50 mL or 100 mL of compatible solution containing an antibiotic reconstituted from powder form 	Timentin [®] , ceftriaxone, cefepime, erythromycin
<ul style="list-style-type: none"> • Infusion administration of an antibiotic supplied by the manufacturer in liquid form 	Gentamicin, clindamycin
<ul style="list-style-type: none"> • Antibiotics purchased from manufacturers as "preloaded" doses, that is, a sterile intravenous solution in a minibag 	Metronidazole

Timentin[®] = ticarcillin and potassium clavulanate

As presented in Table 4.14, the current study showed that frequency of administration had substantial influence on total costs. The delivery cost per dose varied between A\$ 7.30 and A\$ 14.00. Thus, a drug administered once daily was significantly less expensive to deliver than a drug

administered more frequently. Ceftriaxone, for instance, administered once a day, had a total cost per day to acquisition cost ratio of 1.8 compared with 17.3 for cephalothin administered four times a day. This differs from a previous study by Plumridge,²⁸ in which ceftriaxone had a total cost per day to acquisition cost ratio of 1.1 as the current acquisition cost of this drug is three times cheaper than ceftriaxone acquisition cost in 1990.

4.1.9.3. Laboratory Monitoring Costs

In the current study, gentamicin plasma concentration was measured 24 hours after administration of initial dose and then once or twice weekly in a clinically stable patient or daily if the clinical state (especially renal function) were unstable. These practices are consistent with the current TG:A¹ and Australian Medicines Handbook.¹³¹

The Laboratory monitoring costs can have a notable influence on the daily total cost. For example, the laboratory monitoring cost of A\$ 18.00 per assay applicable to gentamicin administered once a day is almost 15 times the acquisition cost of each dose and constitutes 56.4% of the total cost for gentamicin.

4.1.9.4. Comments on Antibiotic Costs

The current study highlights the need for SCGH and other hospitals to develop a global view of intravenous drug administration and acknowledge the interrelationships between departments. The cheapest drug is not always the least expensive to administer. Relatively expensive antibiotics, particularly those which are administered infrequently (e.g. daily), do not require laboratory monitoring and have a low side effect profile, can be effective therapeutic choices.

4.1.10. Cost of Treating Community-Acquired Pneumonia

The current study demonstrated that a history of penicillin allergy significantly ($p < 0.05$) increased the cost of antibiotic treatment and total cost of admission as shown in Table 4.16.

Table 4.16 Cost of antibiotic treatment and total cost of admission

	Severity of pneumonia	Ave AB cost (A\$) ± SD	Ave LOS (day) ± SD	Ave TCA * (A\$) ± SD
Group A	MM	194.37 ± 85.52	5.00 ± 2.98	3 961.49 ± 2 064.12
	Severe	1 118.08 ± 563.93	12.50 ± 5.80	10 662.84 ± 3 833.65
Group B	MM	164.89 ± 51.14	5.00 ± 2.24	3 916.97 ± 1 472.74
	Severe	467.96 ± 263.58	8.00 ± 2.13	6 853.75 ± 1 231.69
	Aspiration	181.58 ± 7.62	8.00 ± 2.33	6 181.58 ± 1 113.70

Group A = patients with a documented of penicillin allergy

Group B = patients without a documented of penicillin allergy

MM = mild to moderate; Ave = average

AB = antibiotic; LOS = length of stay; TCA = total cost of admission

** TCA = total antibiotic cost + accommodation cost (bed charge × LOS)*

p values were calculated using the t tests and they refer to comparisons between mild to moderate and severe CAP patients (Aspiration pneumonia patients were not included to the tests due to small sample size)

4.1.10.1. Drug Costs

As can be seen from the above table, on average, patients with a history of penicillin allergy were more likely to have greater antibiotic costs than those without a history of penicillin allergy ($p=0.008$). Furthermore, there is a significant association between the severity of pneumonia and the drug costs, with severe CAP patients more likely to have greater antibiotic costs than those with mild to moderate CAP patients ($p=0.000$).

4.1.10.2. Length of Stay

The length of each patient's stay is likewise incorporated in the cost evaluations in the current study. According to the Health Department in Western Australia, the hospital running cost in this state is A\$ 750.0 per bed day.

As presented in the table below, the average hospital LOS for mild to moderate CAP patients with and without a history of penicillin allergy was

5.0 days, with an average cost of A\$ 3 750. On the other hand, it shows that there is a significant association between the average hospital LOS for severe CAP patients with and without a history of penicillin allergy ($p=0.012$).

Table 4.17 Length of stay of patients with community-acquired pneumonia

	Severity of pneumonia	Number of patients (%)	Median LOS (days) \pm SD
Group A	Mild to moderate	23 (85.2)	5.0 \pm 2.98
	Severe	4 (14.8)	12.5 \pm 5.80
Group B	Mild to moderate	110 (85.9)	5.0 \pm 2.24
	Severe	16 (12.5)	8.0 \pm 2.13
	Aspiration	2 (1.6)	8.0 \pm 2.33

Group A = patients with a documented of penicillin allergy

Group B = patients without a documented of penicillin allergy

LOS = length of stay

** Median is presented in the table because the data is not normally distributed*

Further analysis shows that there is no significant interaction between the presence of penicillin allergy and the severity of pneumonia in terms of hospital LOS. Since age and other co-morbidities may be a contributing factor to LOS in hospital, they were initially included in the two-way ANOVA. However, they were not significant and so they have been removed. On average, severe CAP patients stayed longer in the hospital compared to mild to moderate CAP patients (12.5 vs 5.0 days for patients with documented penicillin allergy, respectively; 8.0 vs 5.0 days for patients without documented penicillin allergy, respectively).

4.1.10.3. Total Cost of Admission

The current study indicates that there is no significant interaction between the presence of penicillin allergy and the severity of pneumonia in terms of total cost of admission. Since LOS was thought to be a contributing factor to the total cost of admission, it was initially included in the analysis. Yet, it did not meet the assumptions of the test and so it has been removed. The presence of penicillin allergy and the severity of pneumonia individually

were significant predictors of the total cost of admission. As presented in Table 4.16, on average, patients with a history of penicillin allergy and severe CAP had a greater total cost of admission compared to the other group ($p=0.000$).

4.1.10.4. Laboratory Tests Cost

Since laboratory tests are performed routinely for most patients requiring antibiotics intravenously, the cost of these tests was not included in this current study. However, the number of laboratory tests performed was recorded in the study, and it is presented in Table 4.18.

Table 4.18 Number of laboratory tests performed in patients with community-acquired pneumonia

	Severity of pneumonia	Number of patients (%)	Median number of laboratory tests \pm SD
Group A	Mild to moderate	23 (85.2)	2.0 \pm 1.28
	Severe	4 (14.8)	5.0 \pm 2.20
Group B	Mild to moderate	110 (85.9)	2.0 \pm 1.23
	Severe	16 (12.5)	3.0 \pm 1.50
	Aspiration	2 (1.6)	2.5 \pm 0.61

Group A = patients with a documented of penicillin allergy

Group B = patients without a documented of penicillin allergy

** Median is presented in the table because the data is not normally distributed*

Table 4.19 Factors associated with number of laboratory tests performed

Factor	p value *
Penicillin allergy	0.104
Severity of pneumonia	0.004
Length of stay	0.000

** Significance was determined using the two-way ANOVA (Aspiration pneumonia patients were not included in the test due to small sample size)*

The above findings indicate that there is no significant interaction between the presence of penicillin allergy and the severity of pneumonia in terms of the number of biochemistry tests performed. After controlling for different LOS, the severity of pneumonia is a significant predictor of the number of laboratory tests performed, but the presence of penicillin allergy is not (Table 4.19). Higher number of laboratory tests on average for those with severe CAP compared to those with mild to moderate CAP (Table 4.18).

