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DOCTOR OF PHILOSOPHY

SKIN CANCER DIAGNOSIS AND SURGICAL
MANAGEMENT IN GENERAL PRACTICE



Thesis submitted by

Dr Clare Heal MBChB

For the degree of Doctor of Philosophy in
The School of Public Health and Tropical Medicine at James Cook
University
January 2010

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STATEMENT OF THE CONTRIBUTION OF OTHERS

Some of this research was conducted in collaboration or consultation with other practitioners.

I wish to acknowledge the contribution of my co-authors to a number of manuscripts included as part of this thesis:

Chapter 2 Risk factors for wound infection after minor surgery

Dr Petra Buttner performed multivariate analysis and edited the paper.

Chapter 3 Does application of chloramphenicol ointment to sutured wounds decrease the incidence of wound infection?

Dr Petra Buttner contributed to the study design and did statistics. Dr Robert Cruikshank, Dr David Graham, Dr Sheldon Browning, Ms Jayne Pendergast, Dr Herwig Drobetz, Mr Robert Gluer and Dr Carl Lisec contributed to the study design.

Chapter 4 Minor skin excisions in North Queensland

Dr Petra Buttner and Dr Beverly Raasch contributed to study design; performed statistics and proof read and edited this paper.

Chapter 5 Diagnostic accuracy of excised and biopsied skin lesions by Australian general practitioners

Dr Petra Buttner performed the statistics, Dr Beverly Raasch, Dr Petra Buttner and Dr David Weedon contributed to study design and proof read and edited the manuscript.

Chapter 6 Agreement between histological diagnosis of skin lesions by histopathologists and a dermatohistopathologist

Dr Petra Buttner performed statistics, Dr Petra Buttner, Dr Beverly Raasch, Dr David Weedon contributed to the study design and proof read and edited the manuscript.

Chapter 7 Comparing the case-mix and number needed to treat of GPs and skin cancer clinic doctors

Dr Beverly Raasch proof read and edited the manuscript.

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I wish to express my sincere thanks to the many people who contributed to this thesis.

I would like to thank my supervisors, Dr Petra Buttner and Dr Beverly Raasch for their help over the period of my studies.

I would like to thank the General Practitioners in Mackay who contributed to the design and helped to collect data for two large randomised controlled trials conducted in Mackay.

I would particularly like to thank the RACGP research foundation and the Chris Silagy scholarship for the funding of the topical chloramphenicol project.

Finally, I would like to thank my husband Sheldon Browning and daughter Mia Browning for their tolerance and support.

.....
 Signature Date

LIST OF ABBREVIATIONS

AK	Actinic keratosis
APC	Annual PERCENTAGE CHANGE
BCC	Basal cell carcinoma
CM	Cutaneous melanoma
CN	Common naevus
GP	General practitioner
IEC	Intra-epithelial carcinoma
JCU	James Cook University
KA	Keratoacanthoma
MN	Melanocytic naevus
NNT	Number needed to treat
NPV	Negative predictive value
PPV	Positive predictive value
RCT	Randomised controlled trial
SCC	Squamous cell carcinoma
SK	Seborrhoeic keratoses
SSI	Surgical site infection

ABSTRACT

Background

Skin cancer is an extremely important health issue in Australia. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are by far the commonest cancers in Australia with an incidence of more than four times that of all other registrable cancers combined.(1) Cutaneous melanoma (CM) is the fifth most common cancer in Australia, with the estimated risk of developing a melanoma before 75 years of age being one in 26 for Australian men and one in 36 for Australian women.(1) Queensland has the world's highest recorded incidence of all types of skin cancer,(2, 3) with incidence rates being even higher in tropical North Queensland.(4)

In North Queensland, the majority of suspicious skin lesions are managed by general practitioners (GPs),(5) particularly in rural centres such as Mackay where there is no resident plastic surgeon or dermatologist.(6) It is therefore important that the diagnosis and post surgical wound management of GPs is optimal.

In 2006 a group of GPs in Mackay, of which I was chief investigator, published a randomised controlled trial which showed that the wetting of sutures did not increase the incidence of wound infection but the incidence of infection was nevertheless higher than expected after minor skin cancer surgery.(7) This trial formed the background to several of the current studies for this thesis.

The overall aim of the studies presented here was:

1. To improve the management of skin cancer and the conduct of skin cancer surgery by Australian GPs.
2. To increase patient well-being through appropriate use of post-surgery wound management.
3. To assess the ability of GPs and pathologists to diagnose skin lesions.
4. To investigate possibilities of research in GP practice settings.

Methods

The thesis comprises the results of three trials which took part in the Queensland towns of Mackay and Townsville.

The first study proceeded from the 'Can sutures get wet' trial which was a randomised controlled trial conducted in general practice, in Mackay in 2004-5. Data were recorded from 1247 consecutive patients who attended for minor skin excisions. Further exploration and data analysis was undertaken from this trial to investigate 857 of these patients for risk factors for infection, to investigate the numbers needed to treat (by excision) for skin cancers and to examine the case-mix of skin lesions in regular general practice and a skin cancer clinic.

The second 'Topical chloramphenicol' study was also conducted in general practice in Mackay in 2007. This was a prospective double blinded randomised controlled trial. Nine hundred and seventy two patients were assessed for infection after receiving either a single topical dose of chloramphenicol (n=488) or paraffin ointment (n=484; placebo).

The third study had previously been conducted in Townsville and secondary data analysis from the database of this study formed the 'Diagnostic accuracy' and histological agreement studies. All excised and histologically confirmed skin cancers in Townsville/Thuringowa, from December 1996 to October 1999 were recorded. Positive predictive values (PPV) and sensitivities were calculated for the clinical diagnoses and stratified by histological sub-type and body-site. A stratified sample of 407 of 8,694 skin excisions slides was used to compare the "standard" histological diagnosis with the diagnosis from an internationally renowned dermato histo-pathologist.

Results

Secondary data analysis from the 'Can sutures get wet' study showed an overall incidence of infection was 8.6% (95%-confidence interval = [3.5, 13.8]). Excisions from lower legs and feet ($p=0.009$) or thighs ($p=0.005$), excisions of BCC ($p=0.006$) or SCC ($p=0.002$) and diabetes ($p<0.001$) were found to be independent risk factors for wound infection.

Close to half (46.7%) of lesions excised were skin cancers with more SCCs than BCCs (0.74:1). Our number needed to treat (NNT) (melanocytic naevi excised per melanoma) was 8.4. Mean age for excision of melanoma, BCC and SCC was 55, 60.9 and 63.8 yrs respectively. Relative tumour density was greatest in the face, scalp and neck region for all skin cancers.

Further analysis of these data comparing mainstream general practitioners with a doctor working in a designated skin cancer clinic showed that the case-mix of non-melanotic skin cancers was significantly different for the two groups of doctors ($p < 0.001$). The BCC:SCC ratio was much higher for skin cancer clinic doctors (4:1) than for GPs (0.6:1). The NNT (melanocytic naevi excised per melanoma) was 4.7 for the skin cancer doctor and 9.0 for mainstream GPs.

In the 'Topical chloramphenicol' trial, the incidence of infection in the chloramphenicol group (6.6%; 95%-confidence interval = 95%-CI = (4.9 to 8.8)) was significantly lower compared to the incidence in the control group (11.0%; 95%-CI = (7.9 to 15.1)) ($p = 0.010$). The absolute reduction in infection rate was 4.4%, the relative reduction was 40% and the relative risk of wound infection in the control group was 1.7 times higher (95%-CI = (1.1 to 2.5)) than in the intervention group.

The third and fourth studies examined a total of 8694 skin excisions reanalysed from the database of the Townsville study. Positive predictive values (PPV) for the clinical diagnoses were: BCC 0.727, SCC 0.494 and CM 0.333. Sensitivities for the clinical diagnosis were: BCC 0.639, SCC 0.411, and CM 0.338. For BCC, PPVs and sensitivities were higher for the trunk, the shoulders and the face and lower for the extremities. The reverse pattern was seen for SCCs.

Further analysis of the data comparing an expert dermato-pathologist with mainstream histopathologists, showed positive predictive values for the primary histological diagnosis were above 90% for BCC, CM and CN. For SCC the positive predictive value was 72.6% (95%-CI = [65.5, 79.0]).

Overall conclusions

Patients with minor skin excisions in North Queensland have a higher incidence of wound infection. Groups at high risk of infection after minor surgery were diabetics, those undergoing excision of a non-melanocytic skin cancer or excision from the lower limb.

Topical chloramphenicol ointment decreases this incidence moderately. GPs in North Queensland have a high yield of skin cancer from their skin excisions and a low NNT (melanocytic naevi excised per melanoma). Doctors diagnose skin cancers accurately, but there are some areas of diagnostic difficulty, in particular in the diagnosis of actinic keratosis (AK) and SCC. GPs and skin cancer doctors have a different skin cancer case-mix.

Overall recommendations

1. In view of the level of skin infection associated with skin cancer surgery previously identified, antibiotic prophylaxis prior to minor surgery in general practice should be limited to the high risk groups that were identified - the consequences of infection are often minor and side-effects from antibiotics, such as allergy, can potentially be serious.
2. The use of topical chloramphenicol ointment to prevent infection after minor surgery is best reserved for high risk groups. The reduction in infection was only 40%, which was statistically but not clinically relevant. The overutilization of topical antibiotics has potentially adverse consequences such as antibiotic resistance and allergic contact dermatitis.
3. The doctors involved in my study in Mackay could consider lowering their threshold for excision of pigmented lesions. In our sample of Mackay GPs, there was a very high yield of skin cancers from all excisions, and NNT (melanocytic naevi excised per melanoma) of 8.4, was lower than published data from comparable cohorts.
4. Educational programs for doctors regarding the diagnosis of skin cancer could focus on areas of diagnostic weakness which were identified in our study, such as differentiating melanocytic naevi from malignant melanoma, and differentiating between AK and SCC.
5. It is important that doctors excising suspicious skin lesions are aware that there is discordance and lack of agreement between histopathologists regarding the diagnosis of SCC and AK.

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THESIS INTRODUCTION AND OVERVIEW

Introduction and overview

The data for the following thesis were collected from three separate studies conducted in the rural centre of Mackay and the regional centre Townsville, North Queensland. The author was involved as principal investigator of the first two studies which were conducted in Mackay in 2004 and 2007. In addition, data was analysed from a separate study conducted by Drs Beverly Raasch and Petra Buttner in Townsville. Although each study was independent of the other, they are interrelated in that they examine aspects of the diagnosis and management of skin cancer in general practice. In this overview, the background and settings for these studies will be outlined.

Background

The term non-melanocytic skin cancer (NMSC), has previously been used as a collective term to describe the combination of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). This nomenclature has now changed and the terms BCC and SCC will be referred to individually in this document.

Skin cancer is an extremely important health issue in Australia. SCC and BCC are by far the commonest cancers in Australia with an incidence of more than four times that of all other registrable cancers combined.⁽¹⁾ Cutaneous melanoma (CM) is the fifth most common cancer in Australia, with the estimated risk of developing a melanoma before 75 years of age being one in 26 for Australian men and one in 36 for Australian women.⁽¹⁾ Queensland has the world's highest recorded incidence of all types of skin cancer,^(2, 3) with incidence rates being even higher in tropical North Queensland.⁽⁴⁾

In North Queensland, the majority of suspicious skin lesions are managed by general practitioners (GPs),⁽⁵⁾ particularly in rural centres such as Mackay where there is no resident plastic surgeon or dermatologist. It was recently estimated that, in Australia, 54% of patients with BCCs and 65% of patients with SCCs are managed in primary care settings, and it could be projected that these figures would be even higher for rural settings.⁽⁶⁾ Skin excisions form a large proportion of a typical Australian GP's workload, and this proportion is even greater for Queensland GPs.⁽⁵⁾ Skin excisions are also very costly, with over one million skin excisions billed to Medicare (Australia's national health care program) annually⁽⁸⁾ and an estimated cost of \$264 million for BCC and SCC in 2000-1 (9% of the total costs for cancer).⁽⁹⁾

Setting

Mackay is a provincial town in tropical North Queensland. The population of 'Greater Mackay', which includes rural districts belonging to Mackay, (identified as Mackay City Local Government area in the 2006 census) was 84,890, including 3,298 Aboriginal and Torres Strait Islander (ATSI) people.⁽¹⁰⁾ The population of Mackay is slightly younger and has a higher⁽¹⁰⁾ median household income than the Australian population.⁽¹⁰⁾ A large proportion of the population is of European descent. Traditionally, the main industry was cane farming, and Mackay is still the largest sugar-producing area in Australia. More recently coal mining has also become a major industry and the town has experienced an economic boom in the early years of the new millennium.

The combined ATSI population of 3.9% is higher proportionally than the Queensland average (2.9%), or the Australian average of 2.3%.⁽¹⁰⁾ Mackay has the largest population of Australian South Sea Islanders in Australia, which dates back to 'Blackbirding' - the recruitment of indentured labourers to work on cane farms, which took place between 1863 and 1904.⁽¹¹⁾ The actual number is estimated to be between 4,000 and 6,000, but there are no accurate figures available through census information.

Mackay is located on the 21°S latitude, and the climate is hot and humid with the mean daily maximum temperature ranging between 24 and 30°C during the summer months, and a relative humidity of 75% to 79%.⁽¹²⁾

One of the first Europeans to travel through the Mackay region was Captain James Cook, who reached the Mackay coast on June 1, 1770 and named several local landmarks, including Cape Palmerston, Slade Point and Cape Hillsborough. It was during this trip that the Endeavour's botanist, Sir Joseph Banks, briefly recorded seeing Aborigines. The City of Mackay was later founded on Yuibera traditional lands. The first European settlement, Greenmount station situated in the Pioneer valley, was established by Scottish born John Mackay in the 1860s.



Figure 1: Greenmount Station, the first European settlement in Mackay

Townsville is a tropical city in North Queensland. The population of ‘Greater Townsville’ can be calculated from the 2006 census by combining Townsville Statistical local area (SLA) PtB (southern outskirts of Townsville), Townsville statistical division (SD) (Central TSV and Thuringowa) and Thuringowa Statistical local area (SLA) PtB (northern outskirts of Townsville/Thuringowa). The total population of this district was 154,630, including 8,530 ATSI people.(13)

Townsville’s latitude is 19.16° South and the average daily maximum temperature is 28.8°C .(12) Townsville experiences an annual average of 8.4 hours of sunshine per day, and on average there are 171 days with 10 hours of sunshine per day.(14)

Studies involved in this thesis

In 2006 a group of GPs in Mackay, of which I was chief investigator, published a randomised controlled trial which showed that the wetting of sutures did not increase the incidence of wound infection in minor skin cancer surgery.(7) This trial forms the background for this thesis. Secondary analysis of data from this study is used in the second, fourth and seventh chapter of this thesis to explore some aspects of skin cancer management by GPs. Chapter 2 describes the incidence of and risk factors for wound infection after minor surgery.

The ‘Can sutures get wet?’ trial revealed that the incidence of wound infection was high in comparison with similar cohorts in published studies from other geographical locations. The proposed thesis further explores these findings and seeks to evaluate an intervention, the use of topical chloramphenicol ointment, to reduce the infection rate. The broad hypothesis behind this proposal is that attention to infection control improves outcome and reduces morbidity in skin cancer surgery. Chapter 3 reports the results of this trial. Chapter 4 describes the demographics of patients presenting with skin cancers to GPs in Mackay, the sites from which skin cancers are

removed, and their histology. Chapter 7 compares the case-mix between GPs and a skin cancer doctor in Mackay.

Between the end of 1996 and October 1999, all excised and histologically confirmed skin cancers in Townsville, North Queensland, were recorded. Chapter 5 provides a further analysis of these data, comparing clinical with histological diagnosis of excised and biopsied skin lesions by Australian GPs. Another re-analysis takes place in Chapter 6 with a comparison of “standard” histological diagnosis with the diagnosis from an internationally renowned dermato histo-pathologist.

Chapter 8 provides overall conclusions and recommendations of the thesis.

Overall aims of thesis

1. To improve the management of skin cancer and the conduct of skin cancer surgery by Australian GPs.
2. To increase patient well-being through the appropriate use of post-surgery wound management.
3. To assess the ability of GPs and pathologists to diagnose skin lesions.
4. To investigate possibilities of research in GP practice settings.

Specifically, the research questions were:

1. What is the incidence of and risk factors for infection after minor surgery?
2. Does topical chloramphenicol ointment prevent infection after minor surgery in general practice?
3. Amongst GPs in Mackay, what is the case-mix of lesions that GPs excise in the management of skin cancer, from which body sites are they excised and what is the age distribution of patients with skin cancer?
4. Is there a difference in the case-mix of skin cancer managed by mainstream GPs and skin cancer GPs?
5. How accurately do GPs diagnose different types of skin cancer?

6. Is there a difference between the diagnostic accuracy of a specialist dermatologist and pathologists in the diagnosis of skin cancer?

Objectives

The objectives specific to each study will be discussed in the respective chapters.

Methods

The methods used will be discussed within the appropriate chapters.

Collaborations and research support

Primary health care research education and development (PHCRED): Collaboration took place with PHCRED in order to provide research training to doctors and practice nurses. North Queensland Practice Based Research Network has evolved from this collaboration. Mackay evidence based medicine group collaborated in the development of the two randomised controlled trials which were conducted in Mackay.

Professor David Weedon collaborated to the development of chapters 6 and 7.

Available funding

Awarded Chris Silagy scholarship in July 2007 for \$20,000.

PHCRED provided a novice research scholarship of \$17,000 to Mackay evidence based medicine group.

CHAPTER 1: LITERATURE REVIEW

1.1 Scope and limitations of literature review

1.2 Skin cancer incidence in Australia

1.3 Primary care skin cancer management in Australia

1.4 Incidence of and risk factors for infection after skin cancer surgery

1.5 Antibiotic ointments

1.6 Conclusion

1.1 Scope and limitations of literature review

The scope of the literature review with timeframes, limitations and keywords will be discussed in this section.

1.2.1 Incidence of BCC and SCC

This section discusses the incidence of BCC and SCC in Australia since 1982 until data collection commenced for the first study of my thesis (2004). With the exception of Tasmania, this section is limited by lack of registry information since 1999. Comprehensive Medline search using keywords 'BCC, SCC, and incidence and Australia' was used to identify studies involving BCC and SCC. The search revealed a total of 40 articles, of which 11 were found to be suitable

1.2.2 Incidence of melanoma in Australia

This section discusses the incidence of melanoma in Australia since 1982 until data collection commenced for the first study of my thesis (2004). The section is limited by the time lag between the year of melanoma occurrence, and when the data becomes available, usually around 4 years in the case of melanoma registries. Therefore information about melanoma after 2000 has been discussed in the section on conclusions.

Comprehensive Medline search using keywords 'melanoma and incidence and Australia' were used. In addition, clinical practice guidelines for the management of melanoma in Australia and New Zealand(15, 16) and Australian Institute of Health and Welfare (AIHW) cancer registry

information(17) were used to obtain information for the section on melanoma. Information from new clinical practice guidelines on the management of melanoma in Australia is used in the section on conclusions.(16)

1.3 Management of skin cancer by Australian GPs and number needed to treat

Comprehensive Medline search was used to identify published literature regarding the number needed to treat (NNT) by Australian clinicians from 1985 until 2006 when the manuscript in chapter 2 was published. Keywords ‘number needed to treat’, naevus and melanoma and Australia were used. A total of 11 articles were identified, 6 of which were found to be suitable. International literature was excluded from the search. Studies published after 2006 are discussed in the conclusion.

1.4.2 Incidence and risk factors for surgical site infection after dermatological surgery

Comprehensive Medline search using the keywords surgical site infection, and dermatology was used to identify internationally published material recording the incidence of surgical site infection after dermatological surgery from 1985 to 2006, when the manuscript in chapter 3 was published. A total of 66 articles were identified, five of which were found to be suitable. Material regarding surgical site infection after this date is discussed in the conclusion section. Micrographic MOHS surgery has been excluded from this section.

1.4.3 Guidelines for oral antibiotic prophylaxis for surgical wounds

Comprehensive Medline search was used to identify existing guidelines for oral antibiotic prophylaxis for prevention of surgical site infection of dermatological surgery from 1985 to 2006, when the manuscript in chapter 3 was published. Keywords used were antibiotic prophylaxis and dermatology. A total of 47 articles were identified, five of which were found to be suitable. Further guidelines developed since this date will be presented in the conclusion section. Prophylaxis for endocarditis or joint arthroplasty is not included in the scope of this section.

1.5 Antibiotic ointment use

This sub-chapter reviews the literature available regarding antibiotic ointment and its use in wound management. Antiseptics such as povidone-iodine, and silver are excluded from the definition of topical antibiotic for the purposes of this section.

1.5.3 Infection prevention following surgery

This section discusses the use of antibiotic ointments to prevent infection after minor surgery. Comprehensive Medline search was used to identify internationally published randomised controlled trials from 1985 until 2007 when data collection for my randomised controlled trial (RCT) commenced. Keywords used were antibiotic ointment, prophylaxis and infection. A total of 22 articles were identified, five of which were found to be suitable.

1.5.4 Infection prevention in non-surgical wounds

A comprehensive Medline search was used to identify internationally published trials investigating topical antibiotics as infection prophylaxis in minor, non-sutured traumatic injuries. Studies published between 1985 to 2007, when data collection for the chloramphenicol trial commenced, was considered to be within the scope of this section. Trials published after 2007 are discussed in the conclusion. Keywords used were antibiotic ointment, prophylaxis and infection. A total of 22 articles were identified, two of which were found to be suitable

1.5.5 Treatment of secondary infections

A comprehensive Medline search was used to identify internationally published trials in which antibiotic ointments were used to treat secondarily infected wounds. Studies published between 1985 and 2007, when data collection commenced for the chloramphenicol trial commenced, was considered to be within the scope of this section. Trials published after this data are discussed in the conclusion. Keywords used were antibiotic ointment, prophylaxis and infection. A total of 22 articles were identified, three of which were found to be suitable.



Figure 2: Malignant melanoma on foot of patient in Mackay, Qld

1.2 Skin cancer incidence in Australia

1.2.1 Incidence of BCC and SCC

With the exception of Tasmania, the presence of BCC and SCC is currently not recorded by cancer registries in Australia. In Queensland there was compulsory registration of BCC and SCC until 1999, although no incidence rates were provided. Similarly, in most states there was compulsory recording of the incidence of SCC and BCC until 1999. Tasmania still records the incidence of SCC and BCC.

Incidence has been measured either in defined communities at different locations across Australia, and nationally using a series of household surveys conducted in 1985, 1990, 1995 and 2002.

Methods of measuring incidence rates

Because there is no standardised surveillance system to determine and monitor the incidence of BCC and SCC, reported incidence rates need to be critically viewed taking into account factors which can affect the diagnosis of the cases. Incidence is an expression of the number of new cases of a disease that occur in a defined population over a specific period of time, and by convention the incidence date is defined as the date of first diagnosis although the disease may have commenced some time previously. Therefore for BCC and SCC, newly identified skin cancer may have been previously overlooked and have remained undiagnosed for some time. The presence of multiple skin cancers may also affect the measurement of incidence rates, as this may effect the numerator: conventionally only the first lesion of a particular type per patient per given year should be included.(18) On the other hand, the incidence of all malignant lesions can better describe the burden of the illness in the population.(19)

In Australian studies, the incidence rate also varies depending on whether, in the process of age standardisation, world age standardised incidence rates or Australian age standardised incidence rates are used. If Australian age standardised incidence rates are used, the incidence of skin cancer appears to be higher as the Australian population is relatively young in comparison with the world population. The rates are not comparable if different standard populations were used. In addition, incidence rates vary depending on the age of the population which is used as the denominator. In some studies(20) the entire population is used as the denominator, thus giving a conservative estimation of the incidence of skin cancer, as the condition tends to be rare under the age of 40. However in some studies only certain age groups are used as the denominator, which may in contrast over-estimate the incidence of skin cancer in the population.

The validity of skin cancer incidence rates also depends on biopsy rates and standardization of histological diagnosis. Agreement between histologists regarding the diagnosis of skin cancer is discussed later in the literature review. In addition, it is difficult to quantify how many BCC and SCC may be treated by non-surgical procedures in Australia. When excision is not the primary treatment, no histology is available in order to confirm the diagnosis.(21)

Studies of defined communities

The first of the studies involving defined communities was a longitudinal study conducted in Maryborough Victoria, which took place between 1982 and 1986.(20) The study took the form of annual skin examinations. In 1982 a database was established, of 3300 persons aged 40 and older on the electoral register, and they were invited to participate in the study. A total of 2,669 people aged 40 years and older were recruited (81% of the eligible population). The study was conducted for one week at the beginning of spring each year for five years (1982-86 inclusive). Light exposed areas were examined. All participants were asked if they had undergone treatment for any lesions in the interval in between examinations, and permission was given to obtain medical records. The age standardised incidence rates for SCC and BCC combined was estimated to be 873/100,000 per year. The rates for BCC were 672 per 100,000 and SCC 201 per 100,000. Because they had excluded persons under the age of 40 years, but their calculation used the entire population as the denominator, this estimation is therefore a conservative estimation (minimal age standardised incidence rate). The age adjusted incidence rate for combined SCC and BCC in the 40 years or older age group was much higher: 2,152/100,000.

In the Nambour study(22) the incidence and prevalence of BCC and SCC were estimated in a random sample of the population aged 20 to 69 years. In 1986 a random sample of 3,000 individuals were chosen from the 5,100 persons aged 20 to 69 years listed on the electoral roll as residents of Nambour. A total of 2,095 adults attended the initial skin cancer survey in December 1986. Dermatologists examined all participants for prevalent skin cancer – with histological confirmation – on the head neck and upper limbs. A random sample (10%) received full body examinations. A cohort was followed up over a 6 year period. In 1987 a postal survey requested information about skin cancers treated from 1986 to 1987. A further postal survey was administered in 1990, and subjects were examined for new cancers in 1992.

The incidence of BCC and SCC in 1986 was estimated to be 2,389/100,000 person-years at risk in men and 1,908/100,000 women. In 1992 at 6 year follow up the incidence rates were 2,528

/100,000 men and 1679/100,000 in women. In this study 325 patients (16%) were lost to follow-up, which may possibly have caused selection bias and elevated the incidence rates.

Kricker et al(23) conducted a population-based, longitudinal study in Geraldton, Western Australia. Initially a population examination study was conducted. In 1987, residents aged 40 to 64 years whose names were on the electoral roll were invited to undergo a whole body skin examination conducted by a dermatologist.(23) Subjects thought to have skin cancer were asked to attend their GP for definitive diagnosis, and a report of any pathology was requested. Subjects who reported diagnosis and treatment of skin cancer in the preceding 2 years were also asked to provide details of the treating practitioner so medical records could be obtained. The results were age specific rather than aged standardised. Overall the estimated incident rate for combined BCC and SCC in this age group was 1,560 per 100,000 person years. Estimated annual incidence rate for histologically proven BCC was 1,335 per 100,000 person years in men and 817 per 100,000 person years in females. For SCC the figures were 890 and 289 for men and women, respectively. In order to measure the rate at which BCC and SCC develops, a longitudinal follow-up study was then conducted. In 1989 and 1991 subjects were mailed questionnaires about skin cancers treated in the previous 2 years. The medical records of subjects who reported treatments were examined.

The cohort was then re-examined by a dermatologist in 1992.(24) For histologically proven cancers from November 1987 to September 1992 the estimated excision rates per 100,000 person years were for BCC 3,379 in women and 7,067 in men, and for SCC 501 in women and 775 in men. However when only the first skin cancer of each type that occurred during follow up were measured, the incidence rates for BCC were 2,204 per 100,000 person years in women and 3,541 in men, and the incidence rates for SCC were 461 in women and 585 in men. As it is more conventional to record only the first skin cancer of each type as the measure of incidence rates, this figure has been used in Table 1.1 of comparable incidence rates, where as the higher figure can be considered to be an excision rate.

The higher incidence rates in the second study may have been caused by close to 30% of subjects being lost to follow-up. As it is more likely that lower risk subjects were less likely to participate this could be a cause of selection bias.

Buettner and Raasch(4) conducted a prospective population-based survey to collect epidemiological information on all excised and histologically confirmed skin cancers in Townsville. Between December 1996 and December 1997, a total of 3,536 patients with 5,945 histologically confirmed skin cancer lesions were recorded. Age-standardised (world standard

population) incidence rates of BCC were 2,058.3 for men and 1,194.5 for women, 1,332.3 for men and 754.8 for women for SCC, and 49.1 for men and 41.7 for women for CM.(4)

A second study was based on data collection between January 1997 and October 1999 including patients of all ages. A total of 6,708 patients with 13,751 histologically-confirmed NMSC were recorded, with 38.5% of patients having multiple lesions. Yearly age standardised incidence rates for BCC were 1,444.8 for men and 942.7 for women. For SCC the rates were 805.0 for men and 423.6 for women. The occurrence of multiple BCCs and SCCs compromised the estimation of incidence rates.(18) Incidence rates for excision and yearly average incidence rates over the 3 years were also calculated.

National Household Surveys

National incidence rates of SCC and BCC have been determined in Australia in a series of national household surveys of a random sample of the population conducted in 1985, 1990, 1995 and 2002.(2) In the first study, face-to-face interviews were conducted by a market research company. A total of 30,976 Australians were asked whether they had ever been treated for skin cancer, and 1,179 responding affirmatively. The treating doctor or hospital was then approached for confirmation of the diagnosis of people who claimed to have been treated in the previous 12 months. Respondents who reported being treated for skin cancer were asked for permission to confirm this diagnosis with the treatment provider. In the first study the estimated age standardised incidence rates of SCC and BCC combined in the population was 823 per 100,000. For BCC and SCC the rates were 657 and 166 per 100,000, respectively. Rates for BCC and SCC showed a gradient with respect to latitude.

The second study by a market research company in 1990 carried out face-to-face interviews with a stratified random sample of the population. Medical records were checked in those who answered that they had been treated for skin cancer. A total of 63,450 people were interviewed, with 3,201 respondents stating that they had been treated for skin cancer and 2,879 giving sufficient details to be followed up. There was a response from 2,341 (71%) of medical practitioners. In this study the annual age standardised incidence rate for SCC and BCC combined was 977 per 100,000, showing a total increase of 19% since 1985. The rates were 1,189 for men and 769 for women.

The third survey was conducted in 1995.(25) During a 12 month period 63,745 people aged between 14 and 95 years were interviewed, with 10,841 respondents indicating that they had ever been treated for skin cancer, and 4,671 responding that they had been treated in the

previous 12 months. This was confirmed by treating physicians in 2,939 subjects. Estimated age standardised incidence rates for BCC were 788 per 100,000, an increase of 19% since 1985. SCC rates rose by 93% over the same period, from 166 to 321 per 100,000 inhabitants.

In the fourth and most recent survey in 2002,(26), again face-to- face interviews were used using a stratified random sample of households. The age standardised incident rate per 100,000 populations for combined BCC and SCC was 1170: for BCC 884 and for SCC 387.

Over the duration of the four surveys, although the rates of BCC and SCC had increased since 1985, the increase was greatest for people aged 60 years and over. Rates for those younger than 60 years had stabilised.