4.1.11. Opportunity of Cost Avoidance

Identification of patients with intolerance or Severity II may provide the opportunity for costs savings by avoiding the use of more expensive agents (Table 4.20).

Table 4.20 Opportunity of Cost Avoidance

COA	Severity of pneumonia	DCS / 15 weeks	TCS / 15 weeks	DCS / year	TCS / year
Severity II	Mild to moderate	353.76	534.24	1 226.37	1 852.03
	Severe	7 801.44	45 709.08	27 044.99	158 458.14
Intolerance	Mild to moderate	88.44	133.56	306.59	463.01
	Severe	1 950.36	11 427.27	6 761.25	39 614.54

COA = classification of allergy

DCS = drug cost saving (A\$); TCS = total cost saving (A\$)

As can be seen from the above table, identifying patients with intolerance rather than allergies would reduce the total inpatient costs at SCGH by A\$ 463.01 a year for mild to moderate CAP patients and A\$ 39 614.54 a year for severe CAP patients.

4.2. Part Two (Penicillin Allergy without Community-Acquired Pneumonia)

4.2.1. Patient Demographics

4.2.1.1. Number of Patients Recruited

During the 5-week study period, 1 664 adults patients were admitted without a clinical diagnosis of CAP. Of these, 229 (13.8%) were labelled as penicillin allergic in either their medical records or on drug charts. Since 62 patients (27.1%) had communication difficulties (mental/physical disabilities) and 27 (11.8%) did not speak English, they were deemed ineligible for the study. Hence, in total of 140 patients (61.1%) were entered into the study after giving written informed consent.

Although the prevalence rate for documented penicillin-allergic patients of 13.8% in the current study is at least 30% greater than published rates for penicillin allergy,¹³² this figure is still lower than reported amongst CAP patients enrolled into the study (17.4%).

4.2.1.2. Gender and Age of Patients

The current study indicates that there is no significant difference ($p>0.05$) between the number of males ($n=63$) and females ($n=77$) who reported to be allergic to penicillin (Table 4.21). This is consistent with the number of females admitted during the study period (956, 57.5%).

The age of the patients included in the study ranged from 44 to 78 years (mean: 61 years), with approximately 50% (73/140) of these were elderly (Table 4.21).

Table 4.21 Demographics of 140 adult patients with documented penicillin allergy

Characteristic	Value
Male, No. (%)	63 (45.0)
Female, No. (%)	77 (55.0)
Age, mean (\pm SD)	61 \pm 17

4.2.2. Accuracy of Penicillin Allergy Reporting

4.2.2.1. Documentation of Penicillin Allergy

In the current study, the penicillin allergy was documented in the patient's medical record and on drug chart in 130 (92.9%) and 125 (89.3%) cases, respectively. These levels of documentation were not as high as reported in the current study with CAP patients, but still higher than others.^{20, 133}

Drug Alert stickers were attached in 82.1% (115/140) of cases to the front cover of drug charts and 68.6% (96/140) to the drug charts' inside cover. These figures are slightly lower than reported in the present study involving CAP patients, nonetheless, they are much higher than reported by Geibig *et al*,¹³³ in which allergy documentation on the front of patient charts (required by policy at their institution) was performed only 15% to 40% of the time.

The current study involving CAP patients and three other previous studies^{9, 20, 111} found that the standard of documentation for the nature and timing of the adverse reaction were poor. The current study patients without CAP also found a poor result in these areas with less than one-third (28.6%) of either medical records or drug charts having the type of reaction and only 3.6% having the date of reaction documented.

These results indicate that there is significant room for improvement in the description of the penicillin allergy in the medical record and on drug chart. Incomplete documentation can significantly affect patient care and potentially lead to some patients being mislabelled as penicillin allergic because it is difficult to assess the clinical significance of their allergy.

4.2.2.2. Characteristics of Penicillin Allergies Reported

Of the 140 patients entered into the study, only 134 patients (95.7%) were feasible to be interviewed any further as the remaining six patients (4.3%) were not aware of their penicillin allergy. Thus, the results of the patient interviews were based on 134 patients and are listed in Table 4.22.

Table 4.22 Responses to interviews with patients documented penicillin allergy

Question and Response	No. (%)
Aware of allergy?	
Yes	134 (95.7)
No	6 (4.3) ^a
Penicillin causing allergy?	
Amoxicillin	22 (16.4)
Augmentin [®] (amoxicillin and potassium clavulanate)	14 (10.5)
Flucloxacillin	2 (1.5)
Ampicillin	1 (0.7)
Do not remember	95 (70.9)
First occurrence of penicillin allergy? (no. yr ago)	
0-5	25 (18.7)
6-10	20 (14.9)
11-20	25 (18.7)
21-30	12 (8.9)
>30	52 (38.8)
Route of administration when reaction occurred?	
Oral	66 (49.3)
Injection	63 (47.0)
Do not remember	5 (3.7)
Onset of allergy?	
Immediately (within few minutes)	25 (18.7)
≤72 hours	64 (47.8)
>72 hours	28 (20.9)
Do not remember	17 (12.6)
Treatment of allergy?	
Penicillin was ceased	76 (56.7)
Penicillin was ceased and adrenaline	2 (1.5)
Penicillin was ceased and hydrocortisone	2 (1.5)
Penicillin was ceased and unknown drugs given	50 (37.3)
Do not remember	4 (3.0)
Patient told of allergy by whom?	
Doctor	96 (71.6)
Nurse	6 (4.6)
Parents	9 (6.7)
Self ^b	20 (14.9)
Other ^c	3 (2.2)
Told not to receive drug again?	
Yes	90 (67.2)
No	42 (31.3)

Do not remember	2 (1.5)
Told not to receive related compounds again?	
Yes	16 (11.9)
No	116 (86.6)
Do not remember	2 (1.5)
Subsequently received a penicillin again?	
Yes, and a reaction occurred	14 (10.5)
Yes, and no reaction occurred	9 (6.7)
Yes, but do not remember what happened	1 (0.7)
No	109 (81.4)
Do not remember	1 (0.7)
Subsequently received a related compound again?	
Yes, and a reaction occurred	10 (7.5)
Yes, and no reaction occurred	56 (41.8)
Yes, but do not remember what happened	2 (1.5)
No	43 (32.0)
Do not remember	23 (17.2)
Was skin testing ever done?	
Yes	8 (6.0) ^a
No	125 (93.3)
Do not remember	1 (0.7)

^a These patients were not interviewed any further

^b Patient self-diagnosed the allergy

^c Pharmacist, friend

^d Results were unknown

4.2.2.2.1. Penicillin Causing Allergy and First Occurrence of Penicillin Allergy

The current study demonstrated that around 30% of the interviewed patients could remember what type of penicillin they were allergic to – 16.4% (22/134) were allergic to amoxicillin, 10.5% (14/134) were allergic to Augmentin[®], 1.5% (2/134) were allergic to flucloxacillin and 0.7% (1/134) were allergic to ampicillin. This is inconsistent with the findings of the current study with CAP patients, in which approximately 60% of the patients with documented penicillin allergy could recall the penicillin causing their allergy.

The mean period since the patients' first penicillin allergic reaction was 33 years (range: 0 to 70 years ago) – 47.8% (64/134) of patients had their first penicillin allergic reaction more than 20 years ago (Table 4.23). One patient claimed to have the allergic reaction 70 years ago (four years prior Fleming's discovery).⁴ Another patient experienced the reaction 65 years ago (still well before clinical trials with penicillin commenced).^{4, 112} Three patients (2.2%) reported that they have the allergic reaction to Augmentin[®] more than 20 years ago and this cannot be true because this agent was released onto the market in 1990s.¹¹²

Different from the findings reported in CAP patients (Section 4.1.2.2.1), the current study found that there was a significant association between the first occurrence of penicillin allergy and penicillin causing allergy ($p=0.000$), with patients who did not remember the type of penicillin involved more likely to suffer the reaction more than 30 years ago (Table 4.23).

Table 4.23 Association between penicillin causing allergy and time since allergic reaction

Penicillin causing Allergy	First occurrence of penicillin allergy (no. yr ago)					p value *
	0-5 (n=25)	6-10 (n=20)	11-20 (n=25)	21-30 (n=12)	>30 (n=52)	
	n (%)					
Amoxicillin	5 (20.0)	7 (35.0)	6 (24.0)	1 (8.3)	3 (5.8)	0.000
Augmentin [®]	8 (32.0)	3 (15.0)	0 (0)	2 (16.7)	1 (1.9)	
Ampicillin	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	
Flucloxacilli	2 (8.0)	0 (0)	0 (0)	0 (0)	0 (0)	
n						
Do not remember	10 (40.0)	10 (50.0)	19 (76.0)	8 (66.7)	48 (92.3)	

* Significance was determined using the χ^2 test (Amoxicillin, Augmentin[®] (amoxicillin and potassium clavulanate), ampicillin and flucloxacillin were combined to meet the assumptions of the test)

The above data indicated that many patients had understandable difficulty in remembering the facts of their penicillin allergy. The poor recall of some patients was exemplified by those who were convinced that they had had penicillin prior to its availability. This was contradicted by the patients'

precise recollections of the route of administration and time to onset of symptoms. The old age of the patients and the long interval since exposure may account for some of these inconsistencies. Since approximately 40% of the patients suffered their first reaction to penicillin at least 31 years ago, the interval since exposure as well as influencing the patient's recall may also have influenced the patient's penicillin-allergy status, as it is known that sensitisation may be temporary.^{117, 134, 135}

4.2.2.2.2. Route of Administration

Similar to the findings of the current study with CAP patients, this study also found that the majority of the patients could remember how the penicillin was administered when the reaction occurred – 49% of the reactions occurred following oral administration, 47% following parenteral administration and the remaining 4% followed administration by an unknown route.

4.2.2.2.3. Onset of Allergy

Consistent with the results reported in CAP patients (Section 4.1.2.2.3) and of a previous report,²⁰ the current study also found that about 66% (89/134) patients experienced symptoms of their allergy within 72 hours of the drug being administered, with 18.7% (25/134) experiencing symptoms instantaneously (within few minutes).

4.2.2.2.4. Reported Symptoms

The mean (\pm SD) number of symptoms reported by patients during the interview was 3.5 ± 1.8 (range: 1-6). Similar to the current study with CAP patients and a previous findings by Preston *et al*,⁹ rash was the most common symptom of penicillin allergic reactions, followed by itch and swelling (Table 4.24).

Table 4.24 Principal symptom of penicillin allergy

Symptom *	No. (%)
Rash	76 (56.7)
Itch	59 (44.0)
Swelling	49 (36.6)
Nausea	15 (11.2)
Feeling sick	15 (11.2)
Vomiting	14 (10.4)
Difficulty breathing	11 (8.2)
Loss of consciousness	5 (3.7)
Diarrhoea	5 (3.7)
Abdominal pain	4 (3.0)
Anaphylaxis	4 (3.0)
Headache	2 (1.5)
Seizures	2 (1.5)
Rapid heartbeat	1 (0.7)
Confusion	1 (0.7)
Difficulty swallowing	1 (0.7)
Stomach cramps	1 (0.7)

* Patient could have more than one symptom

4.2.2.2.5. Classification of Penicillin Allergy

Of the 140 patients assessed, 108 (77.1%) were classified as allergic: 61 (56.5%) as Severity I and 47 (43.5%) as Severity II, 26 (18.6%) as intolerant and the remaining six (4.3%) as not substantiated because of the following reasons: four (66.6%) could not recall the incident of the allergic reaction and the corresponding symptoms, one (16.7%) denied the allergy and another one (16.7%) reported no penicillin allergy at the time of the interviews. Interestingly, the number of patients classified as intolerant in the study were nearly two times higher than a number of patients quoted as 'intolerant' in the current study involving CAP patients and other previous reports.^{9, 10, 71}

Similar to the results reported in CAP patients (Section 4.1.2.2.5), this present study also indicated that most of the interviewed patients were correctly documented as penicillin-allergic according to the study's criteria. Surprisingly, several patients with Severe II penicillin allergy asked for being rechallenged, while some of the patients admitted that they knew that

they were not 'truly' allergic to penicillin, but still did not want to be rechallenged.

4.2.2.2.6. Diagnosis of Penicillin Allergy

As shown in Table 4.22, around 70% of the interviewed patients were told of their penicillin allergy by doctors and pharmacists. Nonetheless, consistent with the current study involving CAP patients and a previous report,⁹ 14.9% (20/134) had deemed themselves to be allergic to penicillin. Seven of these (35.0%) were classified as allergic according to the study's criteria, whilst the remaining 13 patients (65.0%) were classified as intolerant. Hence, clinicians should not simply accept the diagnosis of the allergy without obtaining a detailed history of the reaction.

4.2.2.2.7. Incidence of Reactions to Multiple Drug Allergies

The current study showed that 39 patients (29.1%) reported multiple drug allergies, with the mean (\pm SD) number of allergies reported per patient being 1.5 ± 1.1 (range: 1-5). Of these, 14 (35.9%) reportedly penicillin-allergic patients also reported an allergy to a related compound – all of these were allergic to cephalosporins. This figure is much higher than reported with CAP patients (Section 4.1.2.2.7) in the current study as well as a study by Sullivan *et al.*⁶⁰

Surprisingly, the current study recorded that of those patients, 30 (76.9%) were able to recite all the drugs they were listed as allergic to in either their medical records or on drug charts.

4.2.2.2.8. Advice for not Receiving Penicillin or Related Compounds in the Future

Of the 42 patients who reported that they were not told to avoid taking penicillin, 27 (64.3%) were classified as allergic and 15 (35.7%) as intolerant. On the contrary, of the 90 patients who reported that they were advised to avoid taking penicillin, 84 (93.3%) were classified as allergic and six (6.7%) as intolerant. This could be because of the past practice of 'defensive medicine' whereby an adverse effect was assumed to be drug-

related and in many cases patients were told that they should never receive that medication again.^{20, 21}

Another surprising and interesting findings of this study is that 86.6% (116/134) of the interviewed patients were advised not to receive the related compounds in the future although some of them claimed to be allergic to cephalosporins.

4.2.2.2.9. Rechallenge with Penicillin Antibiotic

As presented in Table 4.22, 17.9% of the interviewed patients (24/134) reported that they had been subsequently received a penicillin again after the first reaction. Of these, nine patients (37.5%), who had suffered Severe I penicillin reaction more than 20 years ago, stated that the second reaction was the same as the first reaction (swelling, rash and itch), five (20.8%) reported that the second reaction was even worse than the first reaction, nine (37.5%) did not experience any adverse effects in the second reaction and one (4.2%) did not remember what happened. Another interesting and surprising findings is that one patient claimed that he only got rash and itch in the first reaction, but he experienced a life threatening reaction (difficulty in breathing and rapid heartbeat) in the second exposure.