Author and year of publication	Location and year of trial	Population. method	SCC and BCC combined/100,000	BCC/100,000	SCC/100,000
Marks et al (20) 1989	Maryborough, Victoria 1982-86	Annual skin examinations	873 age standardised world standard population	672	201
Green and Battistuta 1990(22)	Nambour, Queensland 1986	20-69, postal surveys and examination	2,389 men, 1,908 women Age adjusted incidence rates world standard population		
Green and Battistuta 1996(22)	Nambour, Queensland 1992	20-69, postal surveys and examination	2,528/100,000 person years at risk men 1,679/100,000 person years women Age adjusted incidence rates world standard population	2,074 men and 1,579 women per 100,000 person years	1,035 men and 472 women per 100,000 person years
Kricker 1990(23)	Geraldton, Western Australia 1987	40-64yrs Whole body skin examination	1,560/100,000. Un-standardised incidence rates	1,335 men 817 women	890 men 289 women
English 1997(24)	Geraldton, Western Australia 1992	40-64yrs Longitudinal study. Postal surveys, whole body skin examination	2,665 women/100,000 4,126/100,000 men Un-standardised incidence rates Can add SCC and BCC rates as only first excision per person was used	2,204/100,000 person years women, 3,541/100,000 person years men	461/100,000 person years women, 585 585/100,000 men
Buettner 1998(4)	Townsville, Australia 1996-1997	All excised skin cancers	3,390.3/100,000 men, 1,948.8/100,000 women Age standardised incidence rates, world standard population Can add SCC and BCC rates as only first excision per person was used	2,058 men 1,194 women	1,332.3 men 754.8 women
Raasch and	Townsville, Australia	All excised skin cancers	2,249.8/100,000 men, 1,366.3/100,000 women	1,444.8 for men and	805.0 for men

Buttner 2002(18)	1997-1999		Age standardised incidence rates, world standard population Can add SCC and BCC rates as only first excision per person was used	942.7 for women.	and 423.6
Giles 1988(2)	National stratified sample 1985	First National survey	823/100,000 Age standardised incidence rates, world standard population	657/100,000	166/100,000
Marks 1993(27)	National stratified sample 1990	Second National survey	977/100,000 1187 men 769 women Age standardised incidence rates, world standard population	726	250
(25)Staples1998	National stratified sample 1995	Third National survey	1,109 Age standardised incidence rates, world standard population	788	321
Staples 2006(26)	National stratified sample 2002	Fourth National survey	1,170/100,000 Age standardised incidence rates, world standard population	884	387

Table 1.1: Studies of defined communities measuring incidence of BCC and SCC in Australia from 1982-2006

Registry Information

In Australia, Tasmania has the only Cancer Registry which still records the incidence of BCC and SCC and also the only registry which has published data from its registry.(28)

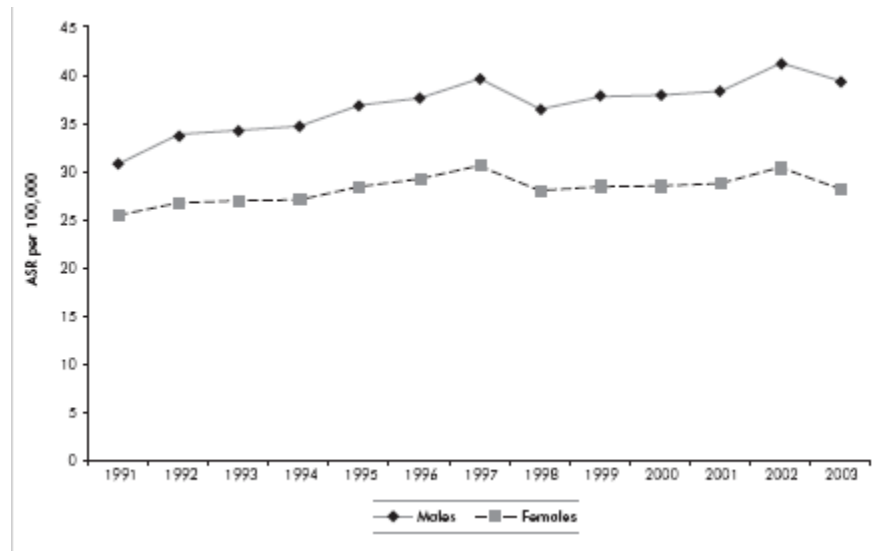
The Tasmanian Cancer Registry has published data based on population-based surveillance of BCC and SCC from 1978 to 1987.(28) Notified cases in Tasmania include all treated BCC and SCC with a histological diagnosis and those where treatment has been provided at the radiation oncology clinics. A total of 8,651 NMSC were recorded in 7,160 individuals, representing an age standardised rate of 161/100,000 per year. Ninety-four per cent of cases were based on histological diagnosis. Incidence of BCC was higher than the incidence of SCC. The incidence of NMSC was twice as high in men as in women. Incidence increased substantially with age, more markedly for SCC than BCC. There was an overall increase of 7% per year in the age standardised incidence rate of NMSC. The increase was more marked for BCC than for SCC, and was consistent across age groups and both sexes. A first BCC or SCC during the study period was associated with a 12-fold increase among men and a 15-fold increase in women of development of a new BCC or SCC in 5 years. BCC or SCC was 42% of all cancer in the Tasmanian registry.

Concluding comments

Although less dangerous and less life-threatening than cutaneous melanoma (CM), SCC and BCC are still invasive cancers, and SCC is capable of metastasing.(29) Because there is generally no registry style information available in Australia, and because alternate methods of measuring incidence rates have many influencing factors, it is difficult to accurately quantify incidence rates.

1.2.2 Incidence of melanoma in Australia

Melanoma is an increasing problem in fair-skinned populations world wide, and Australia as a country has the world's highest incidence of melanoma.(30) World age standardised incidence rates per 100,000 inhabitants for CM were 40.5 for men and 31.8 for women in Australia between the period of 1983-1999.(31) Previously as a region, Queensland had the world's highest incidence rates for melanoma.(32) However it was reported that in 1995, with a world age standardised incident rate of 56.2/100,000, the Auckland population of New Zealand had the world's highest incidence rates of skin cancer.(32)

Figure 1.1: Trends in age standardised incidence rates (ASR) of melanoma in Australia

Incidence of melanoma in Australia is recorded in population-based state registries. A national registry exists which is a compilation of state registries.

In Australia, CM is the fourth most common cancer in males, after prostate cancer, bowel cancer and lung cancer, and the third most common cancer amongst females after breast cancer and bowel cancer.(33) Between 1980 and 1987 the annual incidence of invasive melanoma in Queensland was 55.8 per 100,000 for men and 42.9 per 100,000 for women(34) based on world standard population. The incidence of melanoma in men almost doubled over this period, and this increase was greatest in men older than 50 years. There were similar incidence rates documented in New South Wales, where between 1986 and 1988 the annual incidence of melanoma was 52.5 per 100,000 for men and 42.9 per 100,000 for women.(35) The incidence of melanoma has been decreasing in young women since the mid 1980's but has continued to rise in older age groups.(36)

1.3 Management of skin cancer by Australian GPs and number needed to treat

For the purpose of this section, and in concordance with current NHMRC guidelines, Hutchinson's melanocytic freckle (in situ melanoma) is included in the definition of melanoma and dysplastic naevus is not considered to be malignant or pre-malignant. This is in concordance with research by Kelly et al(37) which showed that, although patients with dysplastic naevus syndrome had a higher absolute risk of developing CM, individual dysplastic naevi did not have a higher risk of malignant change. The term 'melanocytic naevi' will be used as a collective term to describe common naevi and dysplastic naevi.

In Australia the majority of suspicious skin lesions are managed by GPs(38) and the proportion of all skin cancers excised by GPs is increasing.(39) It is therefore important that GPs manage suspicious lesions optimally. The decision to excise is a complex issue which is influenced by factors such as patient concerns about malignancy, medico legal worries about missing melanoma, experience and the likelihood from epidemiological data that a pigmented lesion may be a melanoma.(40)

The number needed to treat (NNT) in skin cancer is often defined as the number of melanocytic naevi that are excised per melanoma. In other words it is the ratio of pigmented lesions (melanocytic naevi and/or seborrhoeic keratosis) to melanoma. It is commonly used as an indicator of quality of practice in skin cancer management (although its use as an indicator of quality has many limitations). A 2006 study derived from analysis of billing data from skin cancer clinics showed a NNT of 28.6.(41) However, in this study, non-pigmented benign lesions were included in the numerator therefore elevating the NNT. It is difficult to make comparisons in NNT as there appear to be several different definitions, however the NNT was found to be between 11 and 29.9 for Australian GPs when based on melanomas and melanocytic naevi only and up to 36 when seborrhoeic keratoses were included.(35, 40, 42-44)

Table 1.2: Australian studies of number of benign lesions excised per melanoma

Author, State	Setting, sample size	Number needed to treat	Numerator	Comments
Burton et al 1993, Hunter region NSW(35)	Pathology laboratory reviewed reports of 1984 and 1988 skin histopathology data, GPs and specialists combined	11 naevi per melanoma 1984, 16 naevi per melanoma 1988	Total number of excised melanocytic naevi	Number of melanoma doubled (91 to 197), number of naevi tripled (1,065 to 3,208)
Marks J et al (Victoria)1989-1994(42)	Analysis of all pigmented cutaneous lesions excised by GPs. Histological data, 31943 pigmented lesions	29.9 all pigmented lesions per melanoma	All pigmented lesions excised (melanocytic lesions and seborrhoeic keratosis, excluding BCCs)	Ratio 11.7: 1 for dermatologists
Del Mar et al 1994 Australia (43)	Audit 1,896 excised melanocytic lesions submitted to pathology service, general practice	19.4 melanocytic naevi per melanoma, 20.6 melanocytic naevi and lentigos per melanoma	Total number of excised melanocytic naevi and lentigo	NNT decreased with age of patient; Secondary data analysis from available data
Del Mar et al 1995 Australia (44)	Examination of 5,823 histopathological reports of melanocytic skin lesions excised during randomised field trial	17.75 melanoma per melanocytic naevi control group, 12.0 melanoma per melanocytic naevi intervention group	melanocytic naevi,	Secondary data analysis from available data
English et al 2004 Australia(40)	Retrospective audit 4,741 pigmented lesions, 468 GPs, 223 practices in Perth, Western Australia	29 pigmented lesions per melanoma 31 if seborrhoeic keratosis excluded	Total number of excised melanocytic naevi and seborrhoeic keratosis	NNT higher for patients who are young, female, lower socio-economic status and recent graduation of GP
Wilkinson et al 2006 Australia(45)	Analysis of billing data primary care skin cancer network	28.6 benign lesions per melanoma	All benign lesions excised from billing data	

1.4 Surgical site infection

1.4.1 Classification of surgical wounds

In order to understand surgical site infection, it is first important to understand the classification of surgical wounds. Surgical wounds are traditionally classified into different categories, and infection rates vary by category. This classification is important in order to predict post-operative infection rates and therefore aid with the decision to prescribe post-operative antibiotics.

Table 1.3: Classification of surgical wounds(46, 47)

Pre-operative classification	Wound type	Maximum expected Post-operative Infection rate	Example of wound
Class 1/ Clean	Non- contaminated wound	5%	Sterile minor skin excision
Class 2/Clean Contaminated	Operative wound in respiratory, alimentary, genital or urinary tract, minor break in aseptic technique	10%	Biliary tract, appendix, vagina, oropharynx
Class 3/Contaminated	Open, fresh, accidental wound, acute non-purulent inflammation, gross spillage from gastro-intestinal tract, major break in aseptic technique	20-30%	Open cardiac massage, gross spillage from gastro-intestinal tract
Class 4/ Dirty-Infected	Purulent inflammation, Gross contamination with foreign bodies, penetrating trauma > 4hrs old, devitalised tissue	30-40%	Old traumatic wound, abscess

Table 1.4: These categories can be adapted to dermatological surgery(48)

Pre-operative classification	Wound type	Maximum expected Post-operative Infection rate	Example of wound
Class1/Clean	Non- contaminated skin	5%	Sterile minor skin excision
Class 2/ Clean Contaminated	Wounds in oral cavity, respiratory tract, axilla/perineum, breaks in aseptic technique	10%	Skin excision from groin
Class3/Contaminated	Trauma, acute non-purulent inflammation, major breaks in aseptic technique	20-30%	Intact inflamed cyst, tumours with clinical inflammation
Class 4/ Dirty- Infected	Gross contamination with foreign bodies, devitalised tissue	30-40%	Ruptured cysts, tumours with purulent necrotic material

There is no published literature which has quantified the prevalence of class 1- class 4 wound types in minor surgical procedures. However clinical experience would suggest that the majority (> 95%) of wounds are class 1 (clean), for example excision of skin cancer, with a few class 2 wounds (clean-contaminated), for example excision from the groin. Occasionally class 3 and 4 wounds will be encountered, for instance the incision or excision of an infected cyst, however these classes of wounds were excluded from the trials in this thesis which analysed post-operative infection rates.

1.4.2 Incidence and risk factors for surgical site infection after dermatological surgery

Surgical site infection following minor surgery contributes to patient morbidity and compromises the cosmetic outcome. Most data regarding incidence and predictors of surgical site infections are based on studies of general surgical procedures.(47, 49-51)

Of studies looking at infection rates following minor dermatological surgery, most have been conducted in a hospital specialist setting.(52-55) The infection rates in these studies have been between 2-3%, with higher infection rates in certain groups. One study was identified which assessed infections in an out of hospital specialist dermatologist setting. In this study infection rates were 2%.(52)

As the majority of skin cancer surgery takes place in general practice in Australia,(39) it is important to study infection in this setting. General practice minor surgery may differ from a hospital setting, with most procedures taking place in treatment rooms rather than formal operating theatres.

The quality of evidence with regard to infection rates following minor surgery in a general practice setting seems to be poor. A comprehensive Medline search revealed only two studies which adequately recorded the incidence of infection following minor surgery in a general practice setting.(56) The earliest study, conducted in South Australia, showed an infection rate of 1.9%.(56) The second study was the 'Can sutures get wet' trial, which showed an overall infection rate of 8%.(7, 57) Secondary analysis of this data to identify risk factors for infection is the subject of chapter 2.

The acceptable rate of infection following clean minor surgery (class 1) is < 5%.(10, 47, 48, 58, 59) Even within cohorts with a low overall risk of infection, some excisions may be at higher risk of infection because of body site, pathology or patient factors and environmental conditions. In these high risk cases infection rate may be greater than 5%. These risk factors (tabled below) may include excisions from the lower leg, excisions of skin cancers and excisions from diabetic patients. Excisions from the ear and nose have also been shown to have a high incidence of infection.(53-56)

Table 1.5: Incidence and risk factors for surgical site infection following dermatological surgery prospective observational studies

Country, year	Setting and sample size	Study design demographics	Wound type (All class 1)	Incidence of infection	Risk factors for infection
Futoryan et al 1995(53) Boston USA	Hospital department of dermatological surgery 1,047 procedures	Retrospective audit patient records	530 Mohs and 517 excisions	24/1047 2.29% Mohs 13/530 2.45% excisions 11/517 2.1%	Ear 6/48 12.5%, Ear involving cartilage 4/14 28.5%
Sylaidis P, 1997(55) UK	Hospital plastic surgery unit. 351 patients, 464 wounds	Prospective observational study	Clean facial surgery	13/464 2.8%	Nasal area (6.5%), auricular area (5.2%) Oncological surgery (12%)
Lathlean 1999(56) Australia	General practice South Australia, 369 patients	Prospective observational study	Minor skin excisions	7/369 1.9%	4/7 infections lower leg, 6/7 age >80yrs actual rates not given
Dettenkofer 2003 Germany(54)	German university hospital dermatology ward, 632 inpatients, 995 dermasurgery procedures	Prospective observational study	Minor dermatological surgery	21/995 2.1%	Excision BCC 13/172(7.6%)
Amici et al 2005 France(52)	Dermatological outpatients 3,788 procedures	Prospective observational study, multicentre	Minor dermatological surgical procedures	79/3,788 2%	Males, anticoagulants, Immunosuppressants Skin flaps

1.4.3 Guidelines for oral antibiotic prophylaxis for surgical wounds

As stated above, in a general surgical setting the acceptable rate of infection following clean surgery (class 1) is set to less than 5%,(10, 47, 48, 58) and in several studies has been shown to be less than 2%.(52, 56) In contrast, clean contaminated wounds (class 2) have a risk of infection of less than 10%. Therefore in a general surgical setting, antibiotic prophylaxis of surgical wounds is usually considered optional for clean procedures, and reserved for certain at risk patients or clean procedures that fulfil specific risk criteria, ie where the risk of infection is greater than 5%.(50, 60)

There is debate about the role of antibiotics prior to skin lesion excision. If guidelines for prophylaxis after general surgery are to be extrapolated to a dermatological surgery setting, then most dermatological procedures should not require prophylaxis. Limited guidelines exist regarding antibiotic prophylaxis of dermatological procedures.(48, 61-63) All of these guidelines are from the United States of America, and there are currently no guidelines in Australian practice. Most guidelines advocate the use of prophylaxis in clean-contaminated (class 2) or contaminated wounds (class 3), but not for clean wounds (class 1). Additionally they have a role prior to skin surgery in patients at risk of infective endocarditis and in those who have had recent joint prosthetic surgery.(54, 67, 68, 69)

As stated in the previous sub-chapter, even within cohorts with a low overall risk of infection, some excisions may be at higher risk because of body site, pathology or patient factors. These risk factors are not well established and identifying these risk factors is important in order to develop antibiotic prophylaxis guidelines.

Table 1.6: Guidelines for oral antibiotic prophylaxis of surgical site infection after derma surgery

Guideline/recommendation	Country	Antibiotics not required	Antibiotics indicated for	Type prophylaxis	Additional recommendations
Haas et al 1995(48)	Department of dermatology, California	Class 1 wounds	Class 2 (clean-contaminated) wounds and higher	Single oral dose	Endocarditis prophylaxis
Maragh et al 2005 (61)	Division dermasurgery Mayo clinic, Minnesota	Class 1 wounds	Class 2 wounds and higher	Cephalexin 2g orally 30-60mins before surgery.	Endocarditis prophylaxis, oral, nasal mucosa, axillary and anogenital lesions, immunocompromised patients, below knee, hand surgery
Messingham S, 2005, (62)	Department of dermatology, Iowa City, Iowa	Class 1 and 2 wounds	Class 3 or 4 wounds	Not specified	Nasal or oral cavity breached, endocarditis
Nestor M(63) 2005	Centre for cosmetic enhancement, Florida	Class 1 wounds	Class 2 wounds and higher	Cephalosporin or dicloxacillin	Endocarditis prophylaxis

1.5 Antibiotic ointment use

1.5.1 Background/introduction

Some general practitioners may apply topical antibiotic ointment to sutured wounds to prevent infection after minor surgery. Although there is no data available on the frequency of this practice amongst GPs in Australia or internationally, a survey of plastic surgeons in the UK revealed that 66% used chloramphenicol eye ointment in their practice, mainly as prophylaxis against infection.(64) Other uses for antibiotic ointment in general practice include for the treatment of secondarily infected wounds,(65) otitis externa, treatment of secondarily infected eczema(65, 66) and the treatment of impetigo.(66) Antibiotic ointments may also have a role in accelerating wound healing in both acute and chronic situations.(67, 68)

In contrast to guidelines for the use of oral antibiotics as infection prophylaxis following minor dermatological surgery, there are no guidelines for the use of topical antibiotics in the same circumstances. The purpose of this sub-chapter is to review the evidence regarding the appropriateness and effectiveness of the use of antibiotic ointment as infection prophylaxis and possible side effects or adverse outcomes.

1.5.2 The ointments

There are several different antibiotic ointments used in clinical practice, some of which are used more commonly in different countries. The most frequently used of these are Chloromycetin, Neosporin and Bactroban. Chloromycetin ointment consists of 10mg/g of chloramphenicol, in plastibase 30W and liquid paraffin.(69) Neosporin ointment is also known as triple antibiotic ointment (TAO) in the USA. Each gram of Neosporin ointment contains polymixin B sulfate 5,000 units, neomycin sulfate 5mg and bacitracin zinc 400 units in a paraffin ointment base.(69) Bactroban ointment contains mupirocin and naturally occurring antibiotic.

Neosporin ointment has been available over the counter in the USA since the 1970s, while it has been confined to a prescription medication in Australia. It ceased to be available in Australia in October 2006, because of non-availability of an ingredient.(69)

Topical ocular Chloromycetin is widely used in the UK and Australia for the treatment of conjunctivitis, but is very rarely prescribed for this indication in the US.(70) There is little evidence for its effectiveness in prophylaxis or treatment of wound infection. Despite this, it is regularly used in areas outside its main indication. As well as being used for infection prevention, the ointment has been used as an adhesive for replacement of the nailbed.(71)

Table 1.7: Properties of antibiotic ointments in common use(66, 72)

Ointment	Trade name, availability	Mode of activity	Range of activity	Main use	Side effects/ additional considerations
Mupirocin	Bactroban	Inhibitor of bacterial protein synthesis	Gram +ve organisms, especially staph aureus	Impetigo, elimination of staph aureus from anterior nares	Anaphylaxis reported(73)
Bactitracin	Ingredient of TAO	Interferes with bacterial cell wall synthesis	Gram +ve organisms	Impetigo, furunculosis, pyodermas	Cross-sensitisation with neomycin
Polymixin B	Available singly, combined with bacitracin or in TAO	Disrupts bacterial cell membrane and increases cell permeability	Gram-ve organisms including P aeruginosa, Enterbacter and E Coli		Limited spectrum of activity
Neomycin	Available alone, or as ingredient of TAO	Interferes with bacterial cell wall synthesis	Aerobic gram +ve and gram –ve bacilli	Prevention of infection in superficial abrasions, cuts or burns	Allergic contact dermatitis
Polymixin B, neomycin and bacitracin	TAO	Combination of mechanisms	Range of gram +ve and gram –ve organisms	Prevention of infection in superficial abrasions, cuts or burns	
Erythromycin	Eryacne	Inhibitor of bacterial protein synthesis	Gram +ve cocci	Acne	Low incidence of sensitisation
Chloramphenicol	Chlormycetin or Chlorsig	Disrupts bacterial cell membrane	Wide range of gram +ve and gram –ve organisms	Bacterial conjunctivitis	

1.5.3 Infection prevention following surgery

Comprehensive Medline search identified a total of 5 randomised trials involving the use of antibiotic ointment as prophylaxis against wound infection following surgery.

Only one study was found relating to the use of topical chloramphenicol ointment on sutured wounds.(74) This study investigated the application of Chloromycetin ointment to wounds following hip replacement. The incidence of superficial wound infection in the intervention group was reduced (4% v 8%) but results should be viewed with caution as the sample size was small and the total number of infections analysed even smaller. Therefore although the results showed statistical significance, clinical significance would be questionable.

Two randomised studies involving Neosporin ointment were identified.(75) (76) One compared application of Neosporin, bacitracin zinc, silver sulfadiazine and paraffin ointment to uncomplicated clean-contaminated sutured wounds in an emergency department setting.(75). This was a positive trial which concluded that neosporin did significantly reduce the incidence of infection (4.5% v 6.6% v 12.1% v 17.6%), however, although the sample size was large, the number of infections involved was small and no sample size calculation was performed prior to this study. A second small pilot study found a similar rate of wound infection and adverse events between uncomplicated sutured soft tissue wounds treated with Neosporin ointment and bactroban (mupirocin) ointment (4% v 0%).(76)

Bacitracin zinc is one of the three antibiotic components of Neosporin ointment. An ointment containing only Bacitracin zinc was compared with white petrolatum ointment for incidence of infection, incidence of allergic contact dermatitis and wound healing in a large randomised controlled trial involving wounds following dermatological procedures.(77) The setting was a general outpatient dermatology clinic and a tertiary referral advanced surgical procedure clinic. The majority of these wounds were shave biopsies, and therefore non-sutured. Infection was lower in the Bacitracin zinc (intervention) group (0.9% v 2.0%) but, despite a sample size of 922 patients, with a total of only 13 infections, numbers were too small to be statistically significant. In addition there was no clinical significant difference in wound healing between the two groups on days 1, 7 and 28. There was no incidence of allergic contact dermatitis in the petroleum group, and four cases in the bacitracin group (0.9%). The study concluded that the low rate of infection and absence of allergic contact dermatitis in the white petroleum (control) group indicated that white petroleum is a safe, effective wound care ointment for ambulatory surgery.

A large randomised controlled trial conducted in Australia compared the application of bactroban (mupirocin) ointment to either paraffin ointment or no ointment to post-operative sutured wounds prior to application of an occlusive dressing.(78) Mupirocin did not significantly decrease the incidence of wound infection compared to sterile paraffin ointment or no ointment (2.3% intervention v 1.6% sterile paraffin, 1.4% no ointment.)

We have previously established in our literature that the rate of infection following dermatological surgery is generally very low (1-5%). In many trials investigating the application of antibiotic ointment after minor surgery, the total number of infections, which is the outcome being measured, is very small. Without attention to sample size calculation, type 2 (beta) error may occur in many of these studies, as the power is simply not sufficient to show a true difference in infection rate. We note that the greatest total number of infections analysed to determine the difference between two treatments was 32, and 42 when looking at the difference between four treatments.

Table 1.8: Randomised controlled trials investigating application of antibiotic ointment after skin surgery

Author and country	Setting and sample size	Wound type	Intervention and infection rate	Control and Infection rate	Significance
Dire et al 1995 USA(75)	Emergency department 426 army recruits. 70/30 M:F	Sutured clean contaminated wounds	Bactitracin zinc 6/109 (5.5%) neomycin 5/110 (4.5%) silver sulfadiazine 12/99(12.1%)	Petroleum 19/108 (17.6%)	P=0.0034
Smack et al 1996 USA(77)	Dermatology outpatients army medical centre 884 patients, 1,207 wounds	Minor dermatological surgical procedures	Bactracin zinc 4/444 (0.9%)	White petroleum 9/440 (2.0%)	P=0.37 (95% CE 0.4- 2.7)
Hood et al 2004 USA(76)	Emergency department 99 patients Mean age 24.7 M:F 70:30	Sutured clean contaminated wounds)	TAO 0/59 (0%)	Mupirocin 2/50 (4%)	P=0.5
Kamath et al 2005 UK(74)	Hospital inpatients post hip replacement 92 patients, mean age 78.6yrs 72:28 M:F	Sutured (clean) hip replacement wounds	Chloramphenicol 4/47 (8.5%)	No ointment 8/45(17.8%)	RR 0.430 95% CI 1.62-32.67
Dixon et al 2006 Australia(79)	Skin cancer surgeon outpatients, 778 patients, 1,801 wounds	Minor dermatological surgical procedures	Mupirocin 13/562 (2.3%)	Sterile paraffin 12/729 1.6%, No ointment 7/510 1.4%	P=0.490

1.5.4 Infection prevention in non-surgical wounds

A comprehensive Medline search identified two randomised controlled trials investigating topical antibiotics as infection prophylaxis in minor, non-sutured traumatic injuries.

The earlier trial investigated 59 well children age 2-5 years at a day care centre in Alabama, of which 75% were black.(80) In this randomised controlled double blinded study, triple antibiotic ointment (TAO) was compared to petroleum control ointment. Ointment was applied three times a day to insect bites or other minor breaks in skin. A total of 19 children developed infections: 4/27 in the intervention group and 15/32 in the control group. The antibiotic ointment was found to be significantly more effective than placebo in preventing impetigo in these children (15% intervention v 47% placebo).

In the second study, a topical antibiotic gel containing Cetrimide, Bacitracin and Polymyxin G sulfate was compared to Povidone iodine antiseptic cream and a placebo ointment containing a vehicle gel.(81) A sample group of 177 5-12 year old children attending five primary schools in Sydney were randomised to receive an assigned topical treatment applied to minor injuries such as scratches cuts and abrasions. There were only 9 resulting infections, 6/48 patients in the placebo group, 2/67 patients in the povidone iodine group and 1/62 patients in the antibiotic ointment group. The incidence of infection was significantly lower in the antibiotic gel intervention group than the placebo ointment group (12.5% v 1.6%). Incidence of infection was also lower in the povidone iodine group than the placebo group, (12.5% v 3.0%) but this did not reach significance. However the number of infections in this trial was very low and the results should be treated with caution.

Table 1.9: Randomised placebo controlled double blind studies of antibiotic ointment use on non-surgical wounds

	Setting and sample size	Wound type	Intervention and infection rate	Control and infection rate	Significance P value
Maddox et al 1985, (80) Alabama USA	Rural day care setting, 59 children	Minor skin trauma and abrasions	TAO (15%)	Petroleum (47%)	P=0.01
Langord et al 1997(81) Australia	5 Primary schools in Sydney, Australia, 177 children	Minor accidental injuries	Novel gel containing cetrimide, bacitracin and polymyxin B (1.6%)	1)Placebo ointment (12.5%) 2)Povidone iodine (3.0%)	P<0.05, 95% CI,0.011to0.207

1.5.5 Treatment of secondary infections

A comprehensive Medline search identified three trials in which antibiotic ointments were used to treat secondarily infected wounds (class 4). All of these trials showed topical antibiotic ointments to be equal or superior to oral antibiotics or antiseptics in the treatment of secondary infection.

In the earliest of these trials, Villiger et al(82) compared topical mupirocin ointment applied three times daily with orally administered flucloxacillin or, in patients allergic to penicillin, erythromycin. All patients were given 4 to 10 days' treatment. The majority of infections were impetigo or infected wounds or lacerations. Clinical response in the 101 patients with mupirocin ointment (86% cured, 13% improved, 1% failed) was significantly better than that seen in the 19 patients treated with erythromycin (47% cured, 26% improved, 26% failed) and similar to that with the 80 patients treated with flucloxacillin (76% cured, 23% improved, 1% failed). Overall, the outcome for the 99 oral antibiotic patients was significantly inferior to the 101 mupirocin patients ($p < 0.05$). When the flucloxacillin and erythromycin data were analysed separately, there was a significant difference between mupirocin and erythromycin ($p < 0.05$), but not mupirocin and flucloxacillin ($p > 0.05$). However, numbers of patients in the erythromycin group were small.

Bactroban cream was found to be as effective as oral cephalexin in the treatment of 706 patients with secondarily infected minor wounds.(65) Neosporin ointment was found to be superior to antiseptics or a wound protectant in eliminating infection in blister wounds deliberately infected with staph aureus.(83)

Leyden et al(83) produced a group of six blisters, three on each of the forearms of volunteers by applying ammonium hydroxide, which caused a dermal blistering reaction. The wounds were then inoculated with staphylococcus aureus. The groups of three blisters were randomised to be treated with either TAO, no treatment (control) or a comparative treatment. The comparative treatments consisted of antiseptics: iodine and benzalkonium chloride, thimerosal, hydrogen peroxide, camphor and phenol, merbromin: a wound protectant (Johnson and Johnson first aid cream): and polymixin-B-bacitracin which is an antibiotic ointment containing two of the three antibiotics in TAO. The blister wounds treated with TAO healed significantly faster than those treated with benzalkonium, hydrogen peroxide, camphor phenol and iodine and those receiving no treatment. Interestingly there was no significance difference in healing times between TAO and the wound protectant, which has no antibacterial activity). The overall clinical appearance

and healing rates of wounds treated with TAO were ranked to superior to all other treatments except the polymyxin-B-bacitracin. However it is noted that all wounds ultimately healed.

Bactroban was also found to be significantly more effective than erythromycin and as effective as flucloxacillin in 200 patients presenting with minor skin infections (mainly impetigo and infected wounds/lacerations) in general practice.(82)

In the most recent study, Kraus et al(65) reported the combined results of two randomised controlled trials with a total of 53 participating centres in the US. Patients of any age presenting with secondarily infected wounds, such as small laceration, abrasion or sutured wound were eligible to participate. Patients were randomised to either receive topical mupirocin or oral cephalexin for 10 days. All patients received a placebo in the alternative dosage form. A total of 706 patients were recruited in this trial, 630 completed the trial and 478 were considered evaluable for clinical efficacy (only if they had a pre therapy pathogen identified). The primary end point was 'clinical response', which was defined as complete resolution or sustained improvement of signs and symptoms of infection. Clinical recurrence was defined as reappearance or worsening of signs and symptoms of infection, and unable to determine was defined as the inability to make a valid assessment of the clinical outcome. Results using patients evaluable for clinical assessment showed a successful clinical outcome in the mupirocin group of 233/45 95.1%, and 22/233 95.3% in the cephalexin group. Intention to treat results were 296/357 (82.9%) in the mupirocin group and 289/349 (82.8%) in the cephalexin group.

Table 1.10: Randomised controlled studies investigating antibiotic ointment in the treatment of infected wounds

	Setting and sample size	Blinding	Wound type	Intervention and outcome	Control and outcome	Outcome
Villiger et al 1986(82)	Primary care 200 patients	Unblinded	Impetigo/ infected lacerations	Mupirocin 86% cured	1)Flucloxacillin 76% cured 2)erythromycin 47% cured	Response to mupirocin ointment significantly better (p<0.05) than erythromycin and not significantly different to (p>0.05) flucoxacillin
Leyden et al 1987(83)	Human –model study	Unblinded	Blisters intentionally inoculated with staph aureus	TAO Mean 9 days to healing	No treatment mean 13.3 days to healing	Wounds treated with TAO healed significantly faster p<0.05
Kraus et al 1998 USA(65)	Primary care 706 patients between two identical RCTs	Double blinded	Secondarily infected lacerations and abrasions	Mupirocin 95.1% cure rate	Cephalexin 95.3% cure rate	Significantly equivalent p=0.89, 95% CI-4.0%-3.6%

1.5.6 Other uses for antibiotic ointment in wound management

It is worth noting that inert petroleum, the vehicle in most antibiotic ointments, may have wound healing and infection prevention properties.(77, 84) This is likely to be caused by liberal application as this provides a degree of occlusion, and occlusive dressings have been shown to shorten wound healing time(85) and provide a barrier against physical infection. Inert petroleum also prevents adherence to dressings.(77) Studies have also shown antibiotic ointments accelerate wound healing times.(86)

Neosporin ointment has been found to be safe, effective and significantly better than simple gauze dressing alone, in minimising the appearance of scars resulting from clean dermabrasion wounds.(68). Topical antibiotics may also be effective in aiding the healing of chronic wounds and ulcers.(87)

1.5.7 Antibacterial effects and antibiotic resistance

In one study, antimicrobial treatment including antiseptics and antibiotic ointment were shown to eradicate bacteria from the skin surface when applied topically.(88) Mupirocin and TAO ointment were also shown to eradicate bacteria from the multiple keratinised layers of the stratum corneum and in addition mupirocin prevented repopulation with resident flora.(88)

There is some concern regarding the overuse of topical antibiotics resulting in antibiotic resistance. Australian guidelines suggest that topical antibiotic use be restricted because of the capacity of most topical drugs to select resistant micro-organisms and to cause sensitization.(66) The guidelines also suggest that antimicrobials recommended for topical use are selected from classes not in use for systemic therapy.(66)

There is a contrary argument that the potential for antimicrobial resistance with topical antibiotics is actually lower than with systemic antibiotics because of the higher local concentration achieved by topical delivery.(72) Patterns of antimicrobial activity and resistance have been examined in vivo for neomycin and mupirocin containing ointments. In one trial, neomycin plus bacitracin was associated with the rapid emergence of drug- resistance organisms in vitro whereas topical silver nitrate was not.(89) However Neosporin ointment has also been shown to have a wider spectrum of antibacterial activity compared with mupirocin and to be usable against mupirocin resistant Gram-positive strains.(90) Chloramphenicol eye drops have been shown to be effective in the treatment of MRSA ocular surface infections.(91)

There is no evidence after more than three decades of extensive use worldwide that, with the exception of mupirocin, topical antibiotics administered on an outpatient basis contribute to any emerging resistance pattern. Increased use of mupirocin has been associated with the emergence of resistance, which has been reported both for MRSA (methicillin resistant staphylococcus aureus) and MSSA (methicillin susceptible staphylococcus aureus). The problem seems to be associated with prolonged treatment.(92, 93)

1.5.8 Adverse effects

Contact dermatitis

There is some concern about the incidence of allergic contact dermatitis with topical neomycin use. This has been shown to be as high as 11% in a population referred for diagnostic patch testing.(94) However there is some evidence that the incidence of this reaction is as low as 1% when the ointment is used in the general population.(95) The reaction is much more common amongst subjects previously exposed to neomycin ointment.(95) Contact allergy has been reported with the use of chloramphenicol ointment but the incidence is thought to be low.(96, 97)

Other adverse outcomes

There is some controversy regarding the link between aplastic anaemia and topical ocular chloramphenicol.(98, 99) There have been a small number of case reports, most of which involved prolonged use.(70) However two international case control studies provided no support to the claim that chloramphenicol eye drops increase the risk of aplastic anaemia.(100) Previous literature provided only weak support to causality based on a few single case reports. Although an association between ocular chloramphenicol and aplastic anaemia cannot be excluded, the risk was estimated to be less than one per million treatment courses.(100) As the baseline incidence of aplastic anaemia in the population is three per million it is difficult to establish any causality.(101)

There has been a report of anaphylaxis in one patient following the application of bactroban ointment.(73)

1.5.9 Conclusion: Should we use topical antibiotics to sutured wounds to prevent infections?

Antibiotic prophylaxis is probably prescribed excessively and inappropriately following dermatological surgery,(49, 62) and is thought best reserved for high risk patients. In contrast to the existing guidelines for the use of oral antibiotics prior to dermatological surgery discussed in Chapter 1.5, there are no existing guidelines for the prophylactic use of topical antibiotics.

Despite widespread use, there is very little evidence available regarding the effectiveness of antibiotic ointment in preventing infection following minor surgery. One reason for the lack of evidence is, that the low risk of infection after clean surgery means that studies of more than 1,000 procedures (sometimes many more) are required to reliably detect a reduction in infection.(102) There is some evidence of a 50% reduction in risk from use of prophylactic oral antibiotics following clean surgery.

Even if more evidence for efficacy became available, the decision to prescribe antibiotic prophylaxis is complicated and in addition to efficacy, antibiotic costs, adverse effects and resistance should be taken into account. However, in some circumstances, topical delivery of antibiotic may be preferably to systemic administration.

If evidence for effectiveness becomes available, it might be justified to consider prophylaxis with antibiotic ointment in situations where incidence of infection is expected to be greater than 5%.

1.6 Conclusion of literature review

This literature review firstly reviewed the incidence of BCC, SCC and melanoma in Australia, in order to set the background of this thesis. Although less dangerous and less life-threatening than cutaneous melanoma, SCC and BCC are still invasive cancers, and SCC is capable of metastasing.(29) Because there is generally no registry style information available in Australia, and because alternate methods of measuring incidence rates have many influencing factors, it is difficult to accurately quantify incidence rates. Australia has one of the world's highest incidences of melanoma, although accurate data are limited by time delays in reporting incidence rates.

A review of number needed to treat (benign and dysplastic naevi excised per melanoma), often used as a marker of quality of skin cancer management, was found to be between 11 and 29.9 for Australian GPs when based on melanomas and naevi only and up to 36 when seborrhoeic keratoses were included.(35, 40, 42-44) A review of studies recording incidence of surgical site

infection after dermatological surgery showed an infection rate of 1.9-2.8%, with higher rates of infection in certain sub-groups. Finally, most studies of antibiotic ointments used in the prophylaxis of infection after clean dermatological surgery found no evidence for efficacy, although a study of clean-contaminated wounds showed some significant difference in infection rates. It was discussed that several of these studies may have been significantly under-powered. There appears to be more evidence for use of antibiotic ointment in the treatment of secondary infections.

This literature review illustrated that there is a high incidence of skin cancer in Australia and in particular North Queensland. It is therefore important that skin cancer is managed optimally by Australian GPs. This led to the thesis focusing on surgical management and diagnosis of skin cancer.

The literature review revealed that there is limited published data which identifies groups at high risk of infection after minor surgery. It is important to establish these high risk groups in order to optimize antibiotic prophylactic management.

CHAPTER 2: RISK FACTORS FOR WOUND INFECTION AFTER MINOR SURGERY

2.1 Background

This chapter analyses the incidence of infection following minor surgery (class 1) conducted by general practitioners in Mackay, and compares this incidence with other studies involving similar patient groups from different geographical locations. Multivariate analysis examines risk factors for infection. The published article appears in Appendix 1.(57)

In the introduction it has been discussed that there is limited data regarding surgical site infection after dermatological surgery and limited data regarding risk factors for infection. There is debate about the role of antibiotics prior to skin lesion excision, and also limited guidelines about this issue. A better knowledge of risk factors for surgical site infection is therefore required in order to predict circumstances in which a high incidence of infection is likely.

It is a secondary analysis of data generated from the 'Can sutures get wet' intervention study described in the introduction.

2.2 Introduction

Surgical site infection following minor surgery contributes to patient morbidity and compromises the cosmetic outcome. Most data regarding incidence and predictors of surgical site infection are based on hospital studies.(47, 49, 51) Of studies looking at infection rates following minor dermatological surgery in an out of the hospital setting, most have been conducted in specialist dermatology clinics.(52-54) On the other hand, the quality of evidence with regard to infection rates following minor surgery in a general practice setting seems to be poor(103) and a comprehensive Medline search revealed only one study which adequately recorded the incidence of infection following minor surgery in a general practice setting.(56)

In north Queensland, the majority of suspicious skin lesions are managed by general practitioners (GPs),(38) particularly in rural centres such as Mackay where there is no resident dermatologist. Skin excisions form a large proportion of a typical Australian GPs workload, and this proportion is even greater for Queensland GPs.(5) There is evidence that performing minor surgery in general practice is cost effective compared with a hospital setting.(104) It is

therefore important that there is adequate data available regarding incidence of and risk factors for complications such as infection following minor surgery in a general practice setting.

The data from the present study was collected incidentally as part of a randomised controlled trial which compared the standard management of keeping wounds dry and covered with allowing wounds to be uncovered and wet in the first 48 hours following minor surgery.⁽⁷⁾ As both arms of the trial showed equivalent infection rates at the 5% significance level (8.4% in the intervention group and 8.9% in the control group) they have been considered as a single group for the purpose of this study and analysed together. Explicitly, both arms of the study, both the control and the intervention group, were considered as a single group and analysed together in this study. The aims of this study were to determine the incidence of and risk factors for surgical site infections following minor skin excisions in a primary care setting.

2.3 Methods

Our prospective study of patients presenting for minor skin excisions was conducted initially as a randomised controlled trial. It is important to describe the methods used for this trial in order to fully understand the secondary analysis of the data that was generated for this chapter. I will therefore now provide a detailed description of the methods used.

2.3.1 Study design

We carried out a randomised controlled, multi-centre trial involving patients presenting for minor skin excisions.

2.3.2 Setting and participants

Nineteen general practitioners (GPs) from four practices in the Mackay area, tropical North Queensland, Australia (latitude 21°S; inhabitants of Mackay area approximately 75,000) participated. The GPs were a self-selected group who attended a monthly evidence based medicine meeting. Data collection took place from October 2004 to May 2005. Consecutive patients presenting for minor skin excisions were invited to take part in the trial. Practice nurses were responsible for recruiting patients and collecting data. Demographic information was collected regarding all patients, as well as clinical information regarding presence or absence of diabetes, or any other significant medical condition (such as peripheral vascular disease, anaemia, chronic obstructive airways disease). A body site map was used to define excision site. At the end of the study practice nurses were asked to re-examine computer records to fill in any

missing data. The principal researcher visited participating GPs and practice nurses to provide training and ensure that recording was standardised.

All patients participating were provided with an information sheet, and were asked to give signed consent. Patients consenting to participate were given written instructions regarding post-operative wound care.

2.3.3 Eligibility criteria

All patients presenting to a participating GP for 'minor skin excision' except for skin excisions on the face were eligible to participate in the study. Patients who were already taking oral antibiotics, or who were on immunosuppressive drugs were excluded from the study. Further exclusion criteria were lacerations, having a flap or 2 layer procedure (tying a 'bleeder' did not count as 2 layer), excision of sebaceous cyst, and skin excision on the face. These exclusions were made in an attempt to standardise the type of wound being studied, and reduce the number of confounding factors.

Patients whom oral or topical antibiotics were clinically indicated immediately postoperatively were also excluded from the study. Specifically, these were patients for whom antibiotics were indicated because of bacterial endocarditis prophylaxis, joint replacement,(105) or patients for whom antibiotics were usually prescribed when they had previously undergone a skin excision. For the purposes of this criteria, 'usually' was defined as in 50 >% of previous skin excisions. At the time of this trial no guidelines existed for the use of antibiotics for infection prophylaxis after minor surgery, so we therefore had to decide on our own criteria for this purpose. The results of our trial have now been used to develop criteria for this medical situation.

2.3.4 Surgical wound management protocol

A workshop took place attended by participating GPs to develop guidelines to ensure that excisions were managed in a standardised manner. The following procedure was agreed upon:

1. Skin preparation – normal saline
2. Usual sterile technique (standard precautions) including sterile gloves
3. Local anaesthetic - type and volume recorded
4. Suture material – nylon – size recorded

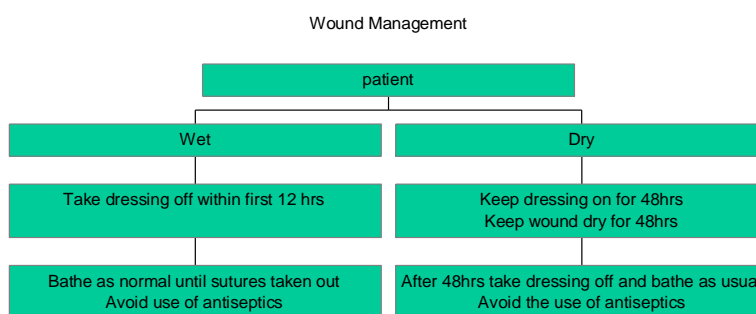
5. No antibiotics, either topical or oral- (if required, or already prescribed exclude from study). No topical antiseptics eg betadine or alcohol. No antiseptic washes or medicated soaps.
6. Dressing type – melolin and tape
7. Removal of sutures (ROS) according to site:
 - Back – 10 days
 - All other sites – 7 days

2.3.5 Intervention

Patients were provided with oral and written instructions regarding post-operative wound management. The dry group were asked to leave the dressing on and keep dry for the first 48 hours, then bathe and undress as normal until sutures were taken out (Figure 2.1). They were asked to avoid the use of antiseptic washes or soaps.

The wet group were asked to take the dressing off within the first 12 hours then bathe as normal until the sutures were taken out. It was felt that patients should leave the GP surgery with a dressing to absorb immediate bleeding, however it was also felt that defining an exact time to remove the dressing would be unrealistic, so ‘within 12hrs’ was considered a reasonable request. They were also asked to avoid the use of antiseptic washes and soaps.

Figure 2.1: Wound management



2.3.6 Clinical outcomes

Wounds were assessed for infection by a practice nurse or doctor on the day of removal of sutures or sooner if the patient re-presented with a perceived infection. Our definition of wound infection was adapted from standardised surveillance criteria for defining surgical site infections (SSI) developed by the Centre for Disease Control's National Nosocomial Infection

Surveillance System (Table 2.1).(49) All participating doctors and nurses were briefed regarding the definition of infection by the primary researcher, and were also given written information.

Table 2.1: Definition of surgical site infection

1) Infection must be within 30 days of excision
2) a) There must be purulent discharge from the wound or
b) The GP must diagnose a wound infection
or
c) The GP commences antibiotics
3) Stitch abscess must not be counted as an infection

2.3.7 Sample size

Sample size was calculated on the basis of a pilot study conducted February to June 2004 involving 543 patients, which showed an overall infection rate of 5.7%. Based on a projected infection rate of 5%, we decided that an increase in incidence of infection of 5% would be clinically significant. To come to this conclusion with statistical confidence a power of 80% and a significance level of 0.05 using a one-sided equivalence test of proportions, a total of 357 patients were required in the intervention group and 357 patients in the control group.

2.3.8 Randomisation

All patients provided written informed consent before enrolling in the study. After agreeing to participate, patients were randomised by picking a ball out of a hat. This method of randomisation was chosen by the practice nurses because of ease and acceptability. The practice nurse enrolled patients and assigned participants to their groups. No blinding took place.

2.3.9 Statistical analysis

We based all analysis on the intention-to-treat principal. Differences between categorical variables were compared using Chi-square tests. Numerical and categorical variables were compared using unpaired t-tests. To decide on non inferiority the one-sided 95%-confidence interval of the difference of infection rates was calculated and compared with the maximum allowable difference of 5%. P-values less than 0.05 were considered to be statistically significant.

Both arms of the study, both the control and the intervention group, were considered as a single group and analysed together in this study. The statistical analysis takes the cluster sampling design (four doctors' practices) into account. Incidence of infection is given together with a 95%-confidence interval (95%-CI). Numerical data was summarized using mean values and standard deviations (\sqrt{SD}) when approximately normally distributed or median values and inter-quartile ranges (IQR) when skewed. Bivariate comparisons were conducted using Chi-square tests (two categorical variables) and unpaired t-tests or non-parametric Mann-Whitney Wilcoxon tests (categorical and numerical variable). Generalized linear modelling was used to identify independent risk factors of infection after minor surgery. Relative risks together with 95%-confidence intervals were estimated using binomial distribution and the logarithmic link function. All variables that were not part of the final model (that is: age, gender, month excision took place, management of wound, and significant medical condition other than diabetes) were assessed for potential confounding of the relationships between body-site of skin lesion, histology of skin lesion, and diabetes with wound infection. Throughout the analysis p-values less than 0.05 (two-sided hypotheses) were considered to be statistically significant. The statistical analysis was conducted using SPSS for Windows, release 12 and STATA for Windows, release 8.

2.3.10 Ethics

Ethics approval was granted by the James Cook University ethics committee - Approval number H1902.

Having described the methods of the 'Can sutures get wet' trial, I will now continue to describe the statistics used in the secondary data analysis of the current chapter.

2.4 Results

2.4.1 Practice and study characteristics

Participating GPs were younger (median age 44 years) and more predominantly female (64%) than average for Australian GPs (modal age category 45-54 years; 32% female). Of the total of 1,247 patients who attended for skin excisions during the collection period from October 2004 to May 2005, 377 patients were excluded (294 were ineligible and 83 non-participants) (Table 2.2).

There were no significant differences in the age (participating: 56.3 years of age (± 16.5); not participating: 58.1 years of age (± 16.2); $p=0.208$) and gender (participating: 47.6% female; not

participating: 44.9% female; $p=0.407$) of participating and excluded patients. A total of 13 participants were eventually lost to follow up. Follow up was completed in 857 (98.5%) patients.

Table 2.2: Reasons for exclusion of 377 patients from study

	Reason	N	% Of excluded
Ineligible	Face	256	20.5
	Biopsy	10	0.8
	Flap	17	1.4
	Immunosuppressed	1	0.1
	Antibiotics	5	0.4
	Not returning for removal of sutures**	5	0.4
Non-participation	Refused	67	5.4
	Forgot*	16	1.3
	Total	377	30.3

*The practice nurse forgot to invite these patients to participate;

**These five patients knew that they would not be able to return for the removal of sutures.

2.4.2 Infections

Infection occurred in 74 of the 857 excisions (8.6%; 95%-CI = [3.5, 13.8]) (Table 2.3). Infection rates for the four centres were 2.9%, 7.8%, 10.0%, and 10.2% ($p=0.0496$). Of all characteristics recorded, only the presence of diabetes was significantly correlated with the higher incidence of infection (18.2% compared to 8.4%; $p=0.019$) (Table 2.3). Participants older than 60 years had a higher incidence of wound infection (12.4%) compared to younger participants (5.6%), however this difference was not significant ($p=0.056$). Squamous cell carcinomas (SCCs) were most prone to be infected (13.5%), while benign naevi (2.5%) and seborrheic keratoses (0%) were least likely to become infected. Of the 74 infections, 25 (33.8%) occurred on the lower leg (below knee) or foot. There was little variation in incidence of infection with the month of year in which the excision took place with no evidence of increased infection during the hotter wet season ($p=0.527$). There was no significant difference in time to removal of sutures between the infected and non-infected groups (median time 8 days, IQR = [7, 10] for both groups, $p=0.538$).

Table 2.3: Bivariate correlates between infection after minor surgery and participants' and lesions' characteristics in 857 patients recorded in Mackay, Australia

Characteristic	Incidence of infection (74/857)	p-value
Age		p = 0.057
≤ 40 years	6.2%	
41 – 50 years	4.8%	
51 – 60 years	5.8%	
61 – 70 years	12.2%	
> 70 years	12.7%	
Gender		p = 0.135
Male	10.2%	
Female	6.9%	
Body site		p = 0.072
Scalp and neck	10.6%	
Trunk	5.3%	
Arms and hands	6.8%	
Thighs	14.0%	
Legs and feet	15.0%	
Histology of lesion		p = 0.118
Melanoma	7.7%	
Basal cell carcinoma	11.4%	
Squamous cell carcinoma	13.5%	
Benign naevus	2.5%	
Dysplastic naevus	10.5%	
Seborrhoeic keratosis	0%	
Solar keratosis	9.6%	
Other	3.4%	
Date of excision		p = 0.527
Wet season (December to February)	9.3%	
Dry season	8.3%	
Presence of diabetes		p = 0.019
No	8.4%	
Yes	18.2%	
Presence of other medical condition*		p = 0.324

No	8.3%
Yes	22.2%

*Medical conditions recorded were COPD(8), anaemia(1), 'aspirin'(2), 'steroids'(3), 'warfarin'(2), ischaemic heart disease (1), and peripheral vascular disease (1). Results were adjusted for the cluster sampling design.

Multivariable generalized linear modeling showed that the body sites legs and feet ($p=0.009$) and thighs ($p=0.005$), the histological subtypes BCC ($p=0.006$), and SCC ($p=0.002$), and prevalence of diabetes ($p<0.001$) were independently correlated to wound infection (Table 2.4).

Table 2.4: Correlates of participants' and lesions' characteristics with infection after minor surgery. Results of multivariable generalised linear modeling based on 857 patients from Mackay, Australia

Characteristic	Without infection (n=783)	With infection (n=74)	Relative risk	95%-CI*	p-value
Age					
≤ 40 years	151	10	1		
41 – 50 years	139	7	0.67	[0.37, 1.2]	0.190
51 – 60 years	162	10	0.69	[0.42, 1.1]	0.139
61 - 70 years	166	23	1.4	[0.66, 2.8]	0.406
> 70 years	165	24	1.2	[0.62, 2.5]	0.534
Gender					
Female	380	28	1		
Male	403	46	1.3	[0.84, 2.0]	0.232
Histology					
All other	467	28	1		
BCC**	124	16	2.1	[1.3, 3.4]	0.004
SCC***	192	30	1.8	[1.3, 2.6]	< 0.001
Body site					
All other	598	42	1		
Legs and feet	142	25	1.9	[1.1, 3.1]	0.019
Thighs	43	7	2.2	[1.3, 3.6]	0.002
Diabetes Mellitus					

No	765	70	1		
Yes	18	4	1.7	[1.4, 2.2]	< 0.001
Date of excision					
Dry season	521	47	1		
Wet season	262	27	1.1	[0.72, 1.6]	0.723
Presence of other medical condition [#]					
No	769	70	1		
Yes	14	4	2.2	[0.43, 10.9]	0.353
Wound management					
Dry group	378	37	1		
Wet group	405	37	0.95	[0.78, 1.1]	0.577

*95%-CI = 95%-Confidence interval; **BCC = basal cell carcinoma; ***SCC = squamous cell carcinoma. [#] Other medical conditions recorded were COPD(8), anaemia(1), 'aspirin'(2), 'steroids'(3), 'warfarin' (2), ischaemic heart disease (1), and peripheral vascular disease (1). The model was adjusted for the cluster sampling design and for the confounding effects of age and gender of the participants. Date of excision, presence of other medical condition, and wound management were not part of the model.

2.5 Discussion

The results of the present study suggest that diabetes, excisions from the lower leg and foot or thighs, and excisions of non-melanocytic skin cancer (SCC and BCC) are independent risk factors for infection after minor surgery. The latter finding is consistent with a study conducted in a specialist dermatology clinic setting which suggested that oncological surgery (excision of skin cancer) is associated with a higher risk of infection.(55) Body extremities, with reduced blood supply have also previously been associated with a higher incidence of infection.(55)

The overall incidence of infection in our study of 8.6% was higher than we expected from published literature looking at a similar general practice cohort (1.9%)(56) and a similar dermatology clinic cohort (2%).(52) However exclusion of facial excisions from our study, which may have a lower incidence of infection,(55) may have falsely elevated our overall incidence of infection. Excluding those for whom antibiotics would

otherwise have been indicated post-operatively would, however, have lowered the infection rate. A German study in a university medical centre setting reported a more comparable infection rate of 8%.⁽⁵⁴⁾ It is difficult however to compare the infection rate between different studies as different variables and methods were used.⁽⁵³⁾

The present study did have several limitations. There are various characteristics influencing the occurrence of infections and although information on as many variables as possible was recorded, it proved difficult to ensure that all possible predictors of infection were recorded. There was inadequate data recorded on suture size and occupation, and consequently, these factors could not be compared. We did not record smoking, which may be a risk factor for surgical site infections.^(49, 106) We also did not record the size of lesion excised, excision margins or overall wound area, and therefore are unable to exclude that the increase in incidence of infection recorded for SCCs and BCCs could be related to the size of the overall wound area rather than the histology. However there is some evidence that more complicated procedures (flaps or skin grafts) are associated with an increased infection rates rather than the size of the excision.⁽⁵²⁾ Exclusion of facial excisions and more complicated surgery such as flap or two level procedures prevented analysis of infection rates in these subgroups, and subsequent comparisons.

Although diabetes was found to be independently correlated to wound infection, the prevalence of diabetes as well as other medically important conditions was probably under-recorded, and power was limited to analyse these subgroups.

Surgical training and technique of the GPs involved is a potential confounder which would be difficult to quantify and was not recorded.

The diagnosis of infection, even when using guidelines, is still subjective and it has been shown to have inter and intra-observer variation.⁽¹⁰⁷⁾ The definition of infection we used certainly has limitations, however it is the most widely implemented standard definition of wound infection⁽¹⁰⁷⁾ and was as close to a gold standard as we could find. We have no evidence to support intra and inter-practice reproducibility of measurement and recording procedures.

In addition, there are some limits to generalizing these findings. The GPs involved were not representative of Australian GPs, being younger and more predominantly female.(108) The population of Mackay is slightly older and has a lower median household income than the Australian population.(109) Mackay is a provincial town in tropical north Queensland and has a hot and humid climate with the mean daily maximum temperature ranging between 24.2 and 30°C during the summer months, and a relative humidity of 75-79%.(110) It is possible therefore that these findings may not be generalize-able to a temperate climate, although there is no published evidence that heat and humidity increase infection rates.

Antibiotic prophylaxis is probably prescribed excessively or inappropriately for dermatological surgery(49, 62) and is thought to be best reserved for high risk patients.(10, 62) There is no data available on the current prescribing habits of Australian GPs regarding antibiotic prophylaxis for minor excisions. Although there is also no evidence available regarding what reduction in the rate of infection we might reasonably expect from the use of prophylactic antibiotics for minor excisions, there is some evidence of a 50% reduction in risk of infection when perioperative antibiotic prophylaxis is used following clean surgery.(102) In addition to efficacy, antibiotic costs, side-effects and resistance must be considered when considering their use prophylactically. However results of this study could encourage the more judicious use of prophylactic antibiotics by defining high-risk groups for infection in a general practice setting, such as diabetics and those undergoing excision of a non-melanocytic skin cancer or excision from the lower limb. Alternatively, other non-pharmaceutical interventions aiming to reduce infection rate could be targeted towards these high risk groups.

2.6 Summary

This study found a high overall incidence rate of infection of 8.6%.

Excisions from lower legs and feet or thighs excisions of BCC or SCC and diabetes ($p < 0.001$) were found to be independent risk factors for wound infection. The results of this study could encourage the more judicious use of prophylactic antibiotics by defining these high-risk groups in a general practice setting, such as diabetics and those undergoing excision of a non-melanocytic skin cancer or excision from the lower limb.

The high incidence of infection in this trial provided stimulus to study an intervention to prevent surgical site infection, as an effective intervention would be useful to reduce this high rate of surgical site infection (see chapter 3). Additionally, the large number of infections occurring

following minor surgery conducted by general practitioners in Mackay would mean that attaining a meaningful sample size according to a sample size calculation designed to avoid type 2 errors is feasible.

CHAPTER 3: DOES APPLICATION OF CHLORAMPHENICOL OINTMENT TO SUTURED WOUNDS DECREASE THE INCIDENCE OF WOUND INFECTION?

3.1 Background

The literature review demonstrated that there is insufficient evidence for the efficacy of topical antibiotic ointment in the prophylaxis of wound infection after minor surgery.

This chapter describes a large randomised controlled trial which explores the effectiveness of an intervention, topical chloramphenicol ointment to reduce infection after minor surgery conducted in general practice. The published article forms Appendix 2.(111)

The objective of the trial was to establish evidence for the application of antibiotic ointment to sutured wounds. If the chloramphenicol ointment was found to be effective this could potentially decrease the incidence of infection following minor surgery in general practice. If the ointment was found not to be effective this could decrease the over use of topical antibiotic ointment and consequence adverse outcomes.

It was also hoped that this study would benefit GP researchers by providing more familiarity with the process of undertaking a practice based clinical trial. It was also hoped that it would benefit general practice knowledge by establishing evidence for the application of antibiotic ointment to sutured wounds.

3.2 Introduction

Chloromycetin[®] ointment consists of 10mg/g of chloramphenicol, in plastibase 30W(112) and soft white and liquid paraffin.(69) Chloramphenicol has a broad spectrum of activity against gram positive and gram negative bacteria, rickettsias and chlamydia.(66) Chloramphenicol ointment is indicated for treatment of bacterial conjunctivitis; however there is little evidence for its effectiveness in prophylaxis or treatment of wound infection. Despite this, it is regularly used in areas outside its main indication. Prior to our study, several of the investigating GPs had applied it to sutured wounds as prophylaxis against wound infection. A survey of UK plastic surgeons reported that 66% used chloramphenicol eye ointment in their practice, mainly as prophylaxis against infection.(64) The ointment has been used as an adhesive for replacement of

the nailbed.(71) A comprehensive Medline search found only one other study relating to the use of topical chloramphenicol ointment on wounds. This study investigated the application of chloramphenicol ointment to wounds following hip replacement.(74) The incidence of wound infection in the intervention group was reduced (4% versus 8%) but the sample size was small and the results not statistically significant.

Topical ocular chloramphenicol is widely used in the UK and Australia for the treatment of conjunctivitis, but is very rarely prescribed for this indication in the US.(70) There was previously some controversy regarding the link between aplastic anaemia and topical ocular chloramphenicol, based on a small number of single case reports,(70) however two international case-control studies provided no support for this association. Although the association between ocular chloramphenicol and aplastic anaemia cannot be excluded, the risk is less than one million per treatment course.(100) There have been no incidences of aplastic anaemia following dermatological application reported, despite widespread use.

A prior study of wound infection following minor surgery involving GPs in Mackay, Queensland, showed an overall incidence of wound infection of 8.6%.(7, 57) This incidence was higher than expected based on published results of a similar Australian general practice cohort (1.9%),(56) a skin cancer clinic cohort (1.5%)(113) and of a European dermatology clinic cohort (2%).(52) The acceptable rate of infection following clean minor surgery is suggested as less than 5%.(47, 48, 58) A low risk of infection after clean surgery means that studies of more than 1,000 procedures (sometimes many more) are required, under normal circumstances, to detect a reduction in infection from an intervention with statistical confidence.(102) Because of the high incidence of infection in our patient cohort, and high minor surgery workload,(114) we decided to utilise the increased capacity to investigate a strategy to reduce infection rate. The present trial sought to establish the effectiveness of topical chloramphenicol ointment in preventing wound infection after dermatological surgery. We used the Chloromycetin® brand of chloramphenicol ointment, and this was applied as a single dose post-operatively, with paraffin ointment used as placebo control.

3.3 Methods

3.3.1 Study design

We carried out a randomised controlled double blind, multi-centre trial involving patients presenting for minor skin excisions. The study was approved by the James Cook University ethics committee (approval number H2590).

3.3.2 Setting and participants

The study was conducted in three private general practices in Mackay, Queensland (latitude 21E8S; inhabitants 67,000), between June 2007 and March 2008. One of the participating practices consisted of one general practitioner working in an ‘open access’ designated skin cancer clinic. Fifteen doctors working in the three practices recruited between one and 200 patients.

The GPs were purposely selected as working at practices that had previously successfully participated in a wound management project.⁽⁷⁾ Consecutive patients presenting for minor skin excisions were invited to take part in the trial. Practice nurses were responsible for recruiting patients and collecting data. Demographic information was collected regarding all patients, as well as clinical information regarding presence of diabetes, or any other predetermined significant medical conditions. A body site map was used to define excision site. At the end of the study practice nurses were asked to re-examine computer records to fill in any missing data. The principal researcher visited participating GPs and practice nurses to provide training and ensure that recording was standardised.