4.2.2.2.10. Rechallenge with Other β -Lactam Antibiotics

In the study, approximately 50% (68/134) of the penicillin-allergic patients reported that they had been rechallenged with a penicillin related compound – five (7.4%) claimed that they suffered severe reactions (e.g urticaria) when cephalosporins were administered, another five (7.4%) experienced rash, itch and GI upset when cephalosporins were administered, 56 (82.3%) had no reactions occurred when they received other β -lactam antibiotics, and the remaining two (2.9%) did not remember what happened when they were rechallenged with a penicillin related compound. These findings are inconsistent with other previous studies,^{14, 136} of which they suggested that the rate of reaction among patients with a history of penicillin allergy that subsequently received cephalosporin antibiotics was around 7% to 8%.

4.2.2.2.11. Penicillin Skin Tests

The study found that 6.0% (8/34) of the interviewed patients had skin testing done for their penicillin allergy in the UK. The results of the tests were unknown. In patients with a more definite and or serious allergic reaction, penicillin skin tests, as previously discussed, are useful in determining which patients are truly at risk of a serious reaction and which patients should or should not be rechallenged with a penicillin or other related compounds.^{19, 20}

4.2.2.3. Comments on Penicillin Allergy Reporting

The findings of the current study illustrated that many patients at SCGH had long-standing, often incomplete and sometimes vague penicillin allergy histories. Inadequate detail of reported reactions in the medical record or on the drug chart often made it difficult to assess their clinical significance. The clinical pharmacists, therefore, should help to ensure that accurate and consistent penicillin allergy documentation is provided by educating healthcare professionals about its importance. Moreover, they should also educate patients about allergy signs and symptoms, definition of a related compound, and perhaps the chance of cross-reaction so that the patient understands that he or she is allergic to a medication and realises the possible ramifications of taking the medication. By improving the standard of penicillin allergy documentation, it is hoped that physicians will be provided with a frame-work for a more meaningful interpretation of the penicillin allergy label.

4.2.3. Influence of Penicillin Allergy on Other Drug Allergies

The current study shows that there is no significant association between the classification of penicillin allergy and the presence of other β -lactam allergies. In contrast, there is a significant association between the classification of penicillin allergy and the presence of other drug allergies, with patients having Severe I penicillin allergy more likely to have other drug allergies (Table 4.25).

Table 4.25 Association between penicillin allergy, other β -lactam allergies and other drug allergies

Characteristic	Classification of penicillin allergy				p value*
	Severity I (n=61)	Severity II (n=47)	Intolerance (n=26)	NS (n=6)	
Other β -lactam allergies	12 (19.7)	1 (2.1)	1 (3.8)	0 (0)	0.220 ^a
Other drug allergies	26 (42.6)	9 (19.1)	3 (11.5)	1 (16.7)	0.007 ^b

NS = not substantiated

* Significance was determined using the χ^2 test

^a Severity I was combined with Severity II and intolerance was combined with not substantiated, respectively to meet the assumptions of the test

^b Intolerance and not substantiated were combined to meet the assumptions of the test

4.3. Part Three (Combined Data of Patients with Penicillin Allergy)

4.3.1. Penicillin Causing Allergy and Time Since Allergic Reaction

As shown in Table 4.26, the combined data demonstrates that there is a significant association between the first occurrence of penicillin allergy and penicillin causing allergy, with patients who did not remember the type of penicillin involved more likely to suffer the reaction more than 30 years ago. This finding is consistent with the current study patients without CAP, but is inconsistent with the results found in Part One of the present study.

Table 4.26 Association between type of penicillin involved and time since allergy reaction

Penicillin causing allergy	First occurrence of penicillin allergy (no. yr ago)					p value *
	0-5 (n=29)	6-10 (n=21)	11-20 (n=33)	21-30 (n=14)	>30 (n=64)	
	n (%)					
Amoxycillin	8 (27.6)	8 (38.1)	9 (27.3)	1 (7.1)	10 (15.6)	0.000
Augmentin®	9 (31.0)	3 (14.3)	1 (3.0)	2 (14.3)	1 (1.6)	
Ampicillin	0 (0)	0 (0)	0 (0)	1 (7.1)	0 (0)	
Flucloxacilli	2 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)	
n						
Do not remember	10 (34.5)	10 (47.6)	23 (69.7)	10 (71.4)	53 (82.8)	

* Significance was determined using the χ^2 test (Amoxycillin, Augmentin® (amoxicillin and potassium clavulanate), ampicillin and flucloxacillin were combined to meet the assumptions of the test)

As previously discuss, it is possible that some of the patients who had their initial exposure more than 30 years ago more likely to be allergic to ampicillin rather than amoxycillin since this drug was released onto the market in 1970s and it was commonly used 30 years ago.¹¹² On the other hand, it cannot be true to find that the three patients claimed to have allergic reaction to Augmentin® more than 20 years ago as this agent was released on the market in 1990s.

4.3.2. Influence of Penicillin Allergy Classification on Other Drug Allergies

Different from the findings reported in Section 4.2.3 above, the combined data, which is presented in Table 4.27, shows that there is a significant association between the classification of penicillin allergy and the presence of other β -lactam allergies, with patients having Severe I penicillin allergy more likely to have other β -lactam allergies.

In contrast, consistent with the results of the current study patients without CAP, the combined data illustrates that there is a significant association between the classification of penicillin allergy and the presence

of other drug allergies, with patients having severe I penicillin allergy more likely to have other drug allergies (Table 4.27).

Table 4.27 Association between classification of penicillin allergy and the present of other drug allergies

Characteristic	Classification of penicillin allergy				p value*
	Severity I (n=73)	Severity II (n=59)	Intolerance (n=29)	NS (n=6)	
Other β -lactam allergies	16 (21.9)	1 (1.7)	2 (6.9)	0 (0)	0.001 ^a
Other drug allergies	34 (46.6)	13 (22.0)	5 (17.2)	1 (16.7)	0.004 ^b

* Significance was determined using the χ^2 test (Intolerance and not substantiated were combined to meet the assumptions of the test)

^a Severity I was combined with Severity II and intolerance was combined with not substantiated, respectively to meet the assumptions of the test

^b Intolerance and not substantiated were combined to meet the assumptions of the test

4.3.3. Chance of Cost Avoidance

Based on the combined figures, identifying patients with intolerance rather than allergies would reduce the inpatient costs at SCGH by a total of A\$ 4 475.74 a year for mild to moderate CAP patients and A\$ 382 940.51 a year for severe CAP patients (Table 4.28).

Table 4.28 Chance of Cost Avoidance

COA	Severity of pneumonia	DCS / year	TCS / year
Severity II	Mild to moderate	6 029.64	9 105.82
	Severe	132 971.21	779 085.87
Intolerance	Mild to moderate	2 963.72	4 475.74
	Severe	65 358.73	382 940.51
Not substantiated	Mild to moderate	613.18	926.02
	Severe	13 522.50	79 229.07

COA = *classification of allergy*

DCS = *drug cost saving (A\$); TCS = total cost saving (A\$)*

4.4. Study Limitations

The current study has several potential limitations that are important to acknowledge. First, in this observational study, patients were not randomised to treatment regimen, leading to potential selection biases in the use of antimicrobial agents. Second, certain components of antimicrobial therapy costs were not taken into account. For example, the cost of biochemical tests performed and costs associated with adverse drug events were not measured in this study. Nonetheless, it is unlikely that these costs would alter substantially the observed pattern of results. Third, the sample size of the patients with a history of penicillin allergy in Part One of this study was small due to limited time of the study period. However, because Part Two of this study was conducted, the present study could adequately characterise the pattern of penicillin allergies of patients admitted to the hospital. Fourth, this study was undertaken at an Australian teaching hospital and may not be generalisable to all patients with CAP. We acknowledge the limitations of this study, yet, the large study sample size, the “real world” nature of the evaluation and the consistencies in outcomes with those of other evaluations are noteworthy.