3.3.3 Eligibility criteria

All patients presenting to a participating GP for ‘minor skin excision’ from all body sites were eligible to participate in the study. Skin flaps and two layer procedures were recorded and included. Patients who were already taking oral antibiotics, for whom oral or topical antibiotics were clinically indicated immediately postoperatively, or who were on immunosuppressive drugs were excluded from the study. Other exclusion criteria were excision of sebaceous cyst, history of allergy to any of the ingredients of Chloromycetin[®] ointment and personal or family history of aplastic anaemia.

3.3.4 Surgical wound management protocol

We ran a workshop for participating GPs to develop guidelines to ensure that excisions were managed in a standardised manner. We were unable to reach consensus regarding skin preparations, so normal saline was used at one centre and chlorhexidine at two centres. The following procedure was agreed upon:

1. Skin preparation – normal saline or chlorhexidine
2. Usual sterile technique (standard precautions) including sterile gloves

3. Local anaesthetic - type and volume recorded
4. Suture material – nylon – size recorded
5. Dressing type – melolin and tape
6. No antibiotics, either topical or oral- (if required, or already prescribed, exclude from study). No topical antiseptics, such as betadine or alcohol. No antiseptic washes or medicated soaps.
7. Removal of sutures (ROS) according to body site: Back – 10 days; All other sites – seven days.

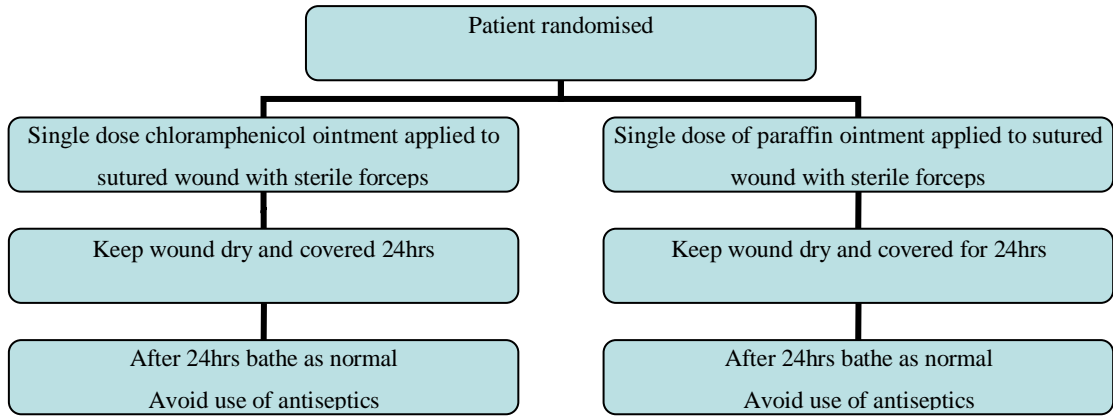
3.3.5 Intervention

Information about the exact proportions of the constituents of the base of Chloromycetin[®] ointment was not obtainable from the manufacturer. The principal investigator visited a compounding pharmacist to develop a close match to the vehicle of the Chloromycetin[®] ointment using a mixture of soft white and liquid paraffin. Single doses of the ointment were prepared in sterile jars and stored in a refrigerator. Immediately after suturing, either paraffin ointment or chloramphenicol ointment was applied to the sutured wounds using sterile forceps. Sufficient ointment was applied to cover the surface of the wound.

3.3.6 Recruitment, randomisation and blinding

All patients provided written informed consent before enrolling in the study. After agreeing to participate, patients were randomised using computer generated random numbers and opaque sealed envelopes. Only the principal investigator was aware of the identity of the coded ointments. The practice nurse enrolled patients and assigned participants to their groups. All participating patients received written instructions on post-operative wound care. Both groups were asked to take their dressing off after 24 hours and avoid the using antiseptics (Figure 3.1).

Figure 3.1: Study protocol for the patient.



3.3.7 Clinical outcomes

Wounds were assessed for infection by the practice nurse or the doctor on the agreed day of removal of sutures or sooner if the patient re-presented with a perceived infection. Outcome assessing practice nurses and doctors were blinded to the allocation of intervention and control groups. Our definition of wound infection was adapted from standardised surveillance criteria for defining superficial surgical site infections developed by the Centre for Disease Control's National Nosocomial Infection Surveillance System (previous Table 2.1).(49) We also developed our own wound scale, after reviewing several existing scales in the literature,(107) in order to improve rigour. This wound scale differentiated: no infection or erythema; stitch abscess; less than 1 cm erythema from the wound margin; greater than 1 cm erythema from the wound margin; and deep infection or systemic symptoms. All participating doctors and nurses were briefed regarding the definition of infection by the primary researcher, and were also given written information. Practice nurses were asked to swab any discharging infections in order to investigate any pattern of antimicrobial resistance.

3.3.8 Sample size

Sample size was calculated on the basis of our previous study which showed an infection rate of 8.6%.(7) Based on a projected infection rate of 10%, we decided that an absolute decrease in incidence of infection of 5% would be clinically significant. To come to this conclusion with statistical confidence a power in excess of 80% and a significance level of 0.05, a total of 473 patients were required in the intervention group and 473 patients in the control group. We did not adjust for clustering in the sample size calculation at the planning phase of the study. This was because the participating doctors were considered to be the primary sample units rather than the practice. As our sample size was large and sufficient for statistical significance we do not feel that this affected the results of our study.

3.3.9 Statistical analysis

All analysis was based on the intention-to-treat principal. Depending on the distribution, numerical data was described as mean value and standard deviation (SD) or median value and inter-quartile range (IQR). Percentages are presented with 95%-confidence intervals (95%-CI). Because the sample was recruited through 15 different general practitioners and outcome might be more similar for patients from one medical professional (clustering) compared to another, confidence interval and the p-value were adjusted for this cluster sampling approach. For the analysis, participating doctors were considered the primary sampling unit. The "survey" commands of the statistical programme STATA, release 8 (STATA cooperation, College Station, Texas, USA) were applied to adjust for

the clustering effects when estimating the standard error. P-values less than 0.05 were considered to be statistically significant.

3.4 Results

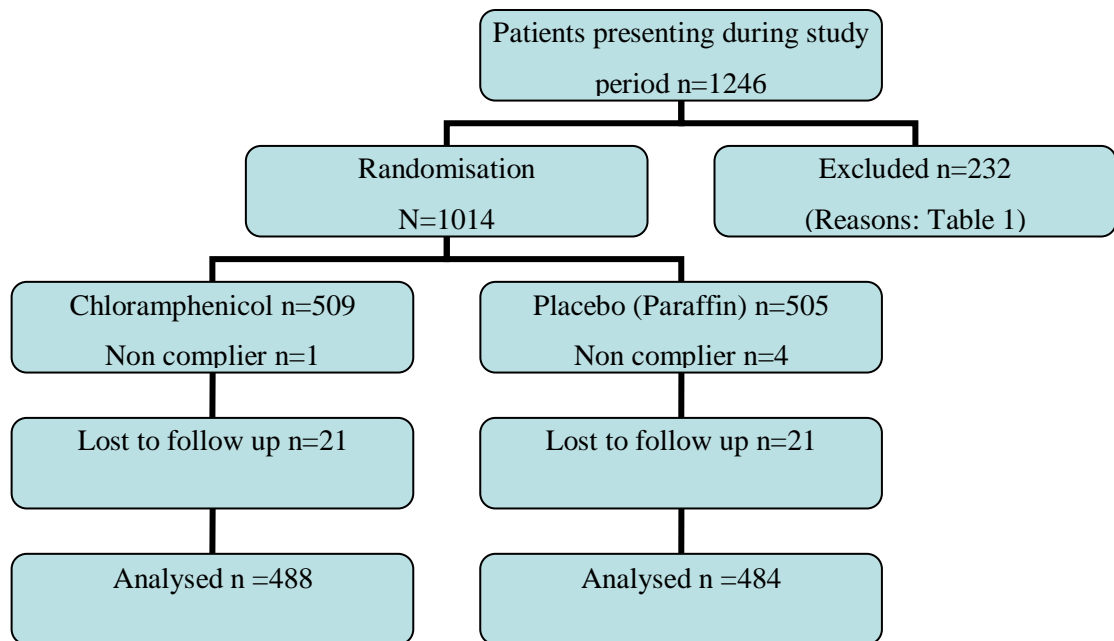
3.4.1 Practice and study characteristics

Of the total of 1,246 patients who attended for skin excisions during the collection period from June 2007 to March 2008, 232 patients were excluded (Table 3.1).

Table 3.1: Reasons for exclusion from study

Reasons for exclusion from study	N=232
Patient declined participation	139 (59.9%)
Patient on oral antibiotics	39 (16.8%)
Doctor did not follow study protocol	20 (8.6%)
History of allergy to Chloromycetin®	2 (0.9%)
Patient did not plan to return for removal of sutures	12 (5.2%)
Shave biopsy conducted	6 (2.6%)
Patient on immune-suppressive drug	4 (1.7%)
Patient with infected sebaceous cyst	10 (4.3%)

Of the remaining 1,014 patients, 509 patients were randomised to the intervention (chloramphenicol) group, and 505 to the placebo (paraffin) group. A total of 42 patients were eventually lost to follow up because they had their sutures removed elsewhere. Follow up was completed in 972 (95.9%) of randomised patients (Figure 3.2).

Figure 3.2: Flow-chart of enrolment, randomisation and follow up of patients.

3.4.2 Comparisons at baseline

There were large differences between the intervention and the control groups at baseline (Table 3.2). In the intervention group 71.7% of patients were diagnosed with non-melanoma skin cancer or solar keratosis compared to 65.1% in the control group.

Table 3.2: Baseline comparisons of intervention (chloramphenicol) and control (paraffin) group

	Intervention group n=488	Control group n=484
<i>Characteristics of patients</i>		
Mean age (SD)*	59.5 (23.2)	59.0 (27.5)
% Male	54.5%	54.1%
Smoking status		
% Never smoked	61.1%	61.9%
% Ex-smoker	22.3%	22.4%
% Current smoker	16.6%	15.7%
% Diabetes mellitus	7.6%	10.4%
% With medical condition**	16.5%	18.1%
<i>Characteristics of lesions</i>		
Body site		
% Neck and face	34.0%	31.4%
% Upper extremities	28.5%	28.9%
% Trunk	22.1%	21.1%
% Lower extremities	15.4%	18.6%
Histology		
% Melanoma and naevi	13.1%	15.3%
% NMSC and precursor***	71.7%	65.1%
% Other#	15.2%	19.6%
<i>Characteristics of procedures</i>		
Mean length of excision (SD) [mm]	20.9 (25.6)	21.0 (28.8)
Median number of days until removal of sutures (IQR) ##	7 (7, 9)	8 (7, 10)
% With flap	0.2%	0.6%
% With two-level procedure	0.8%	0.8%

*SD = standard deviation; ** Medical conditions recorded were COPD(n=14), aspirin or clopidogrel(n=120), oral steroids(n=3), continuous inhaled steroids (n=9) 'warfarin' (n=42), ischaemic heart disease (n=7), peripheral vascular disease (n=6), and current cancer (n=21); *** NMSC= Non-melanoma skin cancer; # Other included seborrhoeic keratosis, re-excisions of melanoma and basal cell carcinoma, sebaceous cyst, epidermal cyst, wart and dermatitis; ##IQR = inter-quartile range.

3.4.3 Incidence of infections

Infection occurred in 85 of the 972 excisions (8.7%). The incidence of infection in the chloramphenicol group (6.6%; 95%-CI = (4.9 to 8.8)) was significantly lower compared to the incidence in the control group (11.0%; 95%-CI = (7.9 to 15.1)) ($p=0.010$; adjusted for cluster sampling). The relative risk of infection was 1.7 times higher in the control compared to the intervention group (Table 3.3). The number needed to treat (NNT) was 22.8 (number of wounds treated for each prevented infection, that is $488/21.4$). It was calculated that there were 53 infections in 484 control people, hence we expected 53.438 infections in 488 (intervention) people. Therefore the study prevented 21.438 infections.

There was no significant difference in the wound score between the control and intervention groups ($p=0.253$), although 5.5% of patients showed erythema greater than 1cm in the intervention group compared to 9.1% of patients in the control group (Table 3). Wound swabs were performed on 24 of the 85 infections. These revealed *Staphylococcus aureus* infections which were resistant to benzylpenicillin, but sensitive to all other antibiotics in 22 cases. In one case, additional resistance to erythromycin but sensitivity to all other antibiotics was noted. In another case *Pseudomonas aeruginosa* was cultivated from the wound. These two swabs were taken from subjects in the control group.

Table 3.3: Incidence of wound infections in intervention (chloramphenicol) and control (paraffin) group

	Intervention group (n=488)	Control group (n=484)	Combined results (n=972)
Number of infections	32	53	85
Incidence of infection	6.6%	11.0%	8.7%
Relative risk of infection (95%-CI)*	1 (reference category)	1.7; (1.1 to 2.5)	
Wound score**			
Stitch abscess	2.9% (n=14)	2.9% (n=14)	2.9% (n=28)
< 1cm Erythema	13.8% (n=67)	12.8% (n=62)	13.2% (n=129)
> 1cm Erythema	5.5% (n=27)	9.1% (n=44)	7.3% (n=71)

*95%-CI = 95% confidence interval; **Wound score had two missing values.

3.5 Discussion

The results of the present study suggest that a single dose of topical chloramphenicol to sutured wounds can produce a relative reduction in infection rate of about 40%. The absolute reduction was 4.4% which fell short of our pre-determined reduction for clinical relevance (5%), therefore this was essentially a negative trial. The incidence of infection in our control group (11%) is much higher than published literature looking at similar cohorts.(52, 56, 113) The intervention therefore may not produce a worthwhile absolute reduction in infection in low risk settings where infection rates are already low, and the number needed to treat in these circumstances, would be much higher than our figure of 22.8.

3.6 Limitations of study

The present study did have several limitations. There are various characteristics influencing the occurrence of infections and although information on as many variables as possible was recorded, it proved difficult to ensure that baseline data was comparable. For example, there were inadequate data recorded on suture size and occupation, and consequently, these factors could not be compared. In addition, the prevalence of diabetes and of other medically important conditions was probably under-recorded, and power was limited to analyse these subgroups. Surgical training and technique of the GPs involved is a potential confounder which would be difficult to quantify and was not recorded. However, statistical analysis was adjusted for the cluster sampling taking the doctor as the primary sampling unit. There was a difference in the type of skin preparation used by the three participating practices, however there was no previously published evidence that this makes any difference to infection rates.(115) A total of 42 participants were lost to follow-up. If all 21 participants who were lost to follow up in the intervention group had developed an infection, then the rates of infection in both groups would have been similar (10.4% and 11.0%); however we feel this scenario is extremely unlikely.

The diagnosis of infection, although using guidelines, is still subjective and there may be inter- and intra-observer variation.(107) The definition we used is the most widely implemented standard definition of wound infection,(49) and we hoped by developing our own wound assessment scale, to reduce the subjectivity of infection diagnosis. We have no evidence to support intra- and inter-practice reproducibility of measurement and recording procedures.

The study did not have an arm in which no ointment was applied, therefore we do not know if the ointment itself had any pro- or anti-infective properties. The ointment base of Chloromycetin[®] consists of a mixture of soft white paraffin, liquid paraffin and plastibase 30W,

which is a plasticized hydrocarbon gel consisting of 95% mineral oil and 5% polyethylene glycol. Information about the exact proportions of these constituents was not obtainable from the manufacturer. Our placebo ointment consisted of 50% soft white paraffin and 50% liquid paraffin, and was not completely identical to the ointment base of Chloromycetin[®] as it did not contain plastibase 30W. Although we think it is unlikely, we are unable to determine if this substance has an effect on infection. Our trial utilized a single dose of chloramphenicol ointment only. We have no evidence to surmise that repeated doses might lead to a greater reduction in infection rate.

3.6.1 Potential of unblinding of intervention

Although there were some large differences observed at baseline, we think it is unlikely that the intervention was unblinded. The placebo ointment was developed using a compound pharmacist using as close as possible to the ingredients of Chloromycetin[®], and the principal researcher also visited the practices regularly during the trial to ensure that the two ointments were identical, both at room and refrigerated temperatures. However we did not test with a formal agreement study to ensure whether the practice nurses remained blinded during the study period, and this must be acknowledged as a weakness of this trial.

3.6.2 At what level would we consider clinical significance?

When the general practitioner evidence based medicine group initially met to discuss the trial, we decided that an absolute reduction of infection of 5%, based on a projected infection rate of 10%, would be clinically significant to our practice. Our control group had an infection rate of 11%, therefore an infection rate of 6% in our intervention group would have been considered to be clinically significant. Our control infection rate was actually 6.6%, so clinical significance was only missed by a narrow margin, however we felt that it was important and ethical to stick implicitly to our predetermined levels of significance.

3.6.3 Generalisability

There are some limits to generalizing these findings. The population of Mackay is slightly older and has a lower median household income than the general Australian population.(109) Mackay is a provincial town in tropical North Queensland. The climate is hot and humid, with the mean daily maximum temperature ranging between 24.2 and 30°C during the summer months, and a relative humidity of 75% to 79%.(110) It is possible that these tropical conditions could increase sweat production and produce damp dressings, which might reduce the effectiveness of wound dressings as a potential barrier against exogenous bacteria.(116-118) This would make wounds

more prone to infection in a tropical environment, and therefore the results may not necessarily be generalisable to a temperate climate, although there is no published evidence that heat and humidity increase infection rates. This might also explain why our infection rates were higher than previous data from temperate climate suggests.(52, 56, 113)

3.6.4 Antibiotic use

There is some concern regarding the overuse of topical antibiotics resulting in antibiotic resistance. British and Australian guidelines suggest that topical antibiotic use be restricted because of the capacity of most topical drugs to select resistant micro-organisms and to cause sensitization. The guidelines also suggest that antimicrobials recommended for topical use are selected from classes not in use for systemic therapy.(66, 119) There is a contrary argument that the potential for antimicrobial resistance with topical antibiotics is actually lower than with systemic antibiotics because of the higher local concentration achieved by topical delivery.(95) Patterns of antimicrobial activity and resistance have been examined for other antibiotic ointments.(92, 93) However there is no evidence, over three decades of extensive use worldwide that, with the exception of mupirocin, topical antibiotics administered on an outpatient basis contribute to any emerging resistance pattern.(95) Chloramphenicol eye drops have been shown to be effective in the treatment of methacillin resistant staphylococcus aureus (MRSA) ocular surface infections.(91)

There is also some concern about the incidence of allergic contact dermatitis with topical antibiotic use. With topical neomycin, this has been shown to be as high as 11% in a population referred for diagnostic patch testing.(120) However there is some evidence that the incidence of this reaction is as low as 1% when the ointment is used in the general population.(95) The reaction is much more common amongst subjects previously exposed to neomycin ointment.(120) Contact allergy has been reported with the use of chloramphenicol ointment but the incidence is thought to be low.(96, 97) Although it is unlikely that there is any connection between the use of topical chloramphenicol and aplastic anaemia,(70, 100) the study is not large enough to fully assess the risk in this setting.

Antibiotic prophylaxis is probably prescribed excessively or inappropriately for dermatological surgery(49, 62) and is thought to be best reserved for high risk patients.(10, 62) There is no data available on the current prescribing habits of Australian GPs regarding oral or topical antibiotic prophylaxis for minor excisions. Although there is also no evidence available regarding what reduction in the rate of infection we might reasonably expect from the use of oral prophylactic

antibiotics for minor excisions, there is some evidence of a 50% reduction in risk of infection when perioperative oral antibiotic prophylaxis is used following clean surgery.(102) A similar reduction in infection rate from a single dose of topical antibiotic, as in this study, may encourage a reduction in the use of oral antibiotics.

The decision to prescribe antibiotic prophylaxis is complicated and in addition to efficacy, antibiotic costs, adverse effects and resistance should be taken into account. However, in some circumstances, topical delivery of antibiotic may be preferable to systemic administration.(66, 119) The results of this study could encourage the judicious use of topical antibiotics following minor skin surgery. However it must be noted that it is unlikely that topical chloramphenicol will produce a worthwhile absolute reduction in infection rates in low risk settings in developed countries. Future research could explore the possibility that important reductions may be seen in higher risk wounds or in more resource poor settings.

3.6.5 Conclusion

The present study suggests application of a single dose of topical chloramphenicol to high risk sutured wounds following minor surgery produces a moderate absolute reduction in infection rate.

3.7 Summary

This trial established that chloramphenicol ointment has limited efficacy in reducing the incidence of wound infection after minor surgery. The incidence of infection in the chloramphenicol group (6.6%; 95%-CI = (4.9 to 8.8)) was significantly lower compared to the incidence in the control group (11.0%; 95%-CI = (7.9 to 15.1)) (p=0.010). The absolute reduction in infection rate was 4.4%; the relative reduction was 40%. The present study suggests application of a single dose of topical chloramphenicol to high risk sutured wounds after minor surgery produces a moderate absolute reduction in infection rate which is statistically but not clinically significant.

The incidence of infection in the control group in this study (11.0%) was comparable with our previous study, and again much higher than for similar groups of patients with class 1 wounds from different geographical locations. One of the risk factors for infection identified from our previous trial was excision of a skin cancer (see chapter 2), while age was actually found to be a confounder rather than a risk factor.

It is therefore important to establish the types of skin lesions that GPs are excising, and the demographics of the patients who are presenting with skin cancer, in order to understand risk factors for infection and effective interventions to prevent infection after minor surgery. The next chapter will examine these factors in more detail.

CHAPTER 4: MINOR SKIN EXCISIONS IN NORTH QUEENSLAND

4.1 Background

This chapter describes the type of skin surgery that is being conducted by general practitioners in North Queensland. This is important in order to understand the epidemiology of skin cancer in this location in order to understand the need for general practitioners to conduct skin surgery. The number needed to treat (NNT) is the number of melanocytic naevi excised per melanoma, and can be used to assess performance in skin cancer practice. This chapter is a secondary analysis of data collected in the 'Can sutures get wet' intervention study. The published article forms Appendix 3.(114)

The objectives of this chapter are to describe the histology of lesions excised by general practitioners in rural North Queensland and calculate the skin cancer yield and NNT; and to describe the sites that skin cancers are removed from and the demographics of patients presenting with skin cancer.

4.2 Introduction

Skin cancer is an extremely important health issue in Australia. Non-melanocytic skin cancer (NMSC), combining basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is by far the commonest cancer in Australia with an incidence of more than four times that of all other registrable cancers combined.(1) Queensland has the world's highest recorded incidence of all types of skin cancer,(2, 3) with incidence rates being even higher in tropical North Queensland.(4)

In North Queensland, the majority of suspicious skin lesions are managed by general practitioners (GPs),(38) particularly in rural centres such as Mackay where there is no resident dermatologist. It was recently estimated that, in Australia, 54% of patients with BCCs and 65% of patients with SCCs are managed in primary care settings,(6) and it could be projected that these figures would be even higher for rural settings. Skin excisions form a large proportion of a typical Australian GP's workload, and this proportion is even greater for Queensland GPs.(5) Skin excisions are also very costly, with over one million skin excisions billed to Medicare

annually(8) and an estimated cost of \$264 million for NMSC in 2000-1 (9% of the total costs for cancer).(9)

The data for the present study was collected incidentally as part of a randomised controlled trial looking at wound management following minor excisions, which has been reported elsewhere.(7) The purpose of examining the present data was to describe the histology of lesions that GPs remove during minor excisions in rural North Queensland, the sites that skin cancers are removed from and the demographics of patients presenting with skin cancer.

4.3 Methods

Sixteen GPs from four practices in the Mackay area, tropical North Queensland, Australia (latitude 21°S; inhabitants of Mackay area approximately 75,000) participated in the present study. There are a total of 104 practising GPs in the Mackay area. The participating GPs were a self-selected group who attended a monthly evidence based medicine meeting. Data collection for the study took place from October 2004 to May 2005. Data was collected from consecutive patients presenting for minor skin excisions. This included all patients who had any skin lesion excised and repaired by direct sutures over the study period. Patients presenting for suturing of a laceration or incision and drainage of a sebaceous cyst were excluded, as were shave or punch biopsies. Explicitly, these patients were 1,246 patients who presented for minor skin excisions during the period of collection for the 'Can sutures get wet' trial described in chapter 3. Of the 1,246 patients, 232 were excluded from the 'Can sutures get wet' trial. The reasons for exclusion are detailed in chapter 3. However, written consent was given from all excluded patients, including the small number that refused to take part in trial, to have data recorded for research purposes. Demographic data and data on types of skin lesion were recorded on all 1,246 patients who presented for minor skin excisions over the study period.

Practice nurses were responsible for collecting data. A body site map was used to define excision site, and histology was recorded for all patients. At the end of the study practice nurses were asked to re-examine computer records to fill in any missing data. The principal researcher visited participating GPs and practice nurses to provide training and ensure that recording was standardised.

The data was collated and analysed using SPSS version 12. Standard descriptive statistics and bivariate statistical tests were applied.

4.3.1 Calculation of relative tumour density

Relative tumour density (RTD) for different body sites was calculated according to Pearl and Scott.(121) This method has previously been described to compare the density of tumours at different body sites relative to the density of tumours over the whole body by taking into account the surface proportion (of the whole body) of a specific body site. Thus the different body sites become comparable assuming that each skin unit has the same potential for developing skin cancer. In this way the distribution of tumours over the body surface can be more readily related to the likely exposure of the surface.

This calculation of relative tumour density (RTD) is performed by taking the proportion of all lesions at a particular body site and dividing this proportion by the surface proportion of the body site. A RTD of one corresponds to the density of tumours on the whole body.

4.4 Results

Participating GPs were younger (median age 44 years) and more predominantly female (64%) than average for Australian GPs (median age category 45-54 years; 32% female).(121) One doctor who participated worked in a designated skin cancer clinic. Data was recorded from 1,247 consecutive patients who attended for minor skin excisions to the participating doctors between October 2004 and May 2005.

4.4.1 Histology

SCC was the most frequently excised lesion, accounting for 25.9% of excisions, and all skin cancers (SCC, BCC or melanoma) together accounted for 46.7% of excisions. This number increased to 68.9% if solar keratoses were included (Table 4.1). Number of benign or dysplastic naevi excised per melanoma (NNT) was 9.4 to 1.

Table 4.1: Histology of 1,247 minor skin excisions recorded in Mackay, North Queensland

HISTOLOGY	N	%
Cutaneous melanoma	20	1.6
Basal cell carcinoma	234	19.2
Squamous cell carcinoma	316	25.9
Benign naevus	145	11.9
Dysplastic naevus	23	1.9
Seborrheic keratosis	24	2.0
Solar keratosis	271	22.2
Basal cell papilloma	41	3.4
Re-excision	16	1.3
Other*	131	10.7
Missing	26	
Total	1247	100.0

'Other' included: 'cyst' (20), sebaceous cyst (11)**, keratosis unspecified (16), lentigo (11), scar tissue/keeloid (6), cutaneous tag (6), verruca vulgaris (5), dermatofibroma (8), lipoma (5), keratoacanthoma (9), haemangioma (12), lichen planus (3), dermatitis (4) granuloma annulare (2), pore of winer (1), fibroxanthoma (1), pyogenic granuloma (2), foreign body (1), neurofibroma (2), xanthogranuloma (1), sebaceous hyperplasia (1), psoriasis (1), and sebaceous hyperplasia (3).

** Although incision and drainage of sebaceous cyst was excluded, sebaceous cyst was an incidental finding on pathology report in these 11 patients.

4.4.2 Demographics of patients presenting for excisions

The majority (84.3%) of skin excisions took place in the over 40 years age category, with the mean age being 56.9 years (SD \forall 16.3). Slightly more (53.2%) of skin excisions took place in men (Table 4.2).

Table 4.2: Age and sex distribution of patients presenting with skin cancers for all skin excisions in Mackay, North Queensland.

	Melanom a (n = 20)	BCC (n = 234)	SCC (n = 316)	All excisions (n = 1247)
Mean age (∇SD) [years]	55 (∇15.0)	60.9 (∇15.0)	63.8 (∇12.5)	56.9 (∇16.3)
Age range [years]	27 - 79	24 - 98	24 - 94	5 - 98
Male to female ratio	0.82 : 1	1.44 : 1	1.56 : 1	1.14 : 1

One BCC was removed from the chest of a 24-year-old male; one SCC was removed from the leg of a 24-year-old female; and another SCC from the chest of a 29-year-old male. The majority of SCCs were excised in the 70 to 89 year age group, and the majority of BCCs were excised from patients 60 to 79 years of age. Eight (40.0%) melanomas were excised from patients who were younger than 50 years.

4.4.3 Body site distribution of skin cancer

The body site distribution and relative tumour density of skin cancers is documented in Table 4.3. There was little difference in site distributions between males and females ($p=0.7013$ for BCC; $p=0.8415$ for SCC; sample size too small for melanoma).

Table 4.3: Body site distribution and relative tumour density (RTD) of skin cancers as recorded in Mackay, North Queensland

Body site	Surface proportion	Melanoma n = 20	RTD CM	BCC n = 234	RTD BCC	SCC n = 314*	RTD SCC	Total n = 554
Upper limb	0.19	3 (15%)	0.78	59 (25%)	1.32	120 (38%)	2.0	182
Lower limb	0.4	7 (35%)	0.85	24 (10%)	0.12	95 (30%)	0.75	126
Trunk	0.32	6 (30%)	0.93	57 (24%)	0.76	29 (9%)	0.28	92
Face, scalp, neck	0.089	4 (20%)	2.25	94 (40%)	4.5	70 (22%)	2.5	168

*Body sites were not recorded for two SCCs.

4.4.4 Comparison of results from designated skin cancer clinic setting to mainstream general practice setting

The total 1,247 excisions included 76 excisions undertaken in a designated skin cancer clinic. There was little difference in the demographics of patients seen in the skin clinic setting in comparison to the patients from GP practices. In the skin clinic, 76% (58/76) of lesions excised were skin cancers (BCC, SCC or melanoma) compared with 512/1145, 45% in mainstream general practice setting. The NNT was 5.7 (14+3/3) (mainstream general practice 10.0 134+19+17/17). The BCC: SCC ratio was 4:1 (44/11) (mainstream general practice 190/305 0.6:1).

4.5 Discussion

There are several limitations to analyzing and generalizing our findings. It is known that the age and gender of general practitioners strongly influences the age and gender of patients who consult them,(108) thus creating potential selection bias. The participating GPs were not representative of Mackay GPs, and patients attending general practice are not representative of the general population.(108) Excisions from the facial region were probably under recorded in our study, which may have influenced the body site distribution. The sample size from the designated skin cancer clinic is small, and the comparison of these data with the overall data must be viewed with caution.

4.5.1 Histology

In 2002, of 374,000 Australians treated for skin cancer it was estimated that 68% were for BCCs and 32% with SCCs,(6) and previous Australian studies have reflected this ratio of BCCs to SCC's.(4, 56) Notably, in our study more SCCs than BCCs were excised. Our ratio of BCC: SCC was 42.5%:52.5% or 0.74:1. One could reflect that the higher incidence of SCC may be due to the high rate of cumulative sun exposure of the cane farming population. Hence, one could speculate that the sun behavior of Mackay residents might differ from other populations. Another possible explanation of this finding could be that more and more early BCCs are being treated with cryotherapy or Imiquimod cream by Mackay GPs and hence have no histopathologic confirmation.

The overall NNT for melanoma of 9.4 was much lower than recent data derived from analysis of billing data from skin cancer clinics (NNT 28.6).(45) However, in this study, non-pigmented benign lesions were included in the denominator therefore elevating their NNT. In other studies, the NNT was found to be between 11 and 29 for Australian GPs when based on melanomas and naevi only (as for our figures) and up to 36 when seborrhoeic keratoses were included.(35, 42-44) However as there were only 20 melanomas excised the interpretation of this data is also limited.

4.5.2 Comparison of histology from skin clinic

The doctor working in the skin cancer clinic excised a higher number of skin cancers per excision and had a lower NNT compared with the overall results. Although with only a total of 76 excisions including 3 melanomas excised in this setting these figures must be interpreted with caution. Most significantly, there was a much larger BCC:SCC ratio (4:1 v 0.74:1). This could reflect either an increased pick up of BCC because of the tendency to undertake full-body skin examination within the skin cancer clinic context and so detect lesions of which the patient is unaware, or an increased use of excision rather than other management options. The differing histology in the skin clinic setting could also be influenced by the differing pathology of patients who self select to attend a skin cancer clinic, the use of epiluminescent microscopy or a difference in the training and experience of the skin clinic doctor.

4.5.3 Body site distribution

Although only 22% of SCCs were excised from the face, scalp and neck and the most common site for excision was from the upper limb (38%), when we calculated the RTD, which takes into account the surface proportion occupied by body sites experiencing different amounts of ultraviolet radiation, 'face scalp and neck' was the most dominant region. Likewise, although melanomas were more commonly excised from the lower limb, when RTD was calculated, face, scalp and neck were the most dominant regions. The largest proportion of BCCs was excised from the head and neck, which was also reflected in the RTD. These findings are consistent with previous studies.(24, 121-123)

4.5.4 Age

The number of SCCs excised appeared to increase steadily with age, while the majority of BCCs were excised in the 6th decade, and the most common decade for melanomas was 40-49

years. This is in keeping with the theory that high cumulative sun exposure is regarded as a risk factor for SCC,(124) while intermittent sun exposure is a consistent risk factor for melanoma,(125) while both factors appear to contribute to the formation of BCCs.(126)

4.5.5 Conclusion

In this sample of Mackay GPs, close to half (46.7%) of lesions excised were skin cancers. We excised more SCCs than BCCs (0.74:1), which contrasts with previous studies of Australian populations. Our NNT is relatively low compared with other studies of Australian GPs, and we could consider lowering our threshold for excising pigmented lesions.

4.6 Summary

Close to half (46.7%) of lesions excised were skin cancers. We excised more squamous cell carcinomas than basal cell carcinomas (0.74:1). Mean age for excision of melanoma, BCC and SCC was 55, 60.9 and 63.8 years respectively.

In this chapter we established that amongst a cohort of GPs in Mackay our skin cancer yield was comparable to similar cohorts. The number needed to treat (melanocytic naevi excised per melanoma) was 8.4 and this NNT was much lower than comparable studies. The conclusion of the study was that the doctors involved in the study could lower our threshold for excising skin pigmented lesions. However the use of NNT as a marker of quality of skin cancer management by general practitioners is complex, and many different factors must be taken into consideration. Firstly, we do not have a measure of the skin cancers that we missed (ie the false negative diagnosis) so a low NNT may not necessarily be a measure of good quality management by GPs. Secondly, the measure will be affected by the background incidence and prevalence of skin cancer in the presenting population. Thirdly the NNT may also be affected by economics, and the desire to generate income by excising more skin lesions. Fourthly it may be influenced by medico-legal concerns which may increase the desire to excise, and also the past clinical experience of a particular doctor. The issue is actually extremely complex, and we make the recommendation of considering lowering the threshold for excision with extreme caution.

This chapter also illustrates the importance of GPs and other medical practitioners to be able to diagnose skin cancer accurately. The next chapter will investigate this in further detail.

CHAPTER 5: DIAGNOSTIC ACCURACY OF EXCISED AND BIOPSIED SKIN LESIONS BY AUSTRALIAN GENERAL PRACTITIONERS

5.1 Background

It has been established in the previous chapter that minor skin surgery conducted by general practitioners in North Queensland produces a high yield of skin cancer. However, there is little data available regarding the diagnostic accuracy of Australian GPs with regard to excised and biopsied skin lesions and no published comparison of the diagnostic accuracy of doctors regarding different subtypes of non-melanotic skin cancer. The published article forms Appendix 4.(127)

This chapter explores the diagnostic accuracy of Australian GPs regarding lesions that they have decided to excise. The objective was to analyse historical data of clinical and histological diagnosis of excised and biopsied non-melanoma skin cancers by Australian GPs.

5.2 Introduction

Skin cancer is an increasing problem in fair-skinned populations world wide, with age standardised incidence rates per 100,000 for cutaneous melanoma (CM) of 40.5, 13.3 and 6.1 for men, and 31.8, 9.4 and 7.7 for women in Australia, the US and the UK respectively.(31) In the UK and US, incidence rates for melanoma are rising rapidly. Non-melanocytic skin cancer (NMSC), combining basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most common cancer in all three countries.

Australia has the world's highest recorded incidence of all types of skin cancer,(26, 31, 128) with incidence rates being even higher in tropical North Queensland.(4) In Australia the majority of suspicious skin lesions are managed by general practitioners (GPs)(38) and the proportion of all skin cancers excised by GPs is increasing.(39) Skin excisions form a large proportion of the typical workload of an Australian GP,(5) with 0.8 per 100 patient encounters involving excision of a skin lesion.(129) The economic cost of skin cancer to the Australian health care system is enormous.

In the UK there is some controversy about the ability of general practitioners to recognise skin cancer and prioritise referrals(130-132) and there is a debate about the appropriateness of both CM and NMSC being managed in a primary care setting.(130, 131) Similarly in Australia, there has recently been interest in the diagnostic performance of doctors with respect to skin lesions which they decide to biopsy or excise.(133, 134) This interest has particularly focused on assessing the performance of practitioners working in 'open access' designated skin cancer clinics, which are primarily staffed by GPs, and have been a recent rapidly emergent phenomenon, particularly in the state of Queensland.(135) The Australian studies have shown that practitioners diagnose a wide range of skin lesions with moderate to high sensitivity.

The main purpose of the present study was to compare the clinical to the histological diagnosis of excised skin lesions from a large data set which represents close to all skin excisions which took place over a three year period in a regional centre in North Queensland, at a time prior to the existence of skin cancer clinics. We aimed to analyse diagnostic accuracy stratified by histological subtype and body-site. We also aimed to examine the histological nature of false positive and false negative diagnoses, in order to make inferences about the decisions to excise and implications of misdiagnoses.

5.3 Methods

The original study was a prospective, population-based survey that aimed to collect information on all excised and histologically confirmed skin cancers in Townsville. Between the end of 1996 and October 1999, all excised and histologically confirmed skin cancers in Townsville/Thuringowa, North Queensland, Australia (latitude 19.16°S; population approximately 130,000) were recorded. During the study, pathology reports on all excised skin cancers were collected from the three local pathology laboratories, which routinely collected reports on NMSC to send to the Queensland Cancer Registry. These laboratories served the pathology requests from all hospitals, GPs and specialists in Townsville (202 GPs and 42 specialists - including one dermatologist, plastic surgeons and general surgeons, during the study period). The data collected on excised skin cancers is likely to be almost complete, as doctors in Townsville routinely seek histology for all excised skin lesions. As Townsville's location is relatively isolated (Brisbane is approximately 1,200 km south) it can be assumed that almost all skin cancers were treated locally. To validate this assumption, 7,370 pathology reports from the periods February/March and May/June 1997, which were sent directly to the

Queensland Cancer Registry from private pathology laboratories and hospitals, were searched for residents of Townsville treated elsewhere and only one patient was identified. Before the onset of the study, a histopathology workshop was organized to reach agreement on criteria for histological diagnosis of skin cancer and other skin lesions. Within the present study BCC and SCC were differentiated, and all *in situ* malignancies were excluded. Within the database multiple skin cancers per patient can be identified. Biopsied lesions were recorded as such and data was subsequently changed, after the entire lesion was excised. We refer to multiple skin cancers either if lesions were presented concomitantly for treatment or if subsequent skin cancers developed and were treated during the study period.(4) Of the 6,708 patients recorded with NMSC, 38.5% had multiple lesions. Prior to the study all participating pathologists attended a workshop to reach agreement on criteria for the histological diagnosis of skin lesions with a consultant dermato-pathologist, and the dermato-pathologist agreed to review a blinded stratified random sample of 407 histology slides. This part of the study is discussed in more detail in chapter 6. In 1999, a total of 8,694 patients (mean age 58.6 years; 55.2% male) with up to 72 excisions per patient were recorded. Incidence rates (per 100,000 inhabitants) of basal cell carcinoma (BCC) were 1,444.8 for men, 942.7 for women, and of squamous cell carcinoma (SCC) were 805.0 for men and 423.6 for women. Compared to incidence rates, age standardised rates of lesions of BCC were 2.1 times higher in men, 1.6 times higher in women, and of SCC were 1.8 times higher in men and 1.4 times higher in women. Details of these incidence rates, and comparison with other studies, are discussed in the literature review.

5.3.1 Statistical analysis

In this present study, positive predictive values (PPV) and sensitivity refer to the doctors' clinical diagnosis of a specific lesion. Histology was considered the "gold standard". PPV is defined as the probability that a person with a clinical diagnosis of a particular skin lesion actually has this skin lesion according to histology. Sensitivity is defined as the probability that a person with the histological diagnosis of a particular skin lesion will "test positive" for this skin lesion according to clinical diagnosis.

PPVs and sensitivities together with exact 95%-confidence intervals (95%-CI) were calculated for the clinical diagnoses of BCC, SCC, intra-epithelial carcinoma (IEC), actinic keratosis (AK), seborrhoeic keratosis (SK), keratoacanthoma (KA), cutaneous melanoma (CM), cutaneous melanoma in situ (CM in situ), atypical naevus (AN) and common naevus (CN). For

PPV and sensitivity only the first lesion per patient with the particular clinical diagnosis was considered; this was to reduce possible bias due to doctors 'learning' the clinical diagnosis from patients presenting for repeated excisions of the same histological type. Sensitivities were calculated including and excluding cases with missing clinical diagnosis in the denominator. To infer whether excision was an appropriate option for diagnosis or treatment, we also combined the squamous cancers and precursors, and similarly the pigmented lesions and determined PPV for combined clinical diagnoses. Additionally, PPVs and sensitivities were calculated for clinical diagnoses stratified by body-site.

We defined the number needed to treat (NNT) as the number of all naevi (CN and AN) excised per CM or CM in situ. This was calculated using histological diagnosis of all excisions during the three year study period. Comparisons between GPs and specialists were conducted using Chi-square tests and Fisher's exact tests. Results were adjusted for multiple testing using the approach by Bonferroni. Statistical analyses were conducted with SPSS for Windows, release 14.

5.4 Results

Between December 1996 and October 1999 a total of 8,694 patients (mean age 58.6 years; 55.2% male) with up to 72 excisions per patient were recorded. Incidence rates (per 100,000 inhabitants) of BCC were 1,444.8 for men, 942.7 for women, and of SCC were 805.0 for men and 423.6 for women. Compared to incidence rates, age standardised rates of lesions of BCC were 2.1 times higher in men, 1.6 times higher in women, and of SCC were 1.8 times higher in men and 1.4 times higher in women. Details of these incidence rates, and comparison with other studies, are discussed in the literature review.

5.4.1 Positive predictive values and sensitivities of clinical diagnosis

PPV for BCC was 72.7%, for SCC 49.4, and for CM 33.3 (Table 5.1). Sensitivity for BCC was 63.9%, for SCC 41.1, and for CM 33.8 (Table 5.2). Sensitivities were higher when cases with missing clinical diagnosis were excluded from the denominator (BCC: 82.0%, SCC: 56.6%, IEC: 7.8%, AK: 14.4%, SK: 17.0%, KA: 29.9%, CM: 39.5%, CM in situ: 26.3%, AN: 14.3%, and CN: 59.0%).

Combining the diagnosis of SCC, IEC and AK, the PPV of clinical diagnosis was 66.9% (95%-CI = [64.7, 69.1]; n=2,708) and sensitivity was 40.2% (95%-CI = [38.7, 41.7]; n=3,933). Combining CM and CM in situ, the PPV of clinical diagnosis was 38.8% (95%-CI = [31.2, 46.4]; n=160) and sensitivity was 38.1% (95%-CI = [32.0, 44.2]; n=160). Combining all naevi, the PPV for clinical diagnosis was 51.2% (95%-CI = [46.7, 55.7]; n=477) and sensitivity was 44.4% (95%-CI = [40.3, 48.5]; n=559). These latter sensitivities were calculated including cases with missing clinical diagnosis in the denominator.

Table 5.1: Positive predictive values (in bold) and 95%-confidence intervals of clinical diagnosis of skin lesions. Results for pigmented lesions were shaded; rows add up to 100%

Clinical diagnosis	Histological diagnosis										
	BCC	SCC	IEC	Actinic keratosis	Kerato-acanthoma	CM	CM in situ	AN	CN	Seborrhoeic keratosis	Other*
BCC (n=4555)	72.7% 71.4, 74.0	10.9%	4.0%	5.0%	1.0%	0.4%	0%	0%	0.9%	1.3%	3.8%
SCC (n=2306)	20.8%	49.4% 47.3, 51.5	7.9%	10.5%	6.3%	0%	0%	0%	0.1%	1.3%	3.5%
IEC (n=141)	39.0%	3.5%	44.7% 36.3, 53.3	7.8%	0%	0%	0%	0%	0%	0.7%	4.3%
Actinic keratosis (n=476)	17.0%	26.9%	9.9%	30.9% 26.8, 35.5	4.0%	0%	0%	0%	0.4%	5.0%	5.9%
Keratoacanthoma (n=357)	3.4%	51.8%	2.0%	3.6%	37.0% 32.0, 42.2	0%	0%	0%	0.3%	0.3%	1.7%
CM (n=138)	16.7%	1.4%	1.4%	2.2%	0%	33.3% 25.5, 41.9	5.1%	0.7%	10.9%	10.1%	18.1%
CM in situ (n=22)	0%	0%	9.1%	4.5%	0%	18.2%	22.7% 7.8, 45.4	4.5%	18.2%	13.6%	9.1%
Atypical naevus (AN) (n=35)	2.9%	0%	0%	0%	0%	8.6%	0%	5.7% 0.7, 19.2	62.9%	8.6%	11.4%
Common naevus	20.0%	2.3%	1.6%	1.6%	0%	6.3%	0.5%	0.9%	48.9%	9.0%	9.0%

(CN) (n=444)										44.1, 53.6	(n=40)
Seborrhoeic	9.9%	6.3%	5.4%	9.0%	0.9%	1.8%	0.9%	0%	5.4%	52.3%	8.1%
keratosis (n=111)										42.6, 61.8	(n=9)

*Main “other” lesions histologically diagnosed:

BCC: 14.9% lichenoid keratosis (26 of 175) and 8.0% skin, no lesion (14 of 175); SCC: 17.3% lichen simplex chronicus (14 of 81) and 11.1% dermatofibroma (9 of 81); CM: 44.0% Skin, no lesion (11 of 25) and 16.0% scar (4 of 25); Common naevus: 20.0% lentigo simplex (8 of 40), 17.5% dermatofibroma (7 of 40) and 15.0% haemangioma (6 of 40).

Table 5.2: Sensitivities (in bold) and 95%-confidence interval of clinical diagnosis of skin lesions. Results for pigmented lesions were shaded; columns add up to 100%

Clinical diagnosis	Histological diagnosis									
	BCC n=5044	SCC n=2672	IEC n=1002	Actinic keratosis n=1389	Kerato- acanthoma n=544	CM n=139	CM in situ n=25	AN n=23	CN n=537	Seborrhoeic keratosis n=495
BCC	63.9% 62.6, 65.2	20.1%	27.1%	25.9%	12.1%	14.4%	8.0%	4.3%	11.4%	19.8%
SCC	8.0%	41.1% 39.2, 43.0	24.1%	25.0%	35.8%	1.4%	0%	0%	0.4%	9.1%
IEC	0.6%	0.1%	5.0% 3.7, 6.5	0.5%	0%	0.7%	0%	0%	0%	0.2%
Actinic Keratosis	1.3%	3.4%	4.7%	9.4% 8.0, 11.1	3.9%	0%	0%	0%	0.6%	6.5%
Keratoacanthoma	0.2%	5.7%	0.6%	0.9%	23.0% 19.5, 26.8	0%	0%	0%	0.2%	0.2%
CM	0.4%	0.1%	0.2%	0.2%	0%	33.8% 26.0, 42.3	28.0%	8.7%	2.8%	2.6%
CM in situ	0%	0%	0.2%	0.1%	0%	2.9%	24.0% 9.4, 45.1	4.3%	1.3%	0.4%
Atypical naevus (AN)	0% (n=1)	0%	0%	0%	0%	2.2%	0%	8.7% 1.1, 28.0	4.1%	0.8%
Common naevus	1.5%	0.3%	0.6%	0.5%	0%	20.9%	8.0%	21.7%	41.0%	8.1%

(CN)							36.8, 45.3				
Seborrheic		0.2%	0.2%	0.5%	0.6%	0.2%	1.4%	4.0%	0%	1.3%	12.5%
Keratosis											9.7, 15.8
Other*		1.8%	1.5%	1.3%	2.3%	1.8% (n=10)	7.9%	4.0%	13.0%	6.5%	6.3% (n=31)
		(n=90)	(n=40)	(n=13)	(n=32)		(n=11)	(n=1)	(n=3)	(n=35)	
Missing clinical diagnosis		22.1%	27.4%	35.7%	34.6%	23.2%	14.4%	24.0%	39.1%	30.5%	33.5%

*Main “other” lesions histologically diagnosed:

BCC: 30.0% pigmented lesion (27 of 90); CM: 54.5% pigmented lesion (6 of 11); Seborrheic keratosis: 45.2% pigmented lesion (14 of 31);

Atypical naevus: 100% pigmented lesion (3 of 3); Common naevus: 48.6% pigmented lesion (17 of 35).

PPV and sensitivities varied with body-site (Tables 5.3 and 5.4). For BCC, PPVs and sensitivities were higher for the trunk, the shoulders and the face and comparatively lower for the extremities. For SCC, PPVs were high for the scalp and the extremities and comparatively lower for shoulders and posterior trunk. PPV for the scalp were above 60% for BCC, SCC, IEC, CM and naevi.

Table 5.3: Positive predictive values of clinical diagnosis of skin lesions stratified by body-sites. Results for pigmented lesions were shaded

Clinical diagnosis	Scalp	Face	Neck	Shoulder	Upper extremities	Anterior trunk	Posterior trunk*	Lower extremities
BCC (n=4517)	67.2%	78.4%	68.4%	82.9%	52.9%	69.6%	82.7%	56.9%
SCC (n=2288)	65.6%	43.4%	44.1%	25.9%	51.8%	43.8%	34.4%	54.2%
IEC (n=139)	66.7%	64.3%	66.7%	28.6%	29.4%	57.1%	16.7%	53.5%
Actinic Keratosis (n=475)	50.0%	37.8%	13.6%	14.3%	32.5%	12.5%	35.7%	25.6%
Keratoacanthoma (n=355)	0%	15.8%	15.4%	44.4%	38.0%	33.3%	40.0%	44.6%
CM (n=134)	66.7%	33.3%	14.3%	38.5%	29.4%	9.1%	32.6%	36.8%
CM in situ (n=22)	/**	22.2%	0%	100.0%	33.3%	0%	0%	50.0%
Atypical naevus (n=35)	0%	0%	/	0%	0%	0%	14.3%	0%
Common naevus (n=440)	66.7%	40.3%	34.6%	23.1%	52.6%	57.3%	56.7%	42.0%
Seborrhoeic Keratosis (n=110)	50.0%	59.4%	87.5%	33.3%	41.7%	55.6%	35.7%	42.1%

*Posterior trunk including buttocks and genitals; **There were no lesions on the scalp clinically diagnosed as CM in situ and there were no lesions clinically diagnosed as atypical naevus on the neck.

Table 5.4: Sensitivities of clinical diagnosis of skin lesions stratified by body-sites. Results for pigmented lesions were shaded.

Histological diagnosis	Scalp	Face	Neck	Shoulder	Upper extremities	Anterior trunk	Posterior trunk*	Lower extremities
BCC (n=4988)	64.1%	71.3%	59.7%	68.0%	50.6%	69.5%	64.3%	38.2%
SCC (n=2641)	37.0%	25.7%	29.7%	22.8%	47.8%	30.6%	30.0%	53.7%
IEC (n=991)	11.1%	2.6%	6.7%	6.5%	3.1%	8.0%	12.5%	7.2%
Actinic Keratosis (n=1388)	5.0%	9.2%	5.9%	0%	12.2%	4.4%	6.8%	8.0%
Keratoacanthoma (n=536)	.0%	16.2%	15.4%	40.0%	24.9%	37.5%	23.5%	21.7%
CM (n=133)	50.0%	42.9%	20.0%	55.6%	31.3%	11.1%	34.8%	23.3%
CM in situ (n=25)	/**	50.0%	0%	50.0%	25.0%	0%	0%	25.0%
Atypical naevus (n=23)	/	0%	0%	0%	0%	0%	22.2%	0%
Common naevus (n=535)	22.2%	25.2%	33.3%	29.2%	49.2%	46.8%	46.8%	46.7%
Seborrhoeic Keratosis (n=494)	11.8%	11.1%	14.6%	5.6%	7.1%	14.3%	9.1%	12.5%

*Posterior trunk including buttocks and genitals; **There were no lesions on the scalp histologically diagnosed as CM in situ or as atypical naevus.

5.4.2 Comparisons between specialists and GPs

Of the 8,694 first excisions 23.5% did not have a clinical diagnosis and 16.6% of those first excisions were conducted by specialists. GPs were more likely to give a clinical diagnosis (77.4%) than specialists (71.6%; $p < 0.001$). For BCC, PPV and sensitivity, when missing values for clinical diagnosis were excluded, were significantly higher for specialists compared to GPs (81.2% versus 70.6% and 89.0% versus 80.3%; $p < 0.001$ respectively). All other comparisons were non-significant when adjusted for multiple testing.

5.5 Discussion

The strengths of our study were a large sample size and close to complete epidemiological data over a three-year period, which implies reduced selection bias, probably resulting in a representative sample of skin lesions and doctors. Previous studies(133, 134) have sampled doctors who may have been biased by having an interest in skin cancer. In the present study doctors were not aware that their performance was being scrutinised.

5.5.1 Positive predictive values

There are limitations to the use of the terms PPV and sensitivity in this setting as we have no information about the lesions that doctors decided not to excise. We feel that PPV, which is calculated from true and false positive clinical diagnoses, is a more accurate representation of diagnostic performance when examining a skin lesion, hence its use in this study. In the interpretation of results it is important to remember that PPV is dependent on the prevalence – the higher the prevalence, the higher the PPV. Therefore the higher prevalence of BCC would have increased PPV, and the lower prevalence of SCC and CM would have decreased the PPV. Reasonable weight can be put on the clinical diagnosis of BCC as it was accurate in almost three quarters of cases. This finding confirms a number of previous studies in general practice.(133, 134, 136-139) Diagnostic performance was lower for the individual clinical diagnoses of SCC, IEC, SK, and CN, which were correct in approximately half of cases and lowest for the individual clinical diagnoses of CM, CM in situ, AK and KA, which were correct in only around one third of cases. In clinical practice it is more important to identify and treat appropriately the most serious lesions (SCC, CM and CM in situ) than to misdiagnose but excise a relatively small number of the less serious (or benign) lesions. Hence from a clinical perspective the relatively low PPVs for SCC, CM, and CM in situ, indicating an over-diagnosis of malignancy, are arguably a sign of caution on the part of the doctors.

In the majority of cases, when an incorrectly diagnosed lesion had been excised, the excision was still justifiable – in other words, the result was the excision of a malignancy rather than of a benign lesion. For example, only 21% of lesions wrongly diagnosed as CM were CN or SK, while 19.5% were actually NMSC and 5.1% CM in situ. Of the clinical diagnoses of AN, the majority were CN although 8.6% were finally diagnosed as CM. It was reassuring that only 6.3% of lesions clinically diagnosed as CN proved to be CM. Seemingly, BCC were more likely to be misdiagnosed as CN than CM, although was not specified if these were pigmented BCCs. Among the 9% of “other” lesions which were clinically called CM were lesions that could, with appropriate dermatoscope training(140-142) be easily recognised as non-pigmented and excision avoided. More than 50% of lesions clinically diagnosed as AK proved to be NMSC, while less than 10% were actually benign lesions. It is likely that AK which were excised rather than treated medically or by ablation were either clinically more abnormal or too thickened to respond to other modalities.(139) Therefore the high proportion of false positive clinical diagnoses that proved to be malignant was unsurprising.

5.5.2 Sensitivities

The reported sensitivities in this study refer to and represent the diagnostic accuracy of excised lesions only. The true sensitivity of a clinical diagnosis can be determined only if all relevant skin lesions are assessed histologically to give the correct number of false negatives. This, however, would be clinically and ethically unacceptable and most likely unnecessary. Sensitivity of clinical diagnosis was highest for BCC, with the majority of the misclassification being SCC again indicating that practitioners usually recognize NMSC. Sensitivity of SCC, although lower, showed that a high proportion of the misclassified clinical diagnoses were actually BCC, AK or KA. These latter lesions can be similar in clinical appearance to one another and may require similar management.

CM were mainly misclassified as CN (20.9%) or BCC (14.4%), which is of clinical significance. Interestingly, CM in situ were less likely (12%) to be diagnosed as a benign lesion and therefore seemed to present less of a diagnostic problem than CM (however, numbers were small). Many excised CN had been correctly diagnosed rather than being excised because they had been misdiagnosed as CM.

For IEC and AK the misclassification was predominantly NMSC, while more than one-third of these lesions had no clinical diagnosis. Almost 500 SK were excised during the three year study period. Seborrhoeic keratoses are considered to be completely benign lesions, and there is no rebate to reward excision in the Australian Medicare system. The misclassification of SK ranged across pigmented and non-pigmented lesions; close to 30% of the SK that were excised had been clinically diagnosed as NMSC, but interestingly only 3% had been clinically diagnosed as melanoma. Seemingly, the majority of SK were excised to exclude NMSC rather than to exclude melanoma.

5.5.3 Different body-sites

Previous studies have shown that the highest density of NMSC occurs on the face when body surface is taken into account.(4, 24, 121, 123) However, further analyses of data from a high sun exposure region have shown that BCC seem to occur more frequently than SCC on the face, trunk and shoulders and that SCC arise more frequently than BCC on upper and lower extremities.(114, 122)

PPV and sensitivity for BCC and SCC stratified by body-site appeared to follow opposite patterns, and were highest in the body-site where these lesions occur more frequently. We may speculate whether learnt behaviour of doctors leads to over-diagnosis of each respective malignancy in the body-sites where it more commonly occurs, and to under-diagnosis in body-sites where it is less common. PPV for the scalp were above 60% for BCC, SCC, IEC, CM and naevi, seeming to indicate that more weight can be put on these clinical diagnoses in this body-site. The present stratified analysis of diagnostic accuracy by body-site is to our knowledge the first of its kind with a large enough sample size to allow detailed analysis. A smaller study in tertiary referral setting showed a similar pattern for sensitivity of diagnosis of BCC and SCC by body site.(143) The only other study(144) which stratified analysis by body sites combined SCC and BCC and so results are difficult to compare.

5.5.4 Comparisons between specialists and GPs

While GPs work in a primary care situation, specialists mostly see referred patients. Because of these differences in clinical context, it is difficult to present a meaningful comparison between the diagnostic accuracy of GPs and specialists.(145) In the present analysis, with the exception of BCCs, there was little difference in the diagnostic performance between the two groups of

doctors. Previous studies in this area have produced varying results, but have again been inadequate in demonstrating any meaningful differences.(145)

5.5.5 Limitations to the study

There are several limitations to the analysis, interpretation and generalisation of these data which must be acknowledged. Firstly, the clinical diagnosis was obtained from completed histology request forms as part of a registry style study, rather than being specifically requested for the purposes of the study. Clinical diagnosis was unrecorded in 23.5% of excisions, and the reason for this remains unclear. We did not measure the certainty of the clinical diagnosis, or clarify whether doctors entered the diagnosis which they felt to be correct, or the one they wished to exclude. We did not measure the reason for the excision. The calculated sensitivities are likely to be under-estimated because missing clinical diagnoses were included in our calculations as true negative diagnosis. We also calculated sensitivities which excluded missing lesions and it is likely that the true figure is somewhere between those values.

Secondly, there were no pre-determined categories for clinical diagnosis, and different clinicians may categorise their clinical diagnosis in different ways. For example some clinicians may use the term SCC to incorporate IEC, or 'changing naevus' rather than 'atypical naevus'. Thirdly, the limitations in the use of PPV and sensitivity have been mentioned before. It must be acknowledged that this study does not assess how many skin cancers were missed and therefore failed to be excised. We neither calculated specificity nor negative predictive value as in the absence of an accurate measurement of the true negative diagnosis we did not feel these calculations would be meaningful.

5.5.6 Increased training for better diagnosis

There is evidence that training can improve diagnostic accuracy.(44, 146, 147) Identification of common types of clinical misclassifications based on histological diagnosis, as in the present study, could help focus and improve skin cancer related educational programs for both specialists and GPs. Facilitating pathology audits of skin cancer diagnoses and performance is another practical way of providing feedback to doctors and has been shown to improve the accuracy of diagnoses.(147, 148) Our present study and others highlight areas where diagnostic performance is lacking so provides very specific educational needs that should be incorporated into under- and postgraduate training in the diagnosis of skin cancer.

5.5.7 Conclusion

Diagnostic accuracy was highest for BCCs, the most prevalent lesion. Most excisions were correctly diagnosed or resulted in the removal of malignant lesions. With non-melanocytic lesions, doctors tended to misclassify benign lesions as malignant, but were less likely to do the reverse, which can be considered safe practice in a high incidence area. Although it was reassuring that only a small number of clinically diagnosed common naevi subsequently proved to be melanoma, a higher proportion of all melanoma had been classified as benign, but the fact that they had been excised suggests a high index of suspicion. When diagnosing SCC, doctors were most accurate in the region of the limbs, and when diagnosing BCC, they were more accurate in the region of the face, trunk and shoulders.

5.6 Summary

In this chapter we explored the ability of medical practitioners to diagnose skin cancer accurately.

A total of 8,694 skin excisions were analysed. PPV for the clinical diagnoses were: Basal cell carcinoma (BCC) 0.727, squamous cell carcinoma (SCC) 0.494, cutaneous melanoma (CM) 0.333. Sensitivities for the clinical diagnosis were: BCC 0.639, SCC 0.411, and CM 0.338. For BCC, PPVs and sensitivities were higher for the trunk, the shoulders and the face and lower for the extremities. The reverse pattern was seen for SCCs.

Diagnostic accuracy was highest for BCC the most prevalent lesion. Most excisions were correctly diagnosed or resulted in the removal of malignant lesions. With non-melanocytic lesions, doctors tended to misclassify benign lesions as malignant, but were less likely to do the reverse. Although a small number of clinically diagnosed common naevi subsequently proved to be melanoma (6.3%), a higher proportion of all melanoma had been classified as common naevi (20.9%). Accuracy of diagnosis was dependant on body-site.

However it is also important for GPs in their diagnosis and management to recognize that there are difficulties for dermato-pathologists to accurately differentiate different types of malignant and pre malignant lesions. The next chapter will further explore this idea.

CHAPTER 6: AGREEMENT BETWEEN HISTOLOGICAL DIAGNOSIS OF SKIN LESIONS BY HISTOPATHOLOGISTS AND A DERMATOPATHOLOGIST

In this chapter we examine the agreement between the histological diagnosis of skin lesions by histopathologists and an expert dermatopathologist. This chapter forms a sub-chapter of chapter 5, as it was developed as a secondary data analysis from the same study from which the previous chapter was also derived. The objective was to compare “standard” pathology diagnosis with the diagnosis from an internationally renowned dermatopathologist. The published article forms Appendix 5.(149)

6.1 Introduction

In Australia the majority of suspicious skin lesions are managed by general practitioners (GPs)(38) and the proportion of all skin cancers excised by GPs is increasing.(39) It is therefore important that doctors diagnose skin cancer correctly, and accurate histological diagnosis is needed to support this. There are several studies in the literature which show inter-observer variation in the histological diagnosis of melanocytic lesions.(150-152) Literature regarding keratonocytic lesions is more limited, but diagnostic discordance between pathologists has been recorded.(153, 154)

The main purpose of the present study was to investigate agreement of the primary histological diagnosis of excised skin lesions on a stratified sample from a large data set, which represents close to all skin excisions which took place over a three year period in a regional centre in North Queensland.