5. Conclusions

Penicillin allergy is common among hospitalised patients. At SCGH, the overall incidence of penicillin allergy was 15.6%, which exceeds population averages. Most, but not all, patients labelled as penicillin allergic had a history consistent with an allergy to the drug. However, a detailed description of the allergy reactions was poorly documented in both medical records and on drug charts. Further, in a few cases, penicillin allergy documented in the patient's medical record was not documented in the patient's medication chart. Therefore, accurate and consistent allergy documentation at SCGH could be improved.

These findings, in combination with the failure to fully characterise penicillin allergies, appear to lead to the unnecessary avoidance of penicillin antibiotics and the use of broader spectrum antimicrobial agents, which do not fit the TG:A and are associated with greater costs. These modified practices may adversely impact the ability to manage emerging antimicrobial resistance.

On average, CAP patients with documented penicillin allergy were more likely to have greater antibiotic costs than those without a history of penicillin allergy. Moreover, there is a significant association between the severity of CAP and the drug costs, with severe CAP patients more likely to receive more expensive antibiotic costs than those with mild to moderate CAP patients (A\$ 1 118.08 vs A\$ 194.37 for patients with documented penicillin allergy, respectively, $p=0.000$; A\$ 467.96 vs A\$ 164.89 for patients without reported penicillin allergy, respectively, $p=0.000$). Further, severe CAP patients with labelled penicillin allergy had a greater total cost of admission compared to the other group (A\$ 10 662.84 vs A\$ 6 853.75, respectively; $p=0.000$).

Identifying patients with intolerance rather than allergies presents a significant opportunity to reduce the inpatient costs at SCGH by a total of A\$ 463.01 a year for mild to moderate CAP patients and A\$ 39 614.54 a year for severe CAP patients.

Further studies are warranted to determine the economic feasibility of confirming hypersensitivity by skin testing patients with a reported penicillin allergy. Until such studies are available, documenting an accurate medication history is of paramount importance.

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Appendices

Appendix 1: Ethics Approval from Curtin University of Technology

MINUTE

Curtin
UNIVERSITY OF TECHNOLOGY

To	Lyna Irawati, Pharmacy
From	Max Page, Executive Officer, Human Research Ethics Committee
Subject	Protocol Approval HR 46/2002
Date	31 May, 2002
Copy	Jeff Hughes and Neil Keen, Pharmacy Graduate Studies Officer, Division of Health Sciences

Office of Research and Development

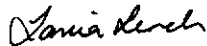
Human Research Ethics Committee

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL t.lerch@curtin.edu.au

Thank you for providing a copy of the ethics approval from Sir Charles Gairdner Hospital for the project "INFLUENCE OF PENICILLIN ALLERGY ON ANTIBIOTIC PRESCRIBING PATTERNS AND COSTS".

The information you have provided has satisfactorily addressed the points raised by the Committee, and final approval is granted.

Approval of this project remains for the period of twelve months **06/Mar/2002 to 05/Mar/2003**. The approval number for your project is **HR 46/2002**. *Please quote this number in any future correspondence.*



PP Maxwell Page
Executive Officer
Human Research Ethics Committee

J:\OR\HREC\REG99\HR 46/2002

Appendix 2: Ethics Approval from Sir Charles Gairdner Hospital

Note: For copyright reasons Appendix 2 has not been reproduced.

(Co-ordinator, ADT Program (Bibliographic Services), Curtin University of Technology, 4/12/2003)

Appendix 3: Patient Information Sheet for Control Patient



PATIENT INFORMATION (for Control Patient)

20th May 2002

Influence of Penicillin Allergy on Antibiotic Prescribing Patterns and Costs

You are being invited to take part in a research study. Before you make your decision, it is important for you to understand why the research is being done and what it would involve. Please take as much time as you need to read the following information carefully and discuss it with friends, relatives and your doctor if you wish. Ask us if there is anything that is not clear or if you would like more information.

The aim of this study is to assess the impact of documented penicillin allergy on the choice of antibiotics and the clinical and financial consequences of changes in prescribing patterns.

You have been invited to participate in this study because you are aged 18 years or over and have been admitted for treatment of community-acquired pneumonia to Sir Charles Gairdner Hospital, Western Australia between June 2002 and September 2002.

It is your decision whether or not to take part. If you decide to take part, you can still withdraw at any time, without giving a reason. If you decide not to participate, or decide later to withdraw, it will not affect the standard of further care you would receive. If you do decide to take part, you will be asked to sign a consent form. You will be given this information sheet to keep and you will receive a copy of your signed consent form.

You do not need to do anything in the study. However, we will collect the following data from your medical records and drug charts: your demographics (age, gender, weight), history of your drug allergies or adverse drug reactions, history of your presenting complaint, clinical diagnosis on admission, past medical history, social history, relevant biochemical tests, chest X-ray findings, antibiotics prescribed – [drug(s), dosage and duration], therapeutic drug monitoring, discharge antibiotic, treatment outcomes and length of hospital stay.

Your participation in this study will assist in developing better guidelines for the selection of antibiotics in patients with and without penicillin allergies.

This study is a non-interventional study, and hence poses no additional hazards to you.

The study records will be kept in the School of Pharmacy during the study and in a locked archive for five years from the time the study is closed, and will be destroyed at that time. Only the investigators of the study will be able to see your records. Personal data, which may be sensitive, (e.g. name, date of birth) will be collected and processed but only for research purposes in connection with this study. All the data will be de-identified with no reference on the completion of data collection.

This study will be carried out in a manner to the principles set out by the "National Statement on Ethics in Research Involving Humans". Both the Curtin University of Technology and Sir Charles Gairdner Hospital Human Research Ethics Committee have reviewed and approved the study.

If you have any questions or concerns now or at any time about the study, should you contact us on the numbers listed below:

Chief investigator: Dr Clay Golledge Phone: 9346 3625

Co-investigators:

- Mr Jeff Hughes, MPharm Phone: 9266 7367
- Mr Neil Keen, BPharm Phone: 9346 2333
- Ms Lyna Irawati Phone: 9450 8721

If you want to discuss the study with someone who is not directly involved in this study (for example, about the information you have received, the conduct of the study or your rights as a participant, or a complaint you have), you can contact either the Curtin University Human Research Ethics Committee Secretariat on 9266 2784 or the Sir Charles Gairdner Hospital Human Research Ethics Committee Secretariat on 9346 2999.

Appendix 4: Patient Information Sheet for Target Patient



PATIENT INFORMATION (for Target Patient)

20th May 2002

Influence of Penicillin Allergy on Antibiotic Prescribing Patterns and Costs

You are being invited to take part in a research study. Before you make your decision, it is important for you to understand why the research is being done and what it would involve. Please take as much time as you need to read the following information carefully and discuss it with friends, relatives and your doctor if you wish. Ask us if there is anything that is not clear or if you would like more information.

The aim of this study is to assess the impact of documented penicillin allergy on the choice of antibiotics and the clinical and financial consequences of changes in prescribing patterns.

You have been invited to participate in this study because you are aged 18 years or over, with a history of antibiotic allergy and have been admitted for treatment of community-acquired pneumonia to Sir Charles Gairdner Hospital, Western Australia between June 2002 and September 2002.