6.2 Methods

As reported in detail in the previous chapter, between the end of 1996 and October 1999, a study was undertaken which recorded all excised and histologically confirmed skin cancers in Townsville/Thuringowa, North Queensland, Australia (latitude 19.16°S; population approximately 130,000).(4, 122)

To reiterate from the previous chapter, for the duration of the study, pathology reports on excised skin cancers were collected from the three local pathology laboratories, which routinely collected reports on NMSC to send to the Queensland Cancer Registry. These laboratories

processed the pathology requests from all hospitals, GPs and specialists in Townsville (202 GPs and 42 specialists - including one dermatologist, plastic surgeons and general surgeons). As Townsville's location is relatively isolated, it can be assumed that almost all skin cancers were treated locally. The data collected on excised skin cancers is likely to be almost complete, as doctors in Townsville routinely seek histology for all excised skin lesions.

Prior to the study all participating pathologists attended a workshop to reach agreement on criteria for the histological diagnosis of skin lesions with consultant dermato-pathologist Dr David Weedon. Dr Weedon agreed to review a blinded stratified random sample of 407 histology slides of BCC, SCC, actinic keratosis (AK), CM, and common naevi (CN) to investigate agreement of the primary histological diagnosis.

6.2.1 Statistical analysis

Positive predictive values (PPVs) together with exact 95%-confidence intervals (95%-CI) were calculated for the histological diagnoses of BCC, SCC, AK, CM, and CN taking the histological diagnosis of the dermato-pathologist as the "gold standard".

6.3 Results

Between December 1996 and October 1999 a total of 8,694 patients (mean age 58.6 years; 55.2% male) with up to 72 excisions per patient were recorded. Further detailed descriptions of the patients and the incidence of skin cancer were previously published.(4, 122)

PPVs for the primary histological diagnosis were above 90% for BCC, CM and CN (Table 6.1), for SCC 72.6% (95%-CI = [65.5, 79.0]), and for actinic keratosis was 82.6% (95%-CI = [73.3, 89.7]). The dermato-histopathologist re-classified 27.4% of histologically classified SCCs to AKs. Similarly he re-classified 10.9% of histologically classified AKs to SCCs.

Table 6.1: Agreement between diagnosis of Townsville histologists and a dermatohistopathology specialist (DW). Positive predictive values (in bold) together with 95% confidence intervals are given

Histological diagnosis	Dermato-histopathology specialist					
	BCC	SCC	Actinic keratosis	Cutaneous melanoma	Common naevus	Other
BCC (n=83)	92.8% 84.9, 97.3	2.4%	2.4%	0%	1.2%	1.2%
SCC (n=179)	0%	72.6% 65.5, 79.0	27.4%	0%	0%	0%
Actinic keratosis (n=92)	2.2%	10.9%	82.6% 73.3, 89.7	0%	1.1%	3.3%
Cutaneous melanoma (n=23)	0%	0%	4.3%	91.3% 72.0, 98.9	4.3%	0%
Common naevus (n=30)	0%	0%	6.7%	0%	93.3% 77.9, 99.2	0%

6.4 Discussion

The strengths of our study were a large sample size and close to complete epidemiological data over a three-year period, which implies reduced selection bias, probably resulting in a representative sample of skin lesions and doctors. Thus the stratified random sample of slides that were analysed were likely to be a representative sample of skin cancers removed by doctors in routine clinical practice.

There are some limitations to the analysis, interpretation and generalisation of these data which must be acknowledged. Our study looked at agreement between a small group of locally based histologists and a single dermatohistologist. We have no demographic information regarding the local histologists, and therefore no information on whether they were representative of Australian or international histologists. We did not assess the individual histological characteristics that lead to a diagnosis, and this may have allowed us to define areas to increase

reliability. We did not grade whether SCCs were considered to be well or poorly differentiated, and we did not attempt to measure the degree of agreement.

Agreement between the histologists and the dermato-histopathologist specialist was highest for BCC, CM and CN. The main area of lack of agreement was between the diagnosis of AK and SCC. The dermato-histopathologist tended to be more likely to re-classify previously diagnosed malignant lesions as benign within this sub-group.

Lack of agreement between pathologists regarding the diagnosis of SCC and AK has been previously recognised in the literature(154, 155) and this is again reflected in our study. This also illustrates the difficulty involved for doctors in accurately clinically diagnosing lesions for which a consensus is hard to reach histologically. However this histological diagnosis is of clinical importance, as the decision on whether to treat a lesion with excision, ablative treatment or topical medication relies on accurate histological diagnosis.(139) In addition, invasive SCCs may have the potential to recur and metastasize.(156)

There is a clinical spectrum between invasive SCC, SCC in situ, and AK, however the boundaries of these conditions are imprecisely defined, and therefore distinction between diagnosis may be unreliable.(156) To confuse matters further, there is also some controversy in the literature regarding the proportion of AK which progress to SCC, and indeed whether all AK should be considered to be SCC.(157)

Given the potential clinical implications of these diagnoses, our results emphasize the need to improve the reliability of these histological diagnoses. Identification of common types of histological misclassifications, as in the present study, could help focus pathologists training and education in order to improve diagnosis.

6.4.1 Conclusion

Agreement between the histologists and the dermato-histopathologist specialist was generally high. The main area of lack of agreement was between the diagnosis of AK and SCC, with the dermato-histologist being more likely to classify lesions initially diagnosed as malignant to be benign.

6.5 Summary

Positive predictive values for the primary histological diagnosis were above 90% for basal cell carcinoma, cutaneous melanoma and common naevus. For squamous cell carcinoma the positive predictive value was 72.6% (95%-CI = [65.5, 79.0]).

Lack of agreement between histopathologists regarding the diagnosis of squamous cell carcinoma and actinic keratosis has been previously recognised in the literature and this is again reflected in our study. The result also illustrates the difficulty involved for doctors in accurately clinically diagnosing lesions for which a consensus is hard to reach histologically.

In the previous three chapters we explored the case-mix (demographic and tumour characteristics) of skin cancer excised by GPs in North Queensland, illustrated the importance of diagnosing skin cancer accurately, and illustrated some of the areas of diagnostic difficulty. We established that pathologists may also disagree in their diagnosis of skin cancer. In the next chapter we use the information from the previous three chapters in order to comment on some of the limitations in comparing skin cancer doctors with mainstream GPs with regard to diagnostic accuracy, and examine the difference in case-mix between these two groups.

CHAPTER 7: COMPARING THE CASE-MIX AND NUMBER NEEDED TO TREAT OF GPs AND SKIN CANCER CLINIC DOCTORS

This chapter presents a letter to the editor in response to a publication comparing the diagnostic accuracy of skin cancer doctors and general practitioners. The letter also presents some original research regarding the relative case-mix and number needed to treat (melanocytic naevi excised per melanoma) using secondary data analysis from the ‘Can sutures get wet?’ project. This chapter is an extension of both chapter 4 (by discussing case-mix and NNT) and chapter 5 (by discussing case-mix and diagnostic accuracy) The published article forms Appendix 6.(158)

7.1 Background

There is little data available regarding the diagnostic accuracy of Australian GPs with regard to excised and biopsied skin lesions. A new recently published study compared the diagnostic accuracy of GPs and skin cancer clinic doctors.

The objectives of this study are:

- (1) To comment on the limitations of comparing skin cancer doctors with mainstream GPs.
- (2) To compare the case-mix and number needed to treat between GPs and mainstream skin cancer doctors using secondary data analysis.

7.2 Letter to the editor

Dear Editor

In a recent article, Youl and colleagues(133) provided information about the ability of doctors to accurately diagnose skin lesions that they excise or biopsy. We wish to offer some comments about the comparison between general practitioners (GPs) and skin cancer clinic doctors.

Firstly, the behaviour of GPs and patients in mainstream practice is different from that of doctors and patients in skin clinics, as is indicated in the comparison of frequency of total skin examinations (GPs 30.4%, Skin clinic 73.2%). The study does not indicate the circumstances under which each decision to excise took place. Did patients become aware of a new or changing skin lesion, and bring it to the attention of the doctor, or did the diagnosis result from

a full body skin check which might have resulted in the diagnosis of an earlier, previously unnoticed and more subtle lesion? It may be useful to separate basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) into histological subtypes, as early superficial BCC and intraepidermal SCC may be more difficult to diagnose than other subtypes.(139)

Secondly, the case-mix of non-melanotic skin cancer was quite different between the two groups (BCC:SCC ratio GPs 1.1:1, skin cancer doctors 2.1:1). This difference in case-mix was reflected in our own study,(114) where we described the histology of 1,247 lesions excised by doctors which included 76 lesions undertaken by one doctor in a designated skin cancer clinic. In an unpublished sub-analysis we divided the results into two settings for comparison (Table 7.1). We found that the skin clinic doctor also had a significantly different (<0.001) non-melanotic skin cancer case-mix than the GPs, with a much larger BCC:SCC ratio (4:1 to 0.6:1). We believe this most likely reflects an increased pick up of BCC because of the frequency of full-body skin examination in the skin clinic context and the consequent detection of lesions of which the patient is unaware.

Table 7.1: Comparison of lesion excisions in skin cancer clinic and general practice settings

	Mean patient age (years)	Proportio n of excised lesions that were malignan t*	BCC : SCC ratio	Number needed to treat†
Skin cancer clinic	56.5	76% (58/76)	4 : 1 (44/11)	4.7 (14/3)
General practice	56.9	45% (512/1145)‡	0.6 : 1 (190/305)	9.0 (154/17)

BCC = basal cell carcinoma. SCC = squamous cell carcinoma. * BCC, SCC or melanoma. † Benign or dysplastic naevi excised per melanoma. ‡ There were 26 cases in which histology results were missing. All were in the general practice setting

Thirdly, the reported sensitivity and specificity in this study refers only to excised lesions. We have no information about the lesions that practitioners decided not to excise. The sensitivity and specificity of a skin examination can only be determined if all relevant skin lesions are assessed. This would give an accurate representation of the number of true and false negative diagnosis. However, this would require multiple excisions which would be clinically

unacceptable. An important limitation of this study is that it does not assess or compare how many skin cancers each group of doctors missed.

In conclusion, although this study provides comprehensive information about diagnostic accuracy, we do not feel a meaningful comparison between the two groups of doctors – based on the information available – can be made.

7.3 Summary

We found that the case-mix of non-melanocytic skin cancers was significantly different for the two groups of doctors ($P < 0.001$). The BCC:SCC ratio was much higher for skin cancer clinic doctors (4:1) than for GPs (0.6:1). The NNT (melanocytic naevi excised per melanoma) was 4.7 for the skin cancer doctor and 9.0 for mainstream GPs.

There are some limitations in comparing skin cancer doctors with mainstream GPs with regard to diagnostic accuracy, and the case-mix between these two groups is actually quite different. We believe the difference in BCC:SCC ratio most likely reflects an increased pick-up of BCC in skin cancer clinics, owing to the higher frequency of full body skin examinations and the consequent detection of lesions of which the patient is unaware.

The previous chapters of this thesis have presented the results of two large clinical trials conducted in general practice in North Queensland. The next chapter will discuss the process of conducting successful practice based research.

CHAPTER 8: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

This thesis comprises a literature review and seven original studies. This chapter will integrate and synthesise the information from the previous chapters. In this chapter, the literature review will be updated and then the conclusions of the individual chapters with recommendations will be discussed.

8.1 Update of literature review

New literature (from 2007-2009) which is notable has become available in the following sections of the literature review.

8.1.1 Incidence of melanoma in Australia

In 2008, new clinical practice guidelines for the management of melanoma in Australia and New Zealand were published, which provided a summary of the incidence of melanoma in Australia. In addition, the AIHW cancer registry produces online information regarding melanoma incidence, although, as stated in the introduction, there is generally a time lag of around four years before this information becomes available. In the most recent registry information⁽¹⁷⁾ the age standardised incidence rates in Australia, based on world aged standardised incidence rates in 2005 were 46.1 for men and 34.6 for women. In 2005 a total of 10,684 melanoma were diagnosed.

A 2002 study used data from the population-based Queensland Cancer Registry to estimate the annual percentage change in rates across 21 years of incidence data for in situ and invasive melanomas, stratified by age and sex. In situ melanomas increased by 10.4% per year among males and 8.4% per year among females. The incidence of invasive lesions has also increased in males 2.6% per year and females 1.2% per year. Although the shift to more in situ lesions would tend to reflect improved surveillance, the age standardised incidence is continuing to increase in all categories. Primary prevention is unlikely to lead to decreases in the overall incidence of melanoma for at least another 20 years.⁽¹⁵⁹⁾

A second study analysed data from the Queensland Cancer Registry to investigate geographical differences and time trends of incidence rate of cutaneous melanoma in Queensland between 1982 and 2002.⁽¹⁶⁰⁾ Yearly age standardised incidence rates world standard population of cutaneous melanoma averaged over 21 years of observation were highest in the south-eastern

part of the state, notably in the statistical division of Moreton for men (54.2) and in Fitzroy for women (51.4). Inland divisions had on average lower rates than coastal areas. For both men and women, age standardised incidence rates of invasive and for in situ melanoma increased between 1982 and 2002 for Queensland as a whole and for almost all its statistical divisions. For invasive cancer, the increase was strongest for Moreton. For Morton, the annual percentage change (APC) was men: 5.4%; women: 4.5%; $p < 0.001$, respectively). APCs were higher for in situ melanoma compared with invasive melanoma for all statistical divisions and both genders. It was concluded that the behavioural and lifestyle choices might create the observed differences between statistical divisions.

In conclusion to this updated literature review, the incidence of melanoma in Australia is still high and increasing, in particular for in-situ melanoma.

8.1.2 Literature update, conclusions, recommendations based on chapter 2: Risk factors for infection after minor surgery in general practice

The aim of this chapter was to determine the incidence of and risk factors for surgical site infections (SSI) following minor surgery in a general practice setting. Excisions from lower legs and feet ($p=0.009$) or thighs ($p=0.005$), excisions of BCC ($p=0.006$) or SCC ($p=0.002$) and diabetes ($p < 0.001$) were found to be independent risk factors for wound infection. We felt that the results of this study could encourage the more judicious use of prophylactic antibiotics by defining these high-risk groups in a general practice setting, such as diabetics and those undergoing excision of a non-melanocytic skin cancer or excision from the lower limb.

In 2006, while our 'Risk factors for infection after minor surgery' paper was in press, a trial was published by Dixon et al.(113) It showed the following results (Table 8.1).

Table 8.1: Risk factors for infection, Dixon et al 2006

	Setting and sample size	Study design	Wound type	Incidence of infection	Risk factors for infection
Dixon et al 2006 Australia	Skin cancer surgery outpatients, 5,091 lesions, 2,424 patients	Prospective observational study	Skin cancer surgery	1.47%	Below knee surgery (6.92%) Groin (10%), Skin grafts (8.7%)

In contrast to our study which had an infection rate of 8.3% this study had a very low infection rate. This study did not show diabetes to be a risk factor for infection. However both studies were in agreement that below knee surgery was a risk factor for infection. Dixon et al used univariate rather than multivariate analysis to determine risk factors for infection.

In 2008 an advisory statement was produced from the Divisions of Dermatological Surgery and Infectious Diseases at the Mayo Clinic regarding antibiotic prophylaxis in dermatological surgery (Appendix 11).(105) These guidelines concluded that for the prevention of SSI, antibiotics may be indicated for procedures on the lower extremities or groin, for wedge excisions of the lip and ear, skin flaps on the nose, skin grafts and for patients with extensive inflammatory skin disease.

The guidelines quote ‘An Australian trial involving 857 cutaneous surgical procedures documented a 8.6% rate of infection, with infections more common in patients with diabetes, for skin cancer rather than benign lesions, and for surgical sites located on the thighs, legs or feet’ and ‘ The study by Dixon et al documents increased risk of SSI on sites below the knees. We have expanded this for patients with prosthetic joints, and to include all sites in the groin and all areas of the lower extremities based on the findings of the study of Heal, Buettner and Browning.’

In conclusion, our study, together with the study by Dixon et al, has helped to define risk factors for infection after dermatological surgery. Even within cohorts with a low overall risk of infection, some excisions may be at higher risk of infection because of body site, pathology or patient factors, and infection rate may be greater than 5%.(57, 113) These risk factors may include excisions from the lower leg, excisions of skin cancers and excisions from diabetic patients. These risk factors have been adopted to develop a guideline for the use of antibiotic prophylaxis for minor dermatological surgery.

8.1.3 Literature update, conclusions and recommendations based on chapter 3: Does single dose of topical chloramphenicol ointment to high risk sutures wound decrease the incidence of wound infection after minor surgery?

The aim of this study was to compare incidence of infection after minor surgery using a single application of chloramphenicol ointment versus using paraffin ointment. We concluded that application of a single dose of topical chloramphenicol to high risk sutured wounds after minor surgery produces a moderate absolute reduction in infection rate which is statistically but not clinically significant.

The study was published in the BMJ with an accompanying editorial which supported our findings and recommended that topical antibiotics should not be used for infection prophylaxis after minor surgery (Appendix 9).(161)

Our article in the BMJ received several rapid responses, some of which questioned our high infection rate, and criticised the fact that we had not measured skin integrity as a variable.(162) We responded to these criticisms in ‘rapid responses’. The editorial did suggest that we had used inflammation as one definition of infection, a matter which we refuted in ‘rapid responses’ (Appendix 10).

Our study analysed a total of 85 infections in order to detect a significant difference between two treatments. This is the largest number of infections that have been analysed in the published literature of this type of study. As previously discussed, we feel that previous studies may have been underpowered to adequately demonstrate the effectiveness of antibiotic ointment in this setting.

In summary, the main recommendation of this chapter is that prophylactic antibiotics should not be used routinely after minor surgery. This was supported by an editorial which accompanied this publication.

8.1.4 Literature update, conclusions and recommendations based on chapter 4: Minor skin excisions in general practice in North Queensland

In 2007 a study was published in AFP which analysed the billing data in the management of skin cancer from 1 July 2005 to 30 June 2006 in three Queensland general practices (metropolitan, provincial, and rural) representing 23,100 patients treated by 23 doctors.(163) As far as possible, methods were matched to those used in two published studies of skin cancer clinics. Of the 1,417 skin cancers the number needed to treat (NNT) was 39, compared with 29 in one skin cancer clinic network and 24 in the other. Fifty-four per cent of all excised lesions were malignant, compared with 60% in one network and 46% in the other, respectively. These results showed the benign to malignant excision rate was similar in general practice and the skin cancer clinic networks. This study showed a much higher NNT than our own study, although skin cancer yield was similar. These results again support our recommendation that GPs in Mackay could lower their threshold for the excision of pigmented lesions.(163)

A study was published in 2009 which calculated the NNT by skin cancer clinic doctors. It utilised a large pathology database. NNT was calculated for 10,612 lesions, 6,796 patients, 57

doctors and 15 clinics. Overall the NNT was 30 without seborrheic keratosis and 23 with seborrheic keratosis in the denominator. However when four outlying doctors were excluded, this was decreased to 21 and 15, respectively. There was found to be substantial variability in individual doctor NNT, with figures varying by individual doctor from 0 to 192 and 117, respectively.

There are some limitations to the calculation and use of the term NNT in order to measure performance in the management of skin cancer. The numerator varies in different definitions of NNT, making results difficult to compare. The measure of NNT may not be indicative of quality. A high or low NNT does not directly indicate the number of false negative diagnosis of melanoma, which is the most important factor in the management of melanoma skin cancer. Case-mix and patient demand may differ in different settings and will influence NNT.

The aim of this chapter was to describe the histology of lesions excised by general practitioners in rural North Queensland, the sites that skin cancers are removed from and the demographics of patients presenting with skin cancer. Our findings were that close to half (46.7%) of lesions excised were skin cancers. We excised more squamous cell carcinomas than basal cell carcinomas (in a ratio of 1:0.74). Our number needed to treat (melanocytic naevi excised per melanoma) was 8.4. Mean age for excision of melanoma, basal cell carcinoma and squamous cell carcinoma was 55, 60.9 and 63.8 yrs respectively. Relative tumour density was greatest in the face, scalp and neck region for all skin cancers.

My conclusion was that in this sample of Mackay GPs, there was a very high yield of skin cancers from all excisions. The doctors involved in the study could consider lowering the threshold for excision of pigmented lesions.

8.1.5 Conclusions and recommendations of chapter 5: Agreement between clinical and histological diagnosis of skin lesions

The aim of this chapter was to compare the clinical with the histological diagnosis of excised skin lesions from a set of epidemiological data. We analysed diagnostic accuracy stratified by histological subtype and body-site and examined the histological nature of misclassified diagnosis.

My conclusion was that diagnostic accuracy was highest for BCC the most prevalent lesion. Most excisions were correctly diagnosed or resulted in the removal of malignant lesions. With non-melanocytic lesions, doctors tended to misclassify benign lesions as malignant, but were

less likely to do the reverse. Although a small number of clinically diagnosed common naevi subsequently proved to be melanoma (6.3%), a higher proportion of all melanoma had been classified as common naevi (20.9%). Accuracy of diagnosis was dependant on body-site. I recommended that increased education and training in areas of diagnostic weakness could improve the management of skin cancers by doctors.

There have been no new papers identified in the literature on the diagnostic accuracy of skin lesions since this article was published. I am currently developing a manuscript which compares the diagnostic accuracy of GPs with specialists in the diagnosis of skin cancer.

8.1.6 Conclusions and recommendations of chapter 6: Agreement between histological diagnosis of skin lesions by pathologists and a histopathologist

The aim of this chapter was to compare agreement for histological diagnosis between local histopathologists with a dermato-histopathologist from a stratified random sample of excised skin lesions derived from a set of epidemiological data.

My conclusion was that lack of agreement between histopathologists regarding the diagnosis of squamous cell carcinoma and actinic keratosis has been previously recognised in the literature and this is again reflected in our study. The result also illustrates the difficulty involved for doctors in accurately clinically diagnosing lesions for which a consensus is hard to reach histologically. There are also implications for the patient - treatment of SCC usually involves excision, while AK can be treated with ablative procedures. There are also financial consequences – treatment of SCC generally results in higher Medicare billings than treatment of AK.

I hope that the results of this study increase awareness between pathologists that there is lack of agreement in diagnosis, and also that GPs managing skin cancer are aware that diagnoses in skin cancer are subject to differences in interpretation.

8.1.7 Conclusions and recommendations of chapter 7: Comparing the case-mix and number needed to treat of GPs and skin cancer clinic doctors

The aims of this chapter were: (1) To comment on the limitations of comparing skin cancer doctors with mainstream GPs and (2) To compare the case-mix and number needed to treat between GPs and mainstream skin cancer doctors using secondary data analysis.

I found that the case-mix of non-melanocytic skin cancers was significantly different for the two groups of doctors ($p < 0.001$), and that the BCC:SCC ratio was much higher for skin cancer clinic doctors (4:1) than for GPs (0.6:1). The NNT (melanocytic naevi excised per melanoma) was 4.7 for the skin cancer doctor and 9.0 for mainstream GPs. I concluded that there are some limitations in comparing skin cancer doctors with mainstream GPs with regard to diagnostic accuracy, and the case-mix between these two groups is actually quite different. We believe the difference in BCC:SCC ratio most likely reflects an increased pick-up of BCC in skin cancer clinics, owing to the higher frequency of full body skin examinations and the consequent detection of lesions of which the patient is unaware. I would recommend that these differences are taken into account in the design and interpretation of any future studies comparing the diagnostic accuracy or NNT between the two groups.

There have been no further studies which have directly compared the diagnostic accuracy or case-mix between the two groups of doctors prospectively. A study was published in AFP which compared the billing data between the two groups and used this to compare the NNT.⁽¹⁶³⁾ I am currently analysing data which compares the diagnostic accuracy between GPs and specialists, and we will use the conclusions and recommendations of this chapter to help with the analysis and interpretation of the new data.

8.2 Overall conclusions

Patients with minor skin excisions in North Queensland have a high incidence of wound infection. Topical chloramphenicol ointment decreases this incidence moderately. GPs in North Queensland have a high yield of skin cancer from their skin excisions and a low number needed to treat (melanocytic naevi excised per melanoma). Doctors diagnose skin cancers accurately, but there are some areas of diagnostic difficulty in particular in the diagnosis of actinic keratosis and squamous cell carcinoma. GPs and skin cancer doctors have a different skin cancer case-mix. Enabling factors to conducting research in general practice include ownership of the project, engaging practice nurses, and adequate funding.

8.3 Overall recommendations

1. I recommend that antibiotic prophylaxis prior to minor surgery in general practice be limited to the high risk groups that were identified. Antibiotic prophylaxis tends to be over-utilised in the management of minor surgery, particularly as the consequences of infection are often minor and side-effects from antibiotics, such as allergy, can potentially be serious.

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2. The use of topical chloramphenicol ointment to prevent infection after minor surgery is best reserved for high risk groups. The reduction in infection was only 40%, which was statistically but not clinically relevant. The overutilization of topical antibiotics has potentially adverse consequences such as antibiotic resistance and allergic contact dermatitis.
 3. The doctors involved in my study in Mackay could consider lowering their threshold for excision of pigmented lesions. In our sample of Mackay GPs, there was a very high yield of skin cancers from all excisions, and NNT (melanocytic naevi excised per melanoma) of 8.4, which was lower than published data from comparable cohorts.
 4. Educational programs for doctors regarding the diagnosis of skin cancer could focus on areas of diagnostic weakness which were identified in our study, such as differentiating melanocytic naevi from malignant melanoma, and differentiating clinically and histologically between actinic keratosis and squamous cell carcinoma.
 5. There is increasing evidence for lack of agreement between histopathologists regarding the diagnosis of squamous cell carcinoma and actinic keratosis, and it is important that doctors are aware of this area of discordance.

8.4 Where to from here – research questions identified and future studies

The studies involved in this thesis have illustrated the very high infection rate following minor surgery in general practice in Mackay. Studies conducted at other locations identified in our literature review report an infection rate following dermatological surgery of 1-5%. In our first RCT which was conducted as a background to this thesis, we reported a high overall infection rates of 8%.(7) The overall infection rate in our antibiotic ointment RCT was 8.7%, with an infection rate in our placebo group of 11%. Further studies could explore theories for this high infection rate. This could take the form of a case-control study of people with infections after minor surgery to identify risk factors for infection, or comparing infection rate in a tropical with a temperate climate. Other factors could be studied in addition to clinical factors such as occupation, personal hygiene factors, humidity, smoking, and factors involving practice doctors and nurses.

The author also plans to combine the results of the two RCTs and analyse the risk factors for infection in a descriptive study, thus providing stronger evidence for risk factors for infection.

There is very little existing evidence in this area, and most are small studies which involve only a small number of infections. Therefore combining these studies would provide much stronger statistical and clinical evidence for risk factors for infection. It is very important clinically to establish risk factors for infection in order to optimise antibiotic prophylaxis and post-operative wound management.

We have explored diagnostic accuracy of doctors and stratified by body site and histological sub-type of lesion. Further research which is currently ongoing compares the diagnostic accuracy of GPs and specialists. Further research could involve the development of educational intervention to target areas of diagnostic inaccuracy such as the interface between squamous cell carcinoma and actinic keratosis.

Other future studies identified from the literature review would be a meta-analysis of studies comparing antibiotic ointments as prophylaxis against wound infection. Again, there are limiting existing published studies in this area, often with very small numbers of infection, and combining these studies would provide more evidence for the efficacy of antibiotic ointment.

The thesis has illustrated that large randomised controlled trials may be conducted successfully in a general practice setting

Following the success of two randomised controlled trials involving minor surgery in general practice, the author is in the process of developing a new RCT which compares the standard management of sebaceous cysts with the 'punch excision technique'.

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**APPENDIX 1.
RISK FACTORS FOR WOUND INFECTION AFTER
MINOR SURGERY IN GENERAL PRACTICE**

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Risk factors for wound infection after minor surgery
in general practice

Clare Heal, Petra Buettner and Sheldon Browning

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APPENDIX 2.
**DOES SINGLE APPLICATION OF TOPICAL
CHLORAMPHENICOL TO HIGH RISK SUTURED
WOUNDS REDUCE INCIDENCE OF WOUND
INFECTION AFTER MINOR SURGERY?
PROSPECTIVE RANDOMISED PLACEBO
CONTROLLED DOUBLE BLIND TRIAL**

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Does single application of topical chloramphenicol to high risk sutured wounds reduce incidence of wound infection after minor surgery? Prospective randomised placebo controlled double blind trial

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ABSTRACT

Objective To determine the effectiveness of a single application of topical chloramphenicol ointment in preventing wound infection after minor dermatological surgery.

Design Prospective randomised placebo controlled double blind multicentre trial.

Setting Primary care in a regional centre in Queensland, Australia.

Participants 972 minor surgery patients.

Interventions A single topical dose of chloramphenicol (n=488) or paraffin ointment (n=484; placebo).

Main outcome measure Incidence of infection.

Results The incidence of infection in the chloramphenicol group (6.6%; 95% confidence interval 4.9 to 8.8) was significantly lower than that in the control group (11.0%; 7.9 to 15.1) (P=0.010). The absolute reduction in infection rate was 4.4%, the relative reduction was 40%, and the relative risk of wound infection in the control group was 1.7 (95% confidence interval 1.1 to 2.5) times higher than in the intervention group. The number needed to treat was 22.8.

Conclusion Application of a single dose of topical chloramphenicol to high risk sutured wounds after minor surgery produces a moderate absolute reduction in infection rate that is statistically but not clinically significant.

Trial registration Current Controlled Trials

ISRCTN73223053.

INTRODUCTION

Chloromycetin ointment consists of 10 mg/g of chloramphenicol in plastibase 30W and soft white and liquid paraffin.¹² Chloramphenicol has a broad spectrum of activity against Gram positive and Gram negative bacteria, rickettsias, and *Chlamydia*.³ Chloramphenicol ointment is indicated for treatment of bacterial conjunctivitis, but little evidence exists for its effectiveness in prophylaxis or treatment of wound

infection. Despite this, it is regularly used in areas outside its main indication. Before our study, several of the investigating general practitioners had applied it to sutured wounds as prophylaxis against wound infection. A survey of UK plastic surgeons reported that 66% used chloramphenicol eye ointment in their practice, mainly as prophylaxis against infection.⁴ The ointment has been used as an adhesive for replacement of the nail bed.⁵ A comprehensive Medline search found only one other study relating to the use of topical chloramphenicol ointment on wounds; this study investigated the application of chloramphenicol ointment to wounds after hip replacement.⁶ The incidence of wound infection in the intervention group was reduced (4% v 8%), but the sample size was small and the results were not statistically significant.

Topical ocular chloramphenicol is widely used in the United Kingdom and Australia for the treatment of conjunctivitis, but is very rarely prescribed for this indication in the United States.⁷ Some controversy previously existed about the link between aplastic anaemia and topical ocular chloramphenicol, on the basis of a small number of single case reports,⁷ but two international case-control studies provided no support for this association. Although the association between ocular chloramphenicol and aplastic anaemia cannot be excluded, the risk is less than one in a million per treatment course.⁸ No incidences of aplastic anaemia after dermatological application have been reported, despite widespread use.

A previous study of wound infection after minor surgery involving general practitioners in Mackay, Queensland, showed an overall incidence of wound infection of 8.6%.^{9,10} This incidence was higher than expected on the basis of the published results of a similar Australian general practice cohort (1.9%), a skin cancer clinic cohort (1.5%), and a European dermatology clinic cohort (2%).¹¹⁻¹³ The acceptable rate of infection after clean minor surgery is suggested to be

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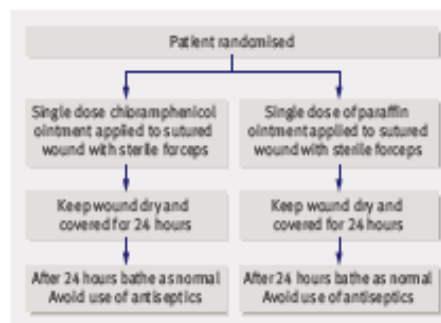


Fig 1 | Study protocol for patients

less than 5%.¹⁴⁻¹⁶ The low risk of infection after clean surgery means that studies of more than 1000 procedures (sometimes many more) are needed, under normal circumstances, to detect a reduction in infection from an intervention with statistical confidence.¹⁷ Because of the high incidence of infection in our patient cohort, and a high minor surgery workload,¹⁸ we decided to use the increased capacity to investigate a strategy to reduce the infection rate. In this trial, we sought to establish the effectiveness of topical chloramphenicol ointment in preventing wound infection after dermatological surgery. We used the Chloromycetin brand of chloramphenicol ointment applied as a single dose postoperatively, with paraffin ointment as placebo control.

METHODS

This was a randomised controlled double blind multi-centre trial involving patients presenting for minor skin excisions.

Setting and participants

We did the study in three private general practices in Mackay, Queensland, between June 2007 and March 2008. One of the participating practices consisted of one general practitioner working in an "open access" designated skin cancer clinic. Fifteen doctors working in the three practices recruited between one and 200 patients each.

We purposely selected the general practitioners as working at practices that had previously successfully participated in a wound management project.⁹ Practice

nurses invited consecutive patients presenting for minor skin excisions to take part in the trial. The nurses collected demographic information on all patients, as well as clinical information on the presence of diabetes or any other predetermined important medical conditions. They used a body site map to define the excision site. At the end of the study we asked the practice nurses to re-examine computer records to fill in any missing data. The principal researcher visited participating general practitioners and practice nurses to provide training and ensure that recording was standardised.

Eligibility criteria

All patients presenting to a participating general practitioner for "minor skin excision" from all body sites were eligible to participate in the study. Skin flaps and two layer procedures were recorded and included. We excluded patients who were already taking oral antibiotics, for whom oral or topical antibiotics were clinically indicated immediately postoperatively, or who were on immunosuppressive drugs. Other exclusion criteria were excision of sebaceous cyst, history of allergy to any of the ingredients of Chloromycetin ointment, and personal or family history of aplastic anaemia.

Surgical wound management protocol

We ran a workshop for participating general practitioners to develop guidelines to ensure that excisions were managed in a standardised manner. We were unable to reach consensus about skin preparations, so normal saline was used at one centre and chlorhexidine at two centres. The procedure shown in box 1 was agreed.

Intervention

We could not get information about the exact proportions of the constituents of the base of Chloromycetin ointment from the manufacturer. The principal investigator visited a compounding pharmacist to develop a close match to the vehicle of the Chloromycetin ointment by using a mixture of soft white and liquid paraffin, prepared single doses of the ointment in sterile jars, and stored them in a refrigerator. Immediately after suturing, the doctor applied either paraffin ointment or chloramphenicol ointment to the sutured wounds by using sterile forceps. Sufficient ointment was applied to cover the surface of the wound.

Recruitment, randomisation, and blinding

We used computer generated random numbers and opaque sealed envelopes to randomise patients. Only the principal investigator was aware of the identity of the coded ointments. The practice nurses enrolled patients and assigned participants to their groups. All participating patients received written instructions on postoperative wound care. Both groups were asked to

Box 1 Excision procedure

1. Skin preparation—normal saline or chlorhexidine
2. Usual sterile technique (standard precautions), including sterile gloves
3. Local anaesthetic (type and volume recorded)
4. Suture material—nylon (size recorded)
5. Dressing type—melolin and tape
6. No antibiotics, either topical or oral (if required, or already prescribed, exclude from study); no topical antiseptics, such as betadine or alcohol; no antiseptic washes or medicated soaps
7. Removal of sutures according to body site: back—10 days; all other sites—seven days

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take their dressing off after 24 hours and to avoid the using antiseptics (fig 1).

Clinical outcomes

The practice nurse or the doctor assessed wounds for infection on the agreed day of removal of sutures or sooner if the patient re-presented with a perceived infection. Practice nurses and doctors assessing outcome were blinded to the allocation of intervention and control groups. We adapted our definition of wound infection from standardised surveillance criteria for defining superficial surgical site infections developed by the Centre for Disease Control's National Nosocomial Infection Surveillance System (box 2).¹⁹ We also developed our own wound scale, after reviewing several existing scales in the literature,²⁰ in order to improve rigour. This wound scale differentiated no infection or erythema; stitch abscess; less than 1 cm erythema from the wound margin; greater than 1 cm erythema from the wound margin; and deep infection or systemic symptoms. The primary researcher briefed all participating doctors and nurses on the definition of infection and also gave them written information. We asked practice nurses to swab any discharging infections to investigate any pattern of antimicrobial resistance.

Sample size

We calculated sample size on the basis of our previous study, which showed an infection rate of 8.6%.⁹ On the basis of a projected infection rate of 10%, we decided that an absolute decrease in incidence of infection of 5% would be clinically significant. To come to this conclusion with statistical confidence—a power in excess of 80% and a significance level of 0.05—we needed a total of 473 patients in the intervention group and 473 patients in the control group.

Statistical analysis

We based all analysis on the intention to treat principle. Depending on the distribution, we describe numerical data as mean value and standard deviation or median value and interquartile range. We present percentages with 95% confidence intervals. Because the sample was recruited through 15 different general practitioners and outcome might be more similar for patients from one medical professional (clustering) than from several, we adjusted confidence intervals and P values for this cluster sampling approach. Participating doctors were the primary sampling unit, and we applied the survey

Box 2 Definition of surgical site infection

- Infection must be within 30 days of excision
- Purulent discharge from the wound must be present, or
 - The general practitioner must diagnose a wound infection, or
 - The general practitioner prescribes antibiotics
- Stitch abscess must not be counted as an infection

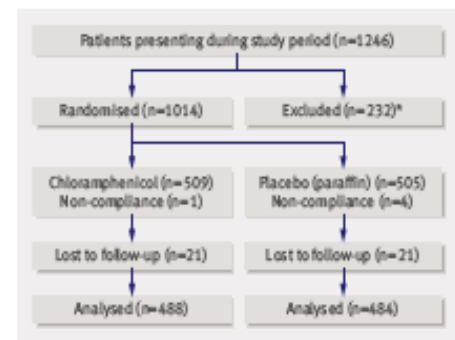


Fig 2 | Flowchart of enrolment, randomisation, and follow-up of patients. *See table 1 for reasons for exclusions

commands of Stata (release 8). We considered P values less than 0.05 to be statistically significant.

RESULTS

Practice and study characteristics

Of the total of 1246 patients who attended for skin excisions during the period from June 2007 to March 2008, 232 patients were excluded (table 1). Of the remaining 1014 patients, 509 were randomised to the intervention (chloramphenicol) group and 505 to the placebo (paraffin) group. A total of 42 patients were eventually lost to follow-up because they had their sutures removed elsewhere. Follow-up was completed in 972 (95.9%) randomised patients (fig 2).

Comparisons at baseline

Large differences existed between the intervention and the control groups at baseline (table 2). In the intervention group, 71.7% of patients were diagnosed with non-melanoma skin cancer or solar keratosis compared with 65.1% in the control group.

Incidence of infections

Infection occurred in 85 (8.7%) of the 972 excisions. The incidence of infection in the chloramphenicol group (6.6%; 95% confidence interval 4.9 to 8.8) was significantly lower than the incidence in the control group (11.0%; 7.9 to 15.1) (P=0.010; adjusted for cluster sampling). The relative risk of infection was 1.7 times higher in the control group compared with the intervention group (table 3). The number needed to treat (number of wounds treated for each infection prevented) was 22.8 (488/21.4).

We found no significant difference in the wound score between the control and intervention groups (P=0.253), although 5.5% of patients showed erythema greater than 1 cm in the intervention group compared with 9.1% of patients in the control group (table 3). Wound swabs were done for 24 of the 85 infections. These revealed *Staphylococcus aureus* infections that were resistant to benzylpenicillin but sensitive to all other antibiotics in 22 cases. In one case, additional resistance to erythromycin but sensitivity to all other antibiotics was noted. In another case, *Pseudomonas*

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Table 1 | Reasons for exclusion from study

Reasons	No (%) patients (n=232)
Patient declined participation	139 (60)
Patient on oral antibiotics	39 (17)
Doctor did not follow study protocol	20 (9)
History of allergy to Chloramphenicol	2 (1)
Patient did not plan to return for removal of sutures	12 (5)
Shave biopsy done	6 (3)
Patient on immunosuppressive drug	4 (2)
Patient with infected sebaceous cyst	10 (4)

aeruginosa was cultivated from the wound. These last two swabs were taken from patients in the control group.

DISCUSSION

The results of this study suggest that a single dose of topical chloramphenicol to sutured wounds can produce a relative reduction in infection rate of about 40%. The absolute reduction was 4.4%, which fell short of our pre-determined reduction for clinical relevance (5%), so this was essentially a negative trial. The incidence of infection in our control group (11%) is much higher than reported in the published literature

looking at similar cohorts.¹¹⁻¹³ The intervention thus may not produce a worthwhile absolute reduction in infection in low risk settings where infection rates are already low; the number needed to treat in these circumstances would be much higher than our figure of 22.8.

Limitations

The study had several limitations. Various characteristics influence the occurrence of infections; although we recorded information on as many variables as possible, ensuring that the baseline data were comparable proved difficult. For example, inadequate data were recorded on suture size and occupation, so we could not compare these factors. In addition, the prevalence of diabetes and of other medically important conditions was probably under-recorded, and power to analyse these subgroups was limited. Surgical training and technique of the general practitioners involved is a potential confounder that would be difficult to quantify and was not recorded. However, we adjusted the statistical analysis for the cluster sampling, taking the doctor as the primary sampling unit. The type of skin preparation used by the three participating practices differed, but we found no previously published evidence that this makes any difference to infection rates.²¹ A total of 42 participants were lost to follow-up. If all 21 participants who were lost to follow-up in the intervention group had developed an infection, the rates of infection in both groups would have been similar (10.4% and 11.0%); however, we believe that this scenario is extremely unlikely.

Diagnosis of infection—even when guidelines are used—is still subjective, and inter-observer and intra-observer variation may occur.²⁰ The definition we used is the most widely implemented standard definition of wound infection,¹⁹ and by developing our own wound assessment scale we hoped to reduce the subjectivity of diagnosis of infection. We have no evidence to support the intra-practice and inter-practice reproducibility of measurement and recording procedures.

The study did not have an arm in which no ointment was applied, so we do not know if the ointment itself had any pro-infective or anti-infective properties. The ointment base of Chloramphenicol consists of a mixture of soft white paraffin, liquid paraffin, and plastibase 30W, which is a plasticised hydrocarbon gel consisting of 95% mineral oil and 5% polyethylene glycol. We could not get information about the exact proportions of these constituents from the manufacturer. Our placebo ointment consisted of 50% soft white paraffin and 50% liquid paraffin and was not completely identical to the ointment base of Chloramphenicol as it did not contain plastibase 30W. We cannot determine if this substance has an effect on infection, although we think that this is unlikely. Our trial used only a single dose of chloramphenicol ointment. We have no reason to surmise that repeated doses might lead to a greater reduction in infection rate.

Table 2 | Baseline comparisons of intervention (chloramphenicol) and control (paraffin) groups. Values are numbers (percentages) unless stated otherwise

Characteristics	Intervention group (n=488)	Control group (n=484)
Patients		
Mean (SD) age (years)	59.5 (23.2)	59.0 (27.5)
Male	266 (54.5)	262 (54.1)
Smoking status:		
Never smoked	298 (61.1)	299/483 (61.9)
Ex-smoker	109 (22.3)	108/483 (22.4)
Current smoker	81 (16.6)	76/483 (15.7)
Diabetes mellitus	37 (7.6)	50/483 (10.4)
With medical condition*	79/478 (16.5)	86/475 (18.1)
Lesions		
Body site:		
Neck and face	166 (34.0)	152 (31.4)
Upper extremities	139 (28.5)	140 (28.9)
Trunk	108 (22.1)	102 (21.1)
Lower extremities	75 (15.4)	90 (18.6)
Histology:		
Melanoma and naevi	64 (13.1)	74 (15.3)
Non-melanoma skin cancer and precursor	350 (71.7)	315 (65.1)
Other†	74 (15.2)	95 (19.6)
Procedures		
Mean (SD) length of excision (mm)	20.9 (25.6)	21.0 (28.8)
Median (interquartile range) No of days until removal of sutures	7 (7-9)	8 (7-10)
With flap	1 (0.2)	3 (0.6)
With two level procedure	4 (0.8)	4 (0.8)

*Chronic obstructive pulmonary disease (n=14), aspirin or clopidogrel (n=120), oral steroids (n=3), continuous inhaled steroids (n=9), warfarin (n=42), ischaemic heart disease (n=7), peripheral vascular disease (n=6), and current cancer (n=21).

†Included sebaceous keratosis, re-excisions of melanoma and basal cell carcinoma, sebaceous cyst, epidermal cyst, wart, and dermatitis.

RESEARCH

Table 3 | Incidence of wound infections in intervention (chloramphenicol) and control (paraffin) groups

Infections	Intervention group (n=488)	Control group (n=484)	Combined results (n=972)
No of infections	32	53	85
Incidence of infection	6.6%	11.0%	8.7%
Relative risk (95% CI) of infection	1 (reference category)	1.7 (1.1 to 2.5)	NA
Wound score:	(n=487)	(n=483)	(n=970)
Stitch abscess	14 (2.9%)	14 (2.9%)	28 (2.9%)
<1 cm erythema	67 (13.8%)	62 (12.8%)	129 (13.3%)
>1 cm erythema	27 (5.5%)	44 (9.1%)	71 (7.3%)

NA=not applicable.

Generalisability

Some limits to generalising these findings exist. The population of Mackay is slightly older than the general Australian population and has a lower median household income.²² Mackay is a provincial town in tropical North Queensland. The climate is hot and humid, with a mean daily maximum temperature ranging between 24.2°C and 30°C during the summer months and a relative humidity of 75-79%.²³ These tropical conditions could increase sweat production and produce damp dressings, which might reduce the effectiveness of wound dressings as a potential barrier against exogenous bacteria.²⁴⁻²⁶ This would make wounds more prone to infection in a tropical environment, so the results may not necessarily be generalisable to a temperate climate, although no published evidence shows that heat and humidity increase infection rates. This might also explain why our infection rates were higher than suggested by previous data from temperate climates.¹¹⁻¹³

Antibiotic use

Some concern exists about the overuse of topical antibiotics resulting in antibiotic resistance. British and Australian guidelines suggest that use of topical antibiotics should be restricted because of the capacity of most topical drugs to select resistant micro-organisms and to cause sensitisation. The guidelines also suggest that antimicrobials recommended for topical use should be selected from classes not in use for systemic treatment.²²⁷ A contrary argument says that the potential for antimicrobial resistance with topical antibiotics is actually lower than with systemic antibiotics because of the higher local concentration achieved by topical delivery.²⁸ Patterns of

antimicrobial activity and resistance have been examined for other antibiotic ointments.^{29,30} However, no evidence exists, over three decades of extensive use worldwide, to show that, with the exception of mupirocin, topical antibiotics administered on an outpatient basis contribute to any emerging resistance pattern.²⁸ Chloramphenicol eye drops have been shown to be effective in the treatment of methicillin resistant *Staphylococcus aureus* ocular surface infections.³¹

Some concern also exists about the incidence of allergic contact dermatitis with use of topical antibiotics. For topical neomycin, this has been shown to be as high as 11% in a population referred for diagnostic patch testing.³² However, some evidence shows that the incidence of this reaction is as low as 1% when the ointment is used in the general population.²⁸ The reaction is much more common among patients previously exposed to neomycin ointment.³² Contact allergy has been reported with the use of chloramphenicol ointment, but the incidence is thought to be low.^{33,34} Although any connection between the use of topical chloramphenicol and aplastic anaemia is unlikely,^{7,8} our study was not large enough to fully assess the risk in this setting.

Antibiotic prophylaxis is probably prescribed excessively or inappropriately for dermatological surgery and is thought to be best reserved for patients at high risk.^{19,25,35} No data are available on the current prescribing habits of Australian general practitioners regarding oral or topical antibiotic prophylaxis for minor excisions. Although no evidence is available on what reduction in the rate of infection we might reasonably expect from the use of oral prophylactic antibiotics for minor excisions, some evidence shows a 50% reduction in risk of infection when perioperative oral antibiotic prophylaxis is used after clean surgery.¹⁷ A similar reduction in infection rate from a single dose of topical antibiotic, as in this study, may encourage a reduction in the use of oral antibiotics.

The decision to prescribe antibiotic prophylaxis is complicated; in addition to efficacy, the antibiotic costs, adverse effects, and resistance should be taken into account. However, in some circumstances, topical delivery of antibiotic may be preferable to systemic administration.³²⁷ The results of this study could encourage the judicious use of topical antibiotics after minor skin surgery. However, topical

WHAT IS ALREADY KNOWN ON THIS TOPIC

A survey of UK plastic surgeons showed that 66% use chloramphenicol ointment in some capacity

A small pilot study suggested that chloramphenicol ointment might reduce the incidence of wound infection

No published studies have been done in a primary care setting

WHAT THIS STUDY ADDS

A single application of topical chloramphenicol to high risk sutured wounds reduced infection by 40%

RESEARCH

chloramphenicol would be unlikely to produce a worthwhile absolute reduction in infection rates in low risk settings in developed countries. Future research could explore the possibility that important reductions may be seen in higher risk wounds or in more resource poor settings.

Conclusion

This study suggests that application of a single dose of topical chloramphenicol to high risk sutured wounds after minor surgery produces a moderate absolute reduction in infection rate.

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Contributors: CFH conceived and designed the study and analysed and interpreted the data. PGB did the sample size calculation and statistical analysis. SB, RC, CL, HD, and DG contributed to the study design. All authors contributed to the manuscript. CFH is the guarantor.

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Competing interests: None declared.

Ethical approval: The study was approved by the James Cook University ethics committee (approval number H2590). All patients provided written informed consent.

Provenance and peer review: Not commissioned; externally peer reviewed.

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**APPENDIX 3.
MINOR SKIN EXCISIONS IN GENERAL
PRACTICE IN NORTH QUEENSLAND**

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Minor skin excisions in general practice in North Queensland

Clare Heal

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MBBS, PhD, FRACGP, is Associate Professor, James Cook University, Queensland.

Sheldon Browning

MBBS, DRACOG, FRACGP, DipDerm, is a general practitioner, Mackay, Queensland.

OBJECTIVE

To describe the demographics of patients presenting with skin cancer to general practitioners in rural North Queensland, the sites from which skin cancers are removed, and their histology.

METHODS

Data was recorded from 1247 consecutive patients who attended for minor skin lesion excisions.

RESULTS

Close to half (46.7%) of lesions excised were skin cancers. We excised more squamous cell carcinomas than basal cell carcinomas (0.74:1). Our number needed to treat (benign or dysplastic naevi excised per melanoma) was 8.4. Mean age for excision of melanoma, basal cell carcinoma and squamous cell carcinoma was 55, 60.9 and 63.8 years respectively. Relative tumour density was greatest in the face, scalp and neck region for all skin cancers.

DISCUSSION

In this sample of Mackay GPs, there was a very high yield of skin cancers from all excisions. We could consider lowering our threshold for excision of pigmented lesions.

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**APPENDIX 4.
ACCURACY OF CLINICAL DIAGNOSIS OF SKIN
LESIONS**

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Accuracy of clinical diagnosis of skin lesions

C.F. Heal,* B.A. Raasch,*† P.G. Buettner* and D. Weedon‡

*Skin Cancer Research Group within the North Queensland Centre for Cancer Research, School of Medicine and School of Public Health, Tropical Medicine and Rehabilitation Sciences, James Cook University, Townsville, Qld, Australia

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**APPENDIX 5.
AGREEMENT BETWEEN HISTOLOGICAL
DIAGNOSIS OF SKIN LESIONS BY
HISTOPATHOLOGISTS AND A
DERMATOPATHOLOGIST**

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Clinical trial

Agreement between histological diagnosis of skin lesions by histopathologists and a dermato-histopathologist

Clare F. Heal¹, FRACGP, MPHTM, David Weedon², AO, MD, FRCPA, Beverly A. Raasch^{1,3}, FRACGP, PhD, Brendan T. Hill⁴, Petra G. Buettner⁴, PhD

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**APPENDIX 6.
DIAGNOSING SKIN CANCER IN PRIMARY
CARE: HOW DO MAINSTREAM GENERAL
PRACTITIONERS COMPARE WITH PRIMARY
CARE SKIN CANCER CLINIC DOCTORS?**

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Diagnosing skin cancer in primary care: how do mainstream general practitioners compare with primary care skin cancer clinic doctors?

Clare Heal and Beverly Raasch

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**APPENDIX 7.
PRACTICE BASED RESEARCH – LESSONS FROM
THE FIELD**

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Clare F Heal

MBChB, DRANZCOG, DipGUMed, FRACGP, MPHTM, is Senior Lecturer, General Practice and Rural Medicine, James Cook University, Mackay, Queensland. clare.heal@jcu.edu.au

Craig Veitch

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Robyn Preston

BA(DevS) (Hons) MHS(HealthProm), is Primary Health Care Research Evaluation and Development (PHCRED) Coordinator, James Cook University, Townsville, Queensland.

Practice based research

Lessons from the field

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APPENDIX 8. ETHICS APPROVAL



JAMES COOK UNIVERSITY
Townsville Qld 4811 Australia

Tina Langford, Ethics Officer, Research Office. Ph: 07 4781 4342; Fax: 07 4781 5521

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APPENDIX 9. CONSENT FORM AND PATIENT INFORMATION SHEET

School: James Cook University School of Medicine
Project: Topical Chloromycetin ointment to sutured wounds
Chief Investigator: Dr Clare Heal
Contact Detail: James Cook University, Mackay Base Hospital, Q4740
Tel 49686630

Ethics Officer Contact detail: Tina Langford Tel 47814342

PATIENT INFORMATION SHEET

We would like to invite you to take part in a research study being conducted by your General Practitioner under the supervision of the James Cook University.

DO YOU NEED TO TAKE PART?

Before telling you anything about the study we need to make it clear that you do not need to take part unless you want to. Whether you decide to participate or not will make no difference to the care you receive as a patient at the practice.

If you do not wish to take part simply inform your doctor or nurse.

There will be no additional cost to you if you are happy to participate

GENERAL INFORMATION ABOUT THE STUDY

The aim of the study is to determine whether applying antibiotic ointment makes any difference to the chance of getting an infection.

IF YOU TAKE PART

If you decide to take part in the study you will be randomly assigned to one of two groups.

TOPICAL ANTIBIOTIC GROUP

You will receive a single application of an antibiotic ointment after your wound has been sutured. Please keep your wound dry and covered for 24hrs. After 24hrs take your dressing off and shower or bathe as normal. If the wound becomes hot, swollen or red, return to your doctor to have the wound checked.

CONTROL GROUP

You will receive a single application of Vaseline ointment after your wound has

been sutured. Please keep your dressing covered and dry for the first 24hrs. After 24hrs you may take your dressing off and shower or bathe as normal. If the wound becomes hot, swollen or red, return to your doctor to have your wound checked

If you have any concerns you can discuss these with your doctor. Your doctor will also ask you to sign the consent form.

WILL THE INFORMATION BE CONFIDENTIAL?

All the information collected during the study will be confidential. Only your GP and the study investigators will know that the information is related to you.

WHAT IF I GET A WOUND INFECTION?

Wound infections occur in around 5-20% of skin excisions, so there is a chance that you will get an infection, whether you have topical antibiotics or not. If you notice that your wound has become infected, we would like you to see your GP straight away. You will also be asked to attend your GP after a suitable period of time to have your sutures removed. If at this point the wound is infected, it will be treated like any other infection, possibly with antibiotic tablets.

POSSIBLE RISKS, DISCOMFORTS, BENEFITS

There is a very small possibility of having a local allergy to the antibiotic ointment. This would not be serious and could be treated with a different ointment.

There may be a tiny risk of developing life-threatening anaemia when Chloromycetin ointment is applied to the eye, however it is thought to be completely safe in a single dose applied to the skin.

Hopefully the results of this study will show if antibiotic ointment can help to prevent infection after minor skin surgery.

INFORMED CONSENT FORM

School: James Cook University School of Medicine

Project: Topical Chloromycetin to sutured wounds

Chief Investigator: Dr Clare Heal

**Contact Detail: James Cook University, Mackay Base Hospital, Q4740
Tel 49686630**

Description:

This study involves being randomly assigned to a group where either antibiotic ointment will be applied to your wound, or no ointment will be applied (our

current normal management) The wound will be reassessed when you come back for removal of sutures, so there is no extra time commitment involved. The outcomes of this study will be used to improve the way wounds are managed by GPs in Mackay. The results of the study may be used for a publication, but all information will be kept confidential.

CONSENT

The aims of this study have been clearly explained to me and I understand what is wanted of me. I know that taking part in this study is voluntary and I am aware that I can stop taking part in it at any time and may refuse to answer any questions.

I understand that any information I give will be kept strictly confidential and that no names will be used to identify me with this study without my approval.

Name: *(printed)*

Signature:

Date:

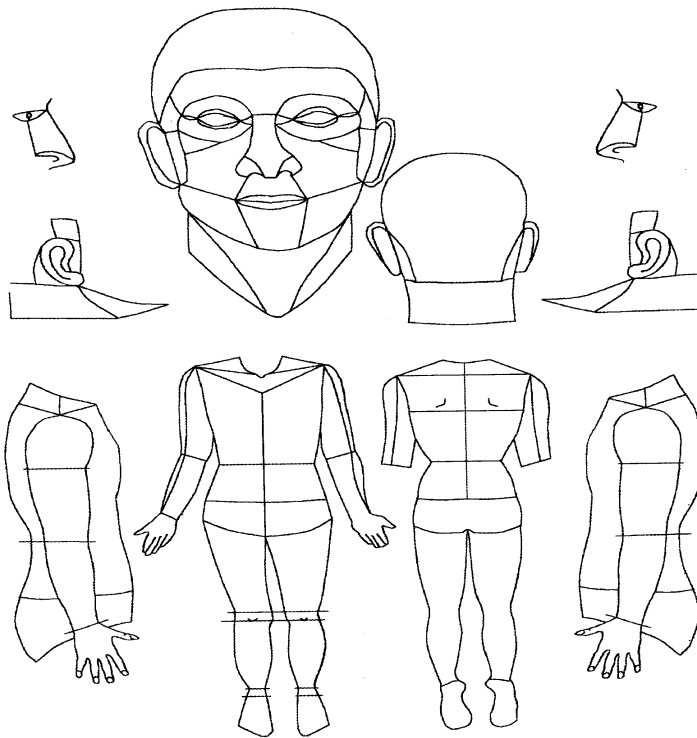


**APPENDIX 10.
DATA COLLECTION SHEETS**

APPENDIX 11. BODY SITE MAP

BODY SITE MAP BODY SITES

- | | | |
|----------------------|--------------------|---------------------|
| 1) Anterior arm | 7) Anterior thigh | 13) Torso posterior |
| 2) Posterior arm | 8) Posterior thigh | 14) Neck |
| 3) Anterior forearm | 9) Anterior leg | 15) Scalp |
| 4) Posterior forearm | 10) Posterior leg | 16) Face |
| 5) Back hand | 11) Foot | 17) Nose |
| 6) Palm hand | 12) Torso anterior | 18) Ear |
| | | 19) Lip |



PRINT SCALING 20%

APPENDIX 12. EXCISION PROTOCOL

EXCISION PROTOCOL

- 1) Skin prep – N Saline
- 2) Usual aseptic technique, including sterile gloves
- 3) Nylon sutures
- 4) Local anaesthetic – 1% lignocaine with adrenaline
- 5) Dressing – Melolin and tape, Primapore, Cutiplast ® or Cosmopor, (not tegaderm, hydrofilm or waterproof dressing)
- 6) No other topical antiseptic or antibiotic

INCLUSION CRITERIA

All sutured wounds:

- Patients presenting for excision of a minor skin lesion
- All body sites including face
- Diabetes, Anaemia, PVD, malignancy (but record chronic disease)
- Flap/2 level procedure
- Multiple excisions on same date (give each excision separate number)
- Excisions on same patient on different dates
- Lacerations
- Sutured punch or shave biopsies
- Excision of sebaceous cyst

EXCLUSION CRITERIA

- Incision and drainage of infected sebaceous cyst
- Immunosuppressive drugs
- Already taking oral antibiotics
- Oral/topical abs clinically indicated postoperatively
- Personal/Family History of Aplastic anaemia
- Non-sutured biopsies, steristripped skin tears
- Allergy to any ingredients of Chloromycetin ointment

DIAGNOSIS OF INFECTION

- 1) Within 30 days of excision
- 2) a) Purulent discharge from wound or
b) Doctor diagnosis infection or commences antibiotics
- 3) Stitch abscess does not count as infection

AND

- | | |
|-------------------|--------------------------------------|
| 0- no infection | 3- Erythema >2cm |
| 1- Stitch abscess | 4- Deep infection/ Systemic symptoms |
| 2- Erythema <2cm | |

BODY SITE CATEGORIES (see body map)

- | | | |
|---------------------|-------------------|--------------------|
| 1)Anterior arm | 7)Anterior thigh | 12)Anterior torso |
| 2)Posterior arm | 8)Posterior thigh | 13)Posterior torso |
| 3)Anterior forearm | 9)Anterior leg | 14)Neck |
| 4)Posterior forearm | 10)Posterior leg | 15)Scalp |
| 5)Back hand | 11)Foot | 16)Face |
| 6)Palm hand | | |

TEA

Tea cup years

average number of cups per day/ number of years consumed for

eg 5/10 = 5 cups of tea per day for 10 years

HISTOLOGY

- 1)MM- Malignant melanoma
- 2)BCC- Basal Cell Carcinoma
- 3)SCC- Squamous Cell Carcinoma
- 4)BN- Benign naevus
- 5)DN- Dysplastic naevus
- 6)SK- Solar keratosis
- 7)SW- Seborrhoeic keratosis

8)Other (write in)

11)RMM- re-excision malignant melanoma

12)RBCC- re-excision Basal Cell Carcinoma

13)RSCC- re-excision Squamous Cell Carcinoma

MEDICAL CONDITIONS TO RECORD

Anaemia

Peripheral vascular disease

Cancer (current)

Oral steroids

Continuous inhaled steroids

Oral warfarin

Aspirin or clopidogrel

Ischaemic Heart Disease

COPD

SMOKING

Yes/No/Ex



APPENDIX 13. STUDY PROTOCOL

Dr Clare Heal – Study Protocol

1. PROJECT INFORMATION

1.1 Project Outline

Aim

To determine whether the application of topical chloramphenicol ointment (Chloromycetin) to sutured wounds reduces the incidence of wound infection following minor surgery.

Background / Literature review:

A previous study of wound infection involving GPs in Mackay, Queensland showed an overall incidence of wound infection of 8.6%, with infection rates at four general practice centres of 2.9%, 7.8%, 10.0% and 10.2%.^{1,2} This was higher than we expected from published results in a similar Australian general practice cohort (1.9%)³ and a similar European dermatology clinic cohort (2%)⁴. The acceptable rate of infection following clean minor surgery is 5%^{5,6,7}. We have consequently decided to investigate a strategy to reduce this infection rate.

Although some practitioners apply topical antibiotic ointment for infection prophylaxis following minor excisions, there is little data available regarding the effectiveness of this treatment. There are several different antibiotic ointments used in clinical practice including Chloromycetin, neosporin and mupirocin.

Chloromycetin ointment consists of 10mg/g of chloramphenicol, in plastibase 30W and liquid paraffin.⁸ It is indicated for treatment of bacterial conjunctivitis and there is little evidence for its effectiveness in prophylaxis or treatment of wound infection. Despite this, it is regularly used in areas outside its main indication. Several of the investigating GPs had applied it to sutured wounds as prophylaxis against wound infection. A survey of UK plastic surgeons reported that 66% used chloramphenicol eye ointment in their

practice, mainly as prophylaxis against infection.⁹ The ointment has been used as an adhesive for replacement of the nailbed.¹⁰ Comprehensive medline search found only one study relating to the use of topical Chloromycetin ointment on wounds. This study investigated the application of Chloromycetin ointment to wounds following hip replacement.¹¹ The incidence of wound infection in the intervention group was reduced (4% v 8%) but the sample size was small and the results not statistically significant.