It is your decision whether or not to take part. If you decide to take part, you can still withdraw at any time, without giving a reason. If you decide not to participate, or decide later to withdraw, it will not affect the standard of further care you would receive. If you do decide to take part, you will be asked to sign a consent form. You will be given this information sheet to keep and you will receive a copy of your signed consent form.

You will be interviewed using a structured questionnaire to obtain detailed information on the nature and severity of your antibiotic allergy. This interview will take approximately five minutes of your time.

A possible benefit of participating in the study is a more accurate classification of your antibiotic allergy. This will assist prescribers in the future in their drug selection.

This study is a non-interventional study, and hence poses no additional hazards to you.

The study records will be kept in the School of Pharmacy during the study and in a locked archive for five years from the time the study is closed, and will be destroyed at that time. Only the investigators of the study will be able to see your records. Personal data, which may be sensitive, (e.g. name, date of birth) will be collected and processed but only for research purposes in connection with this study. All the data will be de-identified with no reference on the completion of data collection.

This study will be carried out in a manner to the principles set out by the "National Statement on Ethics in Research Involving Humans". Both the Curtin University of Technology and Sir Charles Gairdner Hospital Human Research Ethics Committee have reviewed and approved the study.

Appendix 5: Consent Form for Control Patient



CONSENT FORM (for Control Patient)

Project Title: Influence of Penicillin Allergy on Antibiotic Prescribing Patterns and Costs

Investigators:

- Dr Clay Gollidge, Consultant Clinical Microbiology and Infectious Disease, Sir Charles Gairdner Hospital
- Mr Jeff Hughes, MPharm, Senior Lecturer, School of Pharmacy, Curtin University of Technology
- Mr Neil Keen, BPharm, Senior Pharmacist, Sir Charles Gairdner Hospital
- Ms Lyna Irawati, Master of Pharmacy Student, Curtin University of Technology

Subject Name: _____

Date of Birth: _____

I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.

I have been told about the possible advantages and risks of taking part in the study and I give consent for my medical records and drug charts being made available to the researchers of this project.

I have been able to have a member of my family or a friend with me while I was told about the study.

I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation which I may have under statute or common law.

I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

Name of Patient

Signature of Patient

Date

Name of Witness to Patient Signature

Witness of Signature

Date

Name of Investigator

Signature of Investigator

Date

Both the Curtin University of Technology and Sir Charles Gairdner Hospital Human Research Ethics Committee have given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study, you can contact either the Secretary of the Curtin University of Technology Human Research Ethics Committee on 9266 2784 or the Secretary of Sir Charles Gairdner Hospital Human Research Ethics Committee on 9346 2999.

Appendix 6: Consent Form for Target Patient



CONSENT FORM (for Target Patient)

Project Title: Influence of Penicillin Allergy on Antibiotic Prescribing Patterns and Costs

Investigators:

- Dr Clay Golledge, Consultant Clinical Microbiology and Infectious Disease, Sir Charles Gairdner Hospital
- Mr Jeff Hughes, MPharm, Senior Lecturer, School of Pharmacy, Curtin University of Technology
- Mr Neil Keen, BPharm, Senior Pharmacist, Sir Charles Gairdner Hospital
- Ms Lyna Irawati, Master of Pharmacy Student, Curtin University of Technology

Subject Name: _____

Date of Birth: _____

I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.

I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked for.

I have been able to have a member of my family or a friend with me while I was told about the study.

I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation which I may have under statute or common law.

I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

Name of Patient

Signature of Patient

Date

Name of Witness to Patient Signature

Witness of Signature

Date

Name of Investigator

Signature of Investigator

Date

Both the Curtin University of Technology and Sir Charles Gairdner Hospital Human Research Ethics Committee have given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study, you can contact either the Secretary of the Curtin University of Technology Human Research Ethics Committee on 9266 2784 or the Secretary of Sir Charles Gairdner Hospital Human Research Ethics Committee on 9346 2999.

Appendix 7: Data Collection Form



Data Collection Form

Patient Addressograph:

Ward:

Date of Birth:

<input type="text"/>	Age: <input type="text"/> years old
----------------------	-------------------------------------

Gender:

Male / Female

Weight:

Ethnicity:

Date of Admission:

Date of Discharge:

Length of Hospital Stay:

Presence of Penicillin Allergy:

Yes / No

Type of Penicillin Allergy:

Classification of Allergic Reaction: Allergy / Intolerance / Not substantiated

Ranking of Penicillin Allergy: Severity I / Severity II

Other Adverse Drug or Allergic Reactions:

--

Skin Testing: Yes / No

Skin Testing Results:

--

HISTORY OF PRESENTING COMPLAINT

CLINICAL DIAGNOSIS ON ADMISSION

PAST MEDICAL HISTORY

SOCIAL HISTORY

RELEVANT BIOCHEMICAL TESTS

RR (minute ⁻¹)									
pO ₂ (mmHg)									
SaO ₂ (% RA)									
pCO ₂ (mmHg)									
BP (mmHg)									
Urea (mmol/L)									
Cr (μmol/L)									
WCC (10 ⁹ /L)									
T (°C)									

CHEST X-RAY FINDINGS

Date	Results

Severity of Pneumonia:

ANTIBIOTICS PRESCRIBED

Classes	Commenced on	Drug names	Route	Dose (mg)	Doses per day	Duration (days)
Penicillins						
Cephalosporins						
Carbapenems						
Monobactams						
Aminoglycosides						
Macrolides						
Glycopeptides						
Quinolones						
Tetracyclines						
Sulfonamides and Trimethoprim						
Other						

THERAPEUTIC DRUG MONITORING

Date	Antibiotics	Level

ANTIBIOTIC ON DISCHARGE

TREATMENT OUTCOMES

Appendix 8: Antibiotic Allergy Questionnaire



Antibiotic Allergy Questionnaire

1. Have you ever suffered any allergies or adverse reactions (ill effects) to any antibiotic?
 Yes No
2. What antibiotic was involved?
 Penicillins
(amoxicillin, ampicillin, benzathine penicillin, benzylpenicillin, dicloxacillin, flucloxacillin, phenoxymethylpenicillin, piperacillin, procaine penicillin, ticarcillin)

<input type="checkbox"/> Abbocillin [®]	<input type="checkbox"/> Bgramin [®]	<input type="checkbox"/> Flopen [®]
<input type="checkbox"/> Alphacin [®]	<input type="checkbox"/> Cilicaine [®]	<input type="checkbox"/> Floxapen [®]
<input type="checkbox"/> Alphamox [®]	<input type="checkbox"/> Cilamox [®]	<input type="checkbox"/> Flucil [®]
<input type="checkbox"/> Amohexal [®]	<input type="checkbox"/> Cilopen [®]	<input type="checkbox"/> LPV [®]
<input type="checkbox"/> Amoxil [®]	<input type="checkbox"/> Clamoxyl [®]	<input type="checkbox"/> Moxacin [®]
<input type="checkbox"/> Ampicyn [®]	<input type="checkbox"/> Clavulin [®]	<input type="checkbox"/> Penhenxal [®]
<input type="checkbox"/> Augmentin [®]	<input type="checkbox"/> Diclocil [®]	<input type="checkbox"/> Pipril [®]
<input type="checkbox"/> Ausclav [®]	<input type="checkbox"/> Dicloxsig [®]	<input type="checkbox"/> Staphylex [®]
<input type="checkbox"/> Austrapen [®]	<input type="checkbox"/> Distaph [®]	<input type="checkbox"/> Tazocin [®]
<input type="checkbox"/> BénPen [®]	<input type="checkbox"/> Duo Forte [®]	<input type="checkbox"/> Timentin [®]
<input type="checkbox"/> Bicillin [®]	<input type="checkbox"/> Fisamox [®]	

 Cephalosporins
(cefaclor, cefepime, cefotaxime, cefotetan, cefoxitin, cefpirome, ceftazidime, ceftriaxone, cefuroxime, cephalixin, cephalothin, cephamandole, cephalozin)

<input type="checkbox"/> Apatel [®]	<input type="checkbox"/> Cephazolin [®]	<input type="checkbox"/> Keflor [®]
<input type="checkbox"/> Ceclor [®]	<input type="checkbox"/> Cilex [®]	<input type="checkbox"/> Kefzol [®]
<input type="checkbox"/> Cefaclor [®]	<input type="checkbox"/> Claforan [®]	<input type="checkbox"/> Mandol [®]
<input type="checkbox"/> Cefkor [®]	<input type="checkbox"/> Fortum [®]	<input type="checkbox"/> Maxipime [®]
<input type="checkbox"/> Ceflin [®]	<input type="checkbox"/> Ibilex [®]	<input type="checkbox"/> Mefoxin [®]
<input type="checkbox"/> Cefoxitin [®]	<input type="checkbox"/> Keflex [®]	<input type="checkbox"/> Rocephin [®]
<input type="checkbox"/> Cefrom [®]	<input type="checkbox"/> Keflin Neutral [®]	<input type="checkbox"/> Zinnat [®]
<input type="checkbox"/> Cephalothin [®]		

 Carbapenems (imipenem, meropenem)
 Cilastin[®]
 Merrem[®]
 Primacin[®]

 Monobactam (aztreonam)
 Azactam[®]

 Other _____
 Do not remember
3. When did you suffer the reaction?

<input type="checkbox"/> 0-5 years ago	<input type="checkbox"/> 6-10 years ago	<input type="checkbox"/> 11-20 years ago
<input type="checkbox"/> 21-30 years ago	<input type="checkbox"/> >30 years ago	<input type="checkbox"/> Do not remember

4. Could you describe the reaction that you had?
- _____
- _____
- _____
- _____
- _____
- _____
5. How were you given the antibiotic?
 Oral Injection Do not remember
6. How soon after starting the antibiotic did the reaction occur?
 Immediately (within few minutes)
 ≤72 hours after the start of therapy
 >72 hours after the start of therapy
 Do not remember
7. What treatment (if any) did you receive for the reaction?
 Antibiotic was ceased
 Other (_____)
 Do not remember
8. Who told you that you had suffered the reaction?
 Doctor Nurse Parents
 Self Other Do not remember
9. Did anyone advise you not to take the antibiotic again?
 Yes No Do not remember
10. Did anyone advise you not to take any related antibiotics such as Keflex® or Ceclor® in the future?
 Yes No Do not remember
11. Have you ever received the same antibiotic again?
 Yes, and a reaction occurred
 Yes, and no reaction occurred
 Yes, but do not remember what happened
 No
 Do not remember
12. Do you know whether you have received any related antibiotics such as Keflex® or Ceclor® since the reaction?
 Yes, and a reaction occurred
 Yes, and no reaction occurred
 Yes, but do not remember what happened
 No
 Do not remember
13. Have you ever had skin testing done for antibiotic allergies?
 Yes No Do not remember

***End of the Questionnaire
Thank You for Your Co-operation***

Appendix 9: Ethics Approval from Curtin University of Technology (for Part Two of the Study)

MINUTE

Curtin
UNIVERSITY OF TECHNOLOGY

To	Lyna Irawati, Pharmacy
From	Max Page, Executive Officer, Human Research Ethics Committee
Subject	Protocol Approval HR 46/2002
Date	6 August 2002
Copy	Jeff Hughes and Neil Keen, Pharmacy

Office of Research and Development

Human Research Ethics Committee

TELEPHONE 9266 2784

FACSIMILE 9266 3793

EMAIL nlercht@cc.curtin.edu.au

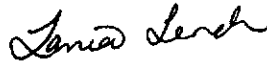
The Human Research Ethics Committee acknowledges receipt of your correspondence, indicating modifications / changes, for the project "INFLUENCE OF PENICILLIN ALLERGY ON ANTIBIOTIC PRESCRIBING PATTERNS AND COSTS".

The proposed modifications have been approved.

Approval for this project remains until **05/Mar/2003**.

Your approval number remains **HR 46/2002**, please quote this number in any further correspondence regarding this project.

Thank you.



MP Maxwell Page
Executive Officer
Human Research Ethics Committee

Appendix 10: Ethics Approval from Sir Charles Gairdner Hospital (for Part Two of the Study)

Note: For copyright reasons Appendix 10 has not been reproduced.

(Co-ordinator, ADT Program (Bibliographic Services), Curtin University of Technology, 4/12/2003)

Appendix 11: Patient Information Sheet (for Part Two of the Study)



PATIENT INFORMATION

24th July 2002

Influence of Penicillin Allergy on Antibiotic Prescribing Patterns and Costs

You are being invited to take part in a research study. Before you make your decision, it is important for you to understand why the research is being done and what it would involve. Please take as much time as you need to read the following information carefully and discuss it with friends, relatives and your doctor if you wish. Ask us if there is anything that is not clear or if you would like more information.

The aim of this study is to assess the impact of documented penicillin allergy on the choice of antibiotics and the clinical and financial consequences of changes in prescribing patterns.

You have been invited to participate in this study because you are aged 18 years or over, with a history of antibiotic allergy and have been admitted to Sir Charles Gairdner Hospital, Western Australia between August 2002 and September 2002.

It is your decision whether or not to take part. If you decide to take part, you can still withdraw at any time, without giving a reason. If you decide not to participate, or decide later to withdraw, it will not affect the standard of further care you would receive. If you do decide to take part, you will be asked to sign a consent form. You will be given this information sheet to keep and you will receive a copy of your signed consent form.

The study simply involves to you being interviewed to obtain detailed information on the nature and severity of your antibiotic allergy. This interview will take approximately five minutes of your time. No personal information will be recorded as part of the interview ensuring your anonymity.

A possible benefit of participating in the study is a more accurate classification of your antibiotic allergy. This will assist prescribers in the future in their drug selection.

This study will be carried out in a manner to the principles set out by the "National Statement on Ethics in Research Involving Humans". Both the Curtin University of Technology and Sir Charles Gairdner Hospital Human Research Ethics Committee have reviewed and approved the study.

If you have any questions or concerns now or at any time about the study, should you contact us on the numbers listed below:

Chief investigator: Dr Clay Gollidge Phone: 9346 3625

Co-investigators:

- Mr Jeff Hughes, MPharm Phone: 9266 7367
- Mr Neil Keen, BPharm Phone: 9346 2333
- Ms Lyna Irawati Phone: 9450 8721

If you want to discuss the study with someone who is not directly involved in this study (for example, about the information you have received, the conduct of the study or your rights as a participant, or a complaint you have), you can contact either the Curtin University Human Research Ethics Committee Secretariat on 9266 2784 or the Sir Charles Gairdner Hospital Human Research Ethics Committee Secretariat on 9346 2999.

Appendix 12: Consent Form (for Part Two of the Study)



CONSENT FORM

Project Title: Influence of Penicillin Allergy on Antibiotic Prescribing Patterns and Costs

Investigators:

- Dr Clay Golledge, Consultant Clinical Microbiology and Infectious Disease, Sir Charles Gairdner Hospital
- Mr Jeff Hughes, MPharm, Senior Lecturer, School of Pharmacy, Curtin University of Technology
- Mr Neil Keen, BPharm, Senior Pharmacist, Sir Charles Gairdner Hospital
- Ms Lyna Irawati, Master of Pharmacy Student, Curtin University of Technology

Subject Name: _____

Date of Birth: _____

I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.