Neosporin ointment is also known as triple antibiotic ointment (TAO) in the USA. Each gram of Neosporin ointment contains polymixin B sulfate 5,000 units, neomycin sulfate 5mg and bacitracin zinc 400units in a paraffin ointment base¹². Comprehensive medline search revealed two randomised studies involving Neosporin ointment. One compared application of Neosporin, bacitracin zinc, silver sulfadiazine and paraffin ointment to uncomplicated sutured wounds. This concluded that neosporin did reduce the incidence of infection (4.5%v 6.6%v12.1%v17.6%); however the sample size was too small for the results to be statistically significant.¹³ A second small pilot study found a similar rate of wound infection and adverse events between uncomplicated sutured soft tissue wound treated with Neosporin ointment or mupirocin ointment (4%v 0%).¹⁴ Neosporin ointment has been found to be safe, effective and significantly better than simple gauze dressing alone, in minimising the appearance of scars resulting from clean dermabrasion wounds.¹⁵

Bactroban ointment contains mupirocin. Interestingly, a recent large Australian study showed that application of mupirocin ointment prior to application of an occlusive dressing did not decrease the incidence of wound infection (2.3% intervention v 1.4% control).¹⁶

There is some concern regarding the overuse of topical antibiotics resulting in antibiotic resistance. Australian guidelines suggest that topical antibiotic use be restricted because of the capacity of most topical drugs to select resistant micro-organisms and to cause sensitization. The guidelines also suggest that antimicrobials recommended for topical use are selected from classes not in use for systemic therapy.¹⁷ Patterns of antimicrobial activity and resistance have been examined for Neosporin and mupirocin ointment. In one trial, neomycin plus bacitracin was associated with the rapid emergence of drug-resistance organisms whereas topical silver nitrate was not.¹⁸ However Neosporin

ointment has also been shown to have a wider spectrum of antibacterial activity compared with mupirocin and to be usable against mupirocin resistant Gram-positive strains.¹⁹ Chloramphenicol eye drops have been shown to be effective in the treatment of MRSA ocular surface infections.²⁰

In one study, antimicrobial treatment including antiseptics and antibiotic ointment were shown to eradicate bacteria from the skin surface when applied topically. Mupirocin and Neosporin ointment were also been shown to eradicate bacteria from the multiple keratinised layers of the stratum corneum and in addition neosporin prevented repopulation with resident flora.²¹ There are no similar medline listed studies involving Chloromycetin ointment.

There is some concern about the incidence of allergic contact dermatitis with topical neomycin use. This has been shown to be as high as 11% in a population referred for diagnostic patch testing.²² However there is some evidence that the incidence of this reaction is as low as 1% when the ointment is used in the general population.²³ The reaction is much more common amongst subjects previously exposed to neomycin ointment.²² Contact allergy has been reported with the use of chloramphenicol ointment but the incidence is thought to be low.^{24,25}

Neosporin ointment has been available over the counter in the USA since the 1970s, while it has been confined to a prescription medication in Australia. It ceased to be available in Australia in Oct 2006, because of non-availability of an ingredient.²⁶ Topical ocular chloramphenicol is widely used in the UK and Australia for the treatment of conjunctivitis, but is very rarely prescribed for this indication in the US.²⁷ There was previously some controversy regarding the link between aplastic anaemia and topical ocular chloramphenicol, based on a small number of single case reports,²⁷ however two international case-control studies provided no support to this association. Although the association between ocular chloramphenicol and aplastic anaemia cannot be excluded, the risk is less than one million per treatment courses²⁸. There have been no incidences of aplastic anamia following dermatological application, despite widespread use. Because of current accessibility in Australia and lack published data we decided to study the use of Chloromycetin ointment.

Our trial seeks to establish the effectiveness of Chloromycetin ointment in preventing wound infection after dermatological surgery. We intend to apply it as a single dose post operatively, with sterile paraffin ointment (Iacrilube) used as a control. Wound infections will be swabbed in order to investigate patterns of antimicrobial resistance.

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1.2 Detailed Methodology

Design

Randomised Control Trial involving 1200 patients presenting for excision of minor skin lesions.

Methods

Our previous study showed an infection rate of 8.6% following minor skin excisions. Sample size calculations based on a baseline infection rate of 8%, with a 50% reduction in incidence of infection to 4% being considered to be clinically significant, indicate that a sample size of 601 will be needed in each of the control and experimental groups.

Practice and study characteristics

It is proposed that 4-6 GPs from around 1-2 practices in the Mackay area participate. The GPs are to be purposively selected from a larger evidence based medicine group. Workshops will be held to agree on the design and methods of the trial.

Recruitment, randomisation and blinding

Patients are to be randomised within each participating practice using computer generated random numbers and opaque sealed envelopes. All patients participating are to be provided with an information sheet, and will be asked to give signed consent. They will also be given written instructions regarding post-operative wound care. Ointment will be placed in numbered sterile vials. The practice nurses will be responsible for the application of ointment. Only the principle researcher will be aware of the identity of the ointments.

Inclusion and Exclusion criteria

Inclusion criteria:

All sutured wounds:

Patients presenting to a participating GP for excision of a minor skin lesion.

All body sites

Lacerations

Sutured biopsies

More than one excision in same patient

Patient presenting for excisions on more than one occasion

Exclusion criteria:

Already taking oral antibiotics

Oral or topical antibiotics clinically indicated immediately postoperatively

Excision of sebaceous cyst

History of allergy to any of ingredients of Chloromycetin ointment.

Personal or family history of aplastic anaemia

Non-sutured biopsies

Steristripped skin tears

Surgical Wound Management Protocol

Skin preparation –Normal saline

Usual sterile technique

1% lignocaine with adrenaline

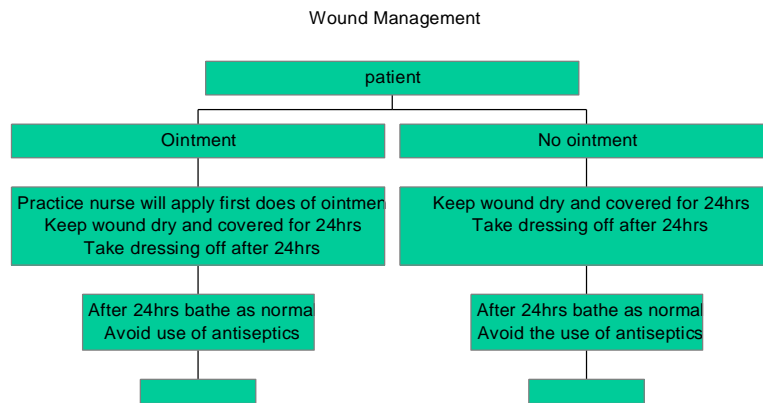
Suture material – nylon

No antibiotics, either topical or oral- (if required or already prescribed exclude from study)

Dressing type – melolin and tape

Ointment will be applied with sterile green spatula

Actual advice to patients



Removal of sutures according to site

Back – 10 days

All other sites – 7 days

Practice nurse or doctor will assess wound for infection on day of ROS, or sooner if patient re-presents with perceived infection.

Wound infection will be defined according to Surgical Site Infection definition defined by National Nosocomial Infection Surveillance System (NNIS) from CDC Atlanta, USA.

A wound swab will be taken from all infected wounds and sent for microscopy, culture and sensitivity testing.

Or

0= No infection

1= Stitch abscess

2=Redness<1cm

3=Redness>1cm

4=Deep infection/systemic symptoms

Ethics

The trial has been given ethical approval through the JCU ethics committee. The trial has been registered.

Data Collection

Data will be collected for 6-9 months from June 2007- March 2008

Date	Patient ID	DOB	Sex	Site (use body map)	DM Y/N	Other Eg PVD Anaemia	Oint	ROS Date	Histology	Inf Y/N	Compliant? Y/N

Data Analysis

Data will be analysed using SPSS.

Data will be analysed by intention-to-treat.

Outcomes and significance

A large GP study giving statistically significant results would be extremely useful, relevant and practical to everyday General Practice. If antibiotic ointment is found to significantly reduce infection rate after minor surgery, then the outcome is likely to be beneficial to the general public and result in reduced infection rates. If application in antibiotic ointment is found to result in no significantly reduced infection rates then reduction in the use of antibiotic ointment will reduce antibiotic resistance and potential allergic reactions.

1.3 Participant welfare particulars

The project would be considered to be experimental category 2 as a basic clinical assessment of the wound site will be involved

Participants will be selected as detailed above.

Informed consent will be obtained from the participant prior to testing following discussion with the General Practitioner.

Results of the project will be available to participants who wish to discuss them with their GP and this is to be advertised in participating practices when available.

Data will be kept in a locked cabinet in researchers office and destroyed after 10 years.

There will be no payment for participation in the project.

Participants will be able to withdraw from the project at any time.

1.4 Confidentiality

Confidentiality will be ensured by using codes as patient identifiers on data collection sheets

1.5 Data Retention and Storage

Data will be held for a sufficient length of time to allow reference (10 years)

1.6 Comments

There have been no other ethics applications for this project.

2 Information page

Attached

3 Informed consent form

Attached

4 Letters of approval/support/permission

The project will take place in General Practices in the Mackay region. Each individual practitioner is responsible for their own workplace and therefore giving permission for the project to take place by participating.

5 Questionnaire

No questionnaire will be involved

6 Current First Aid Certificate

Not required

7 Suitability Cards

This research will not involve working with children

8 Health Service District Patients

The patients involved will be private patients of the individual GPs involved, and the research will not involve the relevant Health Service District.

APPENDIX 14. CONSORT CHECK LIST

CONSORT Checklist of items to include when reporting a randomised trial

PAPER SECTION And topic	Item	Description	Reported on Page #
<i>TITLE & ABSTRACT</i>	1	How participants were allocated to interventions (e.g., "random allocation", "randomised", or "randomly assigned").	3
<i>INTRODUCTION</i> Background	2	Scientific background and explanation of rationale.	4
<i>METHODS</i> Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	6
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	6,7
Objectives	5	Specific objectives and hypotheses.	5
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).	7,8
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	8

Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (e.g., blocking, stratification)	7
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	7
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	7
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.	7
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	8,9
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	10(fig2)
Recruitment	14	Dates defining the periods of recruitment and follow-up.	5
Baseline data	15	Baseline demographic and clinical characteristics of each group.	11

Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	10
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval).	12
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed , including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	N/A
Adverse events	19	All important adverse events or side effects in each intervention group.	N/A
DISCUSSION Interpretation	20	Interpretation of the results , taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	12, 13,14, 15
Generalizability	21	Generalizability (external validity) of the trial findings.	14
Overall evidence	22	General interpretation of the results in the context of current evidence.	14,15

APPENDIX 15.

RAPID RESPONSES TO BMJ CHLORAMPHENICOL ARTICLE

Advanced search

Rapid Responses to:

RESEARCH:
Clare F Heal, Petra G Buettner, Robert Cruickshank, David Graham, Sheldon Browning, Jayne Pendergast, Herwig Drobetz, Robert Gluer, and Carl Lisee
Does single application of topical chloramphenicol to high risk sutured wounds reduce incidence of wound infection after minor surgery? Prospective randomised placebo controlled double blind trial
BMJ 2009; 338: a2812 [Abstract] [Full text]

▶ **Rapid Responses:
Submit a response to this article**

Rapid Responses published:

▼ **Antibiotic Prophylaxis in Dermatological Surgery**
Richard J Motley (24 January 2009)

▼ **Post operative infection rate requires investigation**
Bo Povlsen (26 January 2009)

▼ **Preoperative skin surface integrity predicts infection risk independent of the use of topical antibiotics.**
Sophie C Weatherhead, Clifford M Lawrence (26 January 2009)

▼ **Is topical Chloramphenicol necessary to reduce wound infections?**
David L Wallace (1 February 2009)

▼ **re topical chloramphenicol**
Clare Heal, Petra Buttner (15 February 2009)

Antibiotic Prophylaxis in Dermatological Surgery

24 January 2009



Richard J Motley,
Consultant in Dermatology
and Cutaneous Surgery
Welsh Institute of
Dermatology, University
Hospital of Wales, Cardiff
CF14 4XW

Send response to
Journal:

Re: Antibiotic Prophylaxis in Dermatological Surgery

Heal and colleagues (and the authors of the accompanying editorial) have overlooked the single most important determinant of post operative wound infection in cutaneous surgery i.e. - contaminated surgery on lesions with high levels of pathogenic bacteria: - ulcerated basal cell carcinomas account for the majority of these cases and although 71% of the lesions removed in this study were non-melanoma skin cancers, no mention is made of pre-existing ulceration.

The 11% control rate of infection in this study was high - and may reflect a failure to recognize this risk. Poor surgical technique - overtight or excessive suturing, the creation of

tissue 'dead' spaces and haematoma formation - also increase the risk of infection in otherwise clean cutaneous surgery.

The ulcerated basal cell carcinoma is at risk of post-operative wound infection and with the increasing incidence of skin cancer and cutaneous surgery this should be recognized. Antibiotic prophylaxis is accepted for contaminated surgery in other sites - such as the bowel - and is no less important in these cases.

Competing interests: Twenty years experience in dermatological surgery

Post operative infection rate requires investigation

26 January 2009 ▲ ▼ 🌱

Bo Povlsen,
Consultant Orthopaedic
Surgeon
Guy's Hospital, SE1,
London, England

Send response to
journal:

Re: Post operative infection rate requires investigation

Heal and colleagues' report on the effect of application of chloramphenicol to wounds after elective skin biopsies had been taken in a primary care setting.

The premise for the study is based on what plastic surgeons have known for many years - that topical chloramphenicol minimises skin infections after surgery. The title suggest that the anatomical location or surgical circumstances makes the surgical wound "high risk" though the reality is that the described surgery is classified as low risk as it is performed as a elective procedure of a non-infected and normal skin area. However, the most important finding of the study is that the current practices, under which such skin biopsies are performed, generate an eye watering infection rate of 11%. The authors fail to appreciate that this 5-fold increase of what would be an acceptable 2% infection rate is of much greater clinical importance than the reduction that the topical chloramphenicol achieves.

The reason for this high infection rate and the possible explanation as to why the topical chloramphenicol did not achieve the desired lowering of infection rate could be found in the skin preparation prior to surgery and not in the geographical location as alluded to by the authors. It would appear that many of the patients did not have the skin decontaminated prior to surgery as normal saline was often used instead of conventional antiseptic (chlorhexidine, bethadine or alcohol). It would therefore be of interest to know whether the preoperative skin preparation were evenly divided between the research and infection groups and if so

what further steps the authors suggest to take to investigate the health risk that the current practice represent.

Competing interests: None declared

Preoperative skin surface integrity predicts infection risk independent of the use of topical antibiotics.

26 January
2009



Sophie C Weatherhead,
Wellcome Research
Training Fellow and
Dermatology SpR
Royal Victoria Infirmary,
Newcastle-upon-Tyne, NE1
4LP,
Clifford M Lawrence
Send response to
journal:
Re: Preoperative skin s
urface integrity predicts
infection risk independ
ent of the use of topical
antibiotics.

Heal et al report a reduction in wound infection risk with the use of topical antibiotics after skin surgery. They do however report a very high control group infection risk rate and have ignored the influence of pre-existing skin pathogen carriage as indicated by the appearance of the lesion surface before surgery. Our prospective study shows that this significantly increases the risk of wound infection.

We have shown that patients whose lesion preoperatively had a crusted or ulcerated skin surface were significantly more likely to develop clinical wound infections compared to those with a normal or scaly skin. We included all patients attending for 1-stage excision biopsy in our dermatology department, over a 12 month period, who were able to attend for post-operative follow-up.

We categorised patients into groups according to the pre-operative surface of their skin lesion; i.e. intact or broken (scaly, crusted or ulcerated), and recorded the patient's age, sex, diameter of the lesion, use of topical antibiotics, time to follow-up and experience of the dermatologist excising the lesion. Overall 174 out of 179 patients completed our study, with 81 patients (47%) having intact skin overlying their lesion. In the 93 patients with broken skin, 45% had scaly surfaces, 35% crusted, and 19% an ulcerated surface. We found a significantly increased risk of infection ($p < 0.05$) in patients who had either a crusted/ ulcerated skin surfaces versus intact, or an ulcerated surface versus scaly surface. Infection risk was not affected by the use of perioperative topical antibiotics, site of the lesion, closure technique or surgeon experience. *Staphylococcus aureus* was the causative organism in 90% of infections. Patient age was a significant risk factor, and older patients were more likely to have lesions with a broken skin surface. Our overall infection risk was 3.5% in lesions with an intact surface, 12% for scaly lesions, 18% for crusted lesions and 33% for ulcerated lesions.

Although topical antibiotics may be beneficial to patients undergoing minor skin surgery, our experience highlights the importance of controlling for the integrity of skin surface in such a study. Thus, because we cannot be sure that Heal's two groups shared similar wound infection risk rates, as judged by their pre-treatment skin surface changes, this study needs to be repeated controlling for the integrity of preoperative skin surface.

Competing interests: None declared

Is topical Chloramphenicol necessary to reduce wound infections?

1 February 2009 ▲ ▼ ⤴

David L Wallace,
Plastic & Burns Surgery
SpR
Selly Oak Hospital,
University Hospitals
Birmingham, Radcliffeburn
Road, Birmingham, B29
6JD

Send response to
journal:

Re: Is topical Chloram
phenicol necessary to r
educe wound infection
s?

Heal et al¹ add good evidence to the common plastic surgery practice (in the UK) of chloramphenicol ointment on cutaneous wounds, in order to prevent surgical site infection. There is an impressively honest wound infection rate and a soundly prospectively designed study to avoid a type II error². The treatment and control groups both benefit from the potential "moist wound environment" from the use of ointment, which was demonstrated nearly half a century ago³. Although the main concern, which is alluded to, with the use of chloramphenicol relates to the risk of aplastic anaemia¹. This risk is indeed low, maybe 1 in 30 to 50,000⁴, therefore only a few clinicians will ever see such a problem in their lifetimes. The risk of aplastic anaemia is not only dose related but also idiosyncratic. Death has been reported following topical usage, and absorption has been reported following skin application⁴. Although these are only case reports, with such a grave potential consequence chloramphenicol ointment should be avoided⁵. Especially when there are numerous alternatives, such as Polyfax (which contains polymyxin and bacitracin), that do not have such fatal risks. *Staphylococcus aureus* and *Pseudomonas* were the only isolates in the study, which would be covered by Polyfax.

In the methodology Heal et al state saline was used at one centre and chlorhexidine was used at the other two sites for the preoperative wash. Therefore an analysis of the infection rates from the different practises would be useful to clarify any potential difference from this. Although a difference is unlikely, as a study of 1810 patients demonstrated no difference between soap and chlorhexidine⁷, and the

Cochrane metanalysis finds no definitive evidence of a significantly better preoperative wash regimen⁶.

The types of lesions are described in the study (benign and malignant) but not their infective potential as to whether the lesions were ulcerated or open wounds. The type of surgery correlates well with infection; with clean surgery having a 5.9%, clean contaminated 10.7% and contaminated 24.3% rates⁸. An ulcerated Basal cell carcinoma moves the type of procedure from clean to a higher category dependent on the lesion, and a consequent higher likelihood of infection. Simple manoeuvres can lead to a dramatic decrease in surgical site infections from 33.3% to 3.7% by ensuring the decrusting of lesions, use of monofilament sutures, and meticulous asepsis for minor surgical procedures⁹. Therefore greater infection control may be achieved through meticulous surgical attention and technique, rather than the use of a potentially fatal (albeit remote) topical antibiotic that has alternatives.

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9. Tahir A TO. Reducing infections in cutaneous oncology defects reconstructed using skin grafts. *Eur J Plast Surg* 2005;28:27-31.

Competing interests: None declared

re topical chloramphenicol

15 February 2009



Clare Heal,
Senior Lecturer
JCU Mackay 4750,
Petra Buttner

Send response to
journal:

Re: re topical chloramp
henicol

We would like to thank our colleagues for their interesting and helpful comments, and would like to address some issues raised in our response below.

We were already aware from previous studies (1) that our infection rate following minor surgery is very high compared with similar cohorts. (2) The reason for this is unclear, but may be related to our hot and humid environment. (3) The high infection rate was the main reason for investigating the effectiveness of chloramphenicol. With a lower infection rate a much higher sample size would have been required to show a relevant difference between groups with statistical confidence, making such a study almost unfeasible.(4)

Interestingly, the overall incidence of infection in the practice which used normal saline as skin preparation was 6.5% (36/550), while it was 11.6% (31/266) and 11.5% (18/156) in the two practices which used chlorhexidine. However, as numbers are quite small, and there are several other factors involved, we do not think this is of clinical significance. A Cochrane meta-analysis did not find definitive evidence of a significantly better preoperative skin preparation. (5)

There are many different potential confounding factors which may affect infection rate, and it is difficult for any study to measure all these factors adequately. We did not specifically record the integrity of the skin surface or the presence of ulceration in our study. However the numbers of basal cell carcinoma (BCC) and Squamous cell carcinoma (SCC) were balanced in both intervention and control groups at baseline. Considering the large sample size and meticulous

randomisation, we would hope that the presence of ulceration would be balanced in both groups and therefore should not affect our findings. In previous secondary data analysis we found that BCC, SCC, diabetes, and excisions from the lower limbs to be risk factors for infection. (6)

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Competing interests: None declared

APPENDIX 16.

BMJ EDITORIAL (GREY ET AL)

Editorials represent the opinions of the authors and not necessarily those of the BMJ or BMA

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EDITORIALS

Antibiotic prophylaxis for minor dermatological surgery in primary care

Is usually unnecessary with good preoperative preparation



RESEARCH, p 211

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Keith Harding professor and head of the wound healing research unit, University Hospital of Wales, Cardiff CF14 4XW

Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;338:a2749
doi:10.1136/bmj.a2749

Surgical procedures that disrupt the integrity of the skin predispose the patient to postoperative surgical site infection. Infection occurs after surgery in 1.5–20% of cases, and in Europe the associated costs are around €20bn (£17bn; \$25bn) each year.¹ An increasing amount of minor dermatological surgery is being carried out in primary and secondary healthcare settings. Antibiotic prophylaxis is widely used in such procedures, but how effective is it?

Good quality trials investigating the use of antibiotic prophylaxis in minor surgery are lacking. The linked randomised controlled trial by Heal and colleagues assessed the effect of a single prophylactic application of topical chloramphenicol on the incidence of wound infections after clean minor dermatological surgery.² The trial investigated 973 patients treated in primary care in north Queensland, Australia. The authors found a statistically significant reduction in infection in the treatment group compared with the control group (6.0% (95% confidence interval 4.9 to 8.8) v 11% (7.9 to 15.1)). The result was not clinically significant, however, because the absolute reduction of infection of 4.4% fell short of the authors predetermined reduction for clinical significance of 5%.

Most minor dermatological surgery in primary and secondary care is classified as “clean” (see table). Most surgical site infections are caused by contamination of an incision with micro-organisms from the patient's own body during surgery. The decision to use prophylaxis depends on the patient's risk of infection (increased as a result of age, obesity, smoking, immunosuppression, malnutrition, renal failure, and underlying illness such as diabetes), the consequences of infection, and the risk of harm from the antibiotics. Concerns also remain about the indiscriminate use of antibiotics and the emergence of antibiotic resistance, such as that reported from the use of topical neomycin and mupirocin.

Topical antibiotics have been widely used on wounds that are left to heal by primary closure or secondary intention without much supporting evidence. A randomised controlled trial of prophylactic topical bacitracin on minor surgical wounds found no significant reduction in surgical site infection, although the incidence of contact allergy was higher in the treatment group.³ Other prospective studies of prophylactic topical antibiotic used in clean surgery have shown only a modest reduction in surgical site infection.⁴

Using the correct hand washing technique for at least two minutes before performing surgery significantly reduces the bacterial count.⁵ Good preoperative antisepsis is probably more a function of the method rather than the agent used (although the National Institute for Health and Clinical Excellence (NICE) recommends povidone-iodine or chlorhexidine⁶). Removal of gross contamination and meticulous cleansing of the incision site reduce surgical site infection. Medical staff who sweat profusely are more likely to contaminate the surgical site than staff who do not.⁷ This may be relevant to the study from Queensland.

Rates of surgical site infection reported by practitioners experienced in dermatological surgery in specialist primary care settings, such as cancer clinics and dermatology clinics, are low.^{4,8} However, controversial results from the MiSTIC (minor surgery in the community) study in the United Kingdom reported that the quality of minor surgery carried out by general practitioners was “not as high” as that carried out in hospital (by hospital doctors).⁹ If substantiated, these findings may influence the rate of surgical site infection.

What constitutes a surgical site infection? Visual scales of infection are not always reliable. In studies with multiple investigators, interobserver differences may be high. The study by Heal and colleagues used the presence of erythema as one measure of infection. However, postoperative erythema is common and may not reflect the presence of infection. Even when the erythema represents local infection antibiotics may not be necessary. In one study of surgical site infections only 2% were classified as superficial suppuration, and only 10% of these needed antibiotics.⁸ Moreover, topical antimicrobials such as iodine or silver may be more appropriate for local wound infection. They act at multiple sites within the infecting organism, the risk of resistance is low, and they are tolerated well by patients.

Concerns have been raised about patients undergoing minor dermatological surgery who have prosthetic

Cleanliness status of different types of surgery

Type of surgery	Definition
I: clean	Non-contaminated skin, sterile technique
II: clean-contaminated	Wounds in oral cavity, respiratory tract, axilla, or perineum
III: contaminated	Trauma, acute wound, presence of non-purulent inflammation, or major breaks in aseptic technique
IV: dirty or infected	Foreign body contamination or devitalised tissue

orthopaedic implants that may become infected, or those at risk of developing infective endocarditis. Recommendations from the Mayo clinic¹⁰—based on guidelines from the American Heart Association, American Dental Association, and the American Academy of Orthopaedic Surgeons—no longer recommend antibiotic prophylaxis in clean dermatological surgery that does not involve the oral mucosa or infected skin. Recent guidelines from NICE and the Scottish Intercollegiate Guidelines Network on surgical site infections (although not specifically mentioning minor dermatological surgery) also state that clean minor surgical procedures do not warrant antibiotic prophylaxis.¹¹

Infections have been reported in 1.5% of cases after clean surgery.¹² The consequences of such infection are usually minor so antibiotic prophylaxis in these patients is not normally deemed necessary. Clean dermatological surgical procedures where antibiotic prophylaxis may be needed are those involving the oral mucosa or sites considered to be “dirty,” including the axilla, groin, external genitalia, and lower limbs.¹³

In clean minor surgery meticulous preoperative preparation and aseptic technique by appropriately trained practitioners with access to appropriate facilities will prevent most surgical site infections without antibiotic prophylaxis.

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APPENDIX 17.

RAPID RESPONSES TO BMJ EDITORIAL

Rapid Responses to:

EDITORIALS:

Joseph E Grey, Brendan Healy, and Keith Harding
Antibiotic prophylaxis for minor dermatological surgery in primary care
 BMJ 2009; 338: a2749 [Full text]

Rapid Responses: Submit a response to this article

Rapid Responses published:

☞ **Re Antibiotic prophylaxis for minor dermatological surgery in primary care.**
 Clare Heal (17 January 2009)

☞ **Antibiotic prophylaxis for minor dermatological surgery in primary care**
 NAZAR R DESSOUKI, CYPRUS (18 January 2009)

☞ **Does the initial premise reflect Antipodean experience?**
 Steven Ford (4 February 2009)

Re Antibiotic prophylaxis for minor dermatological surgery in primary care.

17 January
2009



Clare Heal,
 Senior lecturer
 James Cook University,
 Mackay, 4750

Send response to
 journal:

Re: Re Antibiotic prophylaxis for minor dermatological surgery in primary care.

We read this informative article with great interest and agree with its conclusions. However we feel we should clarify one issue. The authors of this article state that in our study of topical chloramphenicol(1) we use erythema as a measure of infection. Our primary definition of wound infection was the standardised surveillance criteria for defining superficial surgical site infections developed by the Centre for Disease Control's national nosocomial infection surveillance system (2). Although definitions of surgical wound infection used in clinical practice vary, this is the most widely implemented standard definition available(2). Erythema is not included in this definition of infection. We agree that the definition of infection is subjective and subject to intra and inter- observer variation(3). In order to improve rigour we also developed our own wound scale, which included erythema, as a secondary measure. We found that 5.5% of patients showed erythema larger than 1 cm in the intervention group compared with 9.1% of patients in the control group, however there was no

statistical difference in the presence of less than 1cm of erythema between the two groups. We agree that erythema does not necessarily indicate infection. Our results and conclusions are based on our primary definition of infection, which does not include erythema.

1 Heal CF et al. Does a single dose of topical chloramphenicol to high risk sutured wounds reduce the incidence of wound infection after minor surgery. A prospective, randomized double blind trial. *BMJ* 2009;338:a2812

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Competing interests: None declared

Antibiotic prophylaxis for minor dermatological surgery in primary care

18 January
2009



NAZAR R, DESSOUKI,
CONSULTANT SURGEON
TPMH, RAF, AKROTIRI,
CYPRUS

Send response to
journal:

Re: Antibiotic prophylaxis for minor dermatological surgery in primary care

For the prevention of surgical site infections, antibiotics may be indicated for procedures on the lower extremities or groin, for wedge excisions of the lip and ear, skin flaps on the nose, skin grafts, and for patients with extensive inflammatory skin disease.

Competing interests: None declared

Does the initial premise reflect Antipodean experience?

4 February
2009



Steven Ford,
Retired GP
Haydon Bridge. NE47 6HJ

Send response to
journal:

Re: Does the initial premise reflect Antipodean experience?

Editor

The opening paragraph declares that the prophylactic antibiotics in primary care minor surgery are 'widely used'. I dispute this.

In thirty years of minor surgical experience in primary care in the UK, involving all areas of the body, from the crown of the head to the little toe, I have almost never prescribed prophylactic systemic antibiotics. Exceptions include lesions that are obviously infected (abscesses), some pre-existing dermatological problems (psoriasis, dermatoses), female

external genitals and surgical exploration and removal of foreign bodies. For the avoidance of doubt - not all wounds were sutured.

Some years ago a colleague performed an audit of my work and noted a 2% infection rate.

Topical application of antibiotics seems to wax and wane in popularity. Does this reflect each surgical cohort's learning curve or memory span or, perhaps, some fluctuation in commensal populations or their pathogenicity?

A wry smile stole over my features whilst reading this item as the only legal action against me, so far, related to scarring after minor surgery. The surgeon for the other side, in presenting his opinion, started from the a priori assumption that all primary care surgical wounds are infected - summarily discounting the contemporaneous documentation to the contrary.

Ah! Such certainty! Bless!

Yours sincerely

Steven Ford

Competing interests: Thirty years of primary care minor surgery experience.

**APPENDIX 18.
ANTIBIOTIC PROPHYLAXIS IN
DERMATOLOGIC SURGERY:
ADVISORY STATEMENT 2008 (WRIGHT ET AL)**

DERMATOLOGIC SURGERY

**Antibiotic prophylaxis in dermatologic surgery:
Advisory statement 2008**

Tina I. Wright, MD,^a Larry M. Baddour, MD,^b Elie F. Barbari, MD,^b Randall K. Roenigk, MD,^a
P. Kim Phillips, MD,^a M. Amanda Jacobs, MD,^a and Clark C. Otley, MD^a
Rochester, Minnesota

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APPENDIX 19. CAN SUTURES GET WET?

Cite this article as: BMJ, doi:10.1136/bmj.38800.628704.AE (published 24 April 2006)

Research

Can sutures get wet? Prospective randomised controlled trial of wound management in general practice

Clare Heal, Petra Buettner, Beverly Raasch, Sheldon Browning, David Graham, Rachel Bidgood, Margaret Campbell, Robert Cruikshank

Abstract

Objective To compare standard management of keeping wounds dry and covered with allowing wounds to be uncovered and wet in the first 48 hours after minor skin excision.

Design Prospective, randomised controlled, multicentre trial testing for equivalence of infection rates.

Setting Primary care in regional centre, Queensland, Australia.

Participants 857 patients randomised to either keep their wound dry and covered (n = 442) or remove the dressing and wet the wound (n = 415).

Results The incidence of infection in the intervention group (8.4%) was not inferior to the incidence in the control group (8.9%) ($P < 0.05$). The one sided 95% confidence interval for the difference of infection rates was ∞ to 0.028.

Conclusion These results indicate that wounds can be uncovered and allowed to get wet in the first 48 hours after minor skin excision without increasing the incidence of infection.

Introduction

Guidelines for managing surgical wounds that are closed primarily (that is, those with the skin edges re-approximated at the end of the procedure) instruct that patients should keep their wounds dry and covered for 24–48 hours.¹ Before our study, the four participating general practices were implementing these guidelines and advising patients to keep their wounds dry and covered for 48 hours after minor excisions. For patients living in the tropics of North Queensland, with increased heat and humidity, this recommendation is impractical and a nuisance