I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked for.

I have been able to have a member of my family or a friend with me while I was told about the study.

I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation which I may have under statute or common law.

I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

Name of Patient

Signature of Patient

Date

Name of Witness to Patient Signature

Witness of Signature

Date

Name of Investigator

Signature of Investigator

Date

4. Could you describe the reaction that you had?

5. How were you given the antibiotic?
 Oral Injection Do not remember

6. How soon after starting the antibiotic did the reaction occur?
 Immediately (within few minutes)
 ≤72 hours after the start of therapy
 >72 hours after the start of therapy
 Do not remember

7. What treatment (if any) did you receive for the reaction?
 Antibiotic was ceased
 Other (_____)
 Do not remember

8. Who told you that you had suffered the reaction?
 Doctor Nurse Parents
 Self Other Do not remember

9. Did anyone advise you not to take the antibiotic again?
 Yes No Do not remember

10. Did anyone advise you not to take any related antibiotics such as Keflex® or Ceclor® in the future?
 Yes No Do not remember

11. Have you ever received the same antibiotic again?
 Yes, and a reaction occurred
 Yes, and no reaction occurred
 Yes, but do not remember what happened
 No
 Do not remember

12. Do you know whether you have received any related antibiotics such as Keflex® or Ceclor® since the reaction?
 Yes, and a reaction occurred
 Yes, and no reaction occurred
 Yes, but do not remember what happened
 No
 Do not remember

13. Have you ever had skin testing done for antibiotic allergies?
 Yes No Do not remember

Other drug allergies: _____

**End of the Questionnaire
Thank You for Your Cooperation**

Appendix 14: Publication

This project was presented in the APSA (Australasian Pharmaceutical Science Association) 2002 Conference, Melbourne, 8-11 December 2002, and was awarded the outstanding poster presentation in pharmacy practice.

Influence of Penicillin Allergy on Antibiotic Prescribing and Costs

L Irawati¹, J Hughes¹, N Keen², C Golledge³

¹School of Pharmacy, Curtin University of Technology, WA; ²Department of Pharmacy and ³Department of Microbiology, Sir Charles Gairdner Hospital, WA

Purpose. The objectives of this study were to i) determine the pattern of antibiotic prescribing in adult patients with a history of penicillin allergy and ii) evaluate the economic impact of penicillin allergies.

Methods. The medical records of all patients aged ≥ 18 years admitted with community-acquired pneumonia to Sir Charles Gairdner Hospital over a 15-week period were reviewed. The severity of patients' penicillin allergies was assessed using a structured questionnaire. The antibiotic cost was calculated using acquisition, delivery (labour and equipment) and laboratory monitoring costs. The antimicrobial selections and costs were then compared for those patients with (Group A) and without (Group B) penicillin allergy.

Results. 155 patients were reviewed (males 71, females 84) with an average age of 68 ± 18 years. Of these, 27 (17.4%) had documented penicillin allergies; of which 12 were classified as Severity I (e.g. anaphylaxis, urticaria), 12 as Severity II (e.g. rash, itch) and three as intolerance (e.g. GI upset). A history of penicillin allergy significantly ($p < 0.05$) increased the cost of antibiotic treatment and total cost of admission as shown below:

	Severity of pneumonia	Number of patients (%)	Average AB cost (A\$)	Average LOS (day)	Average TCA* (A\$)
Group A	MM	23 (85.2)	194.37	5.0	3 961.49
	Severe	4 (14.8)	1 118.08	12.5	10 662.84
Group B	MM	110 (85.9)	164.89	5.0	3 916.97
	Severe	16 (12.5)	467.96	8.0	6 853.75
	Aspiration	2 (1.6)	181.58	8.0	6 181.58

MM = mild to moderate; AB = antibiotic

LOS = length of stay; TCA = total cost of admission

** TCA = total antibiotic cost + accommodation cost (bed charge × LOS)*

Conclusions. Patients with a history of penicillin allergy had greater antibiotic costs, and longer durations of therapy and hospital stay. Identifying patients with intolerance rather than allergies may reduce these costs.

1. Verbally advise the candidate that they are the recommended applicant for the position and obtain their verbal acceptance that they would take the position if offered.
2. The Recruiting School/Area needs to both seek in writing and receive written permission of the Releasing School/Area to release the candidate. Refusal of approval must be substantiated by evidence that severe disruption to: client service, the completion of projects and/or the delivery of documented strategic objectives would occur.
3. Once acceptance has been obtained, a Recommendation for Secondment/Transfer is to be completed and sent to Staff Services.
4. A formal offer is then generated. The candidate must sign and return the contract as formal acceptance.
5. Towards the end of the developmental opportunity, the Recruiting School/Area must formally advise the Releasing School/Area and Staff Services that either
 - o the secondment is coming to an end and the candidate will be returning to their substantive position; or
 - o they wish to offer a second period of secondment, if in compliance with the relevant Agreement. In which case steps 1 to 4 are repeated.

Rules

1. Wherever practicable, employees should advise their Manager of their application for secondment opportunity or of proposed extensions to existing secondments. It must be established that participation will not disadvantage the University and will benefit the employee by being relevant and appropriate to that person's current employment or possible future career path at the University.
2. To assist in staff planning for that area. A notice period of two weeks for staff currently holding a fixed term contract of employment should be provided. For continuing staff, a notice period of four weeks should be provided.
3. Redeployees will have first option to register their interest in available positions, prior to their advertisement.
4. Any parties involved in arranging a development opportunity will identify the supervisor to whom the employee will be reporting, and will make appropriate arrangements governing the working patterns (eg. ordinary hours of work, homebased work, 'Healthy Lifestyle' activities, study leave, previously arranged annual leave etc.) prior to the developmental opportunity being taken up.
5. With approval of both Releasing and Recruiting Schools/Areas, employees may negotiate to exchange positions but reciprocity need not be simultaneous, nor in the same employment field. For example, this may be used to undertake cross-training within a School/Area.
6. The University will ensure that salary and allowance payments continue uninterrupted. Leave entitlements during the secondment period shall be funded by the Recruiting School/Area as they accrue, all entitlements accrued prior to the developmental opportunity shall be funded by the Releasing School/Area. Any other agreement on leave arrangements should be reached by the parties before the development opportunity takes place. Any recoup shall be arranged directly between the Recruiting and Releasing Schools/Areas.
7. Development opportunity placements shall only be terminated if all parties agree, or in circumstances which gave rise to the opportunity, change.
8. At the completion of a development opportunity, the employee(s) shall return to the same position and similar duties to those vacated on commencing the opportunity, unless circumstances in the Releasing School/Area have changed. However, should changes in University requirements occur during the period in which an employee is undertaking a development opportunity, the University cannot guarantee employees will be allocated exactly the same duties, or role on their return to their substantive position.
9. In the event that significant changes to a work area may be necessary, the Head of the Releasing School/Area will write to the employee undertaking the development opportunity. The written communication should include all relevant information about the possible changes including the nature of the changes proposed; the expected effects of the changes on the employee and any other matters likely to affect the employee and request their input and comment.
10. In the event of the introduction of change to a work area resulting in the employee's substantive position no longer being required the employee will be subject to the appropriate processes outlined in the relevant agreement.
11. Any disciplinary action taken during the period of the developmental opportunity, shall be consistent with the provisions outlined in the relevant agreement.

External Development Opportunities

External development opportunities includes opportunities for staff members to work in external

University's Grievance Procedures and relevant agreement. Staff Services should be contacted in the first instance.



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CRICOS provider code 00301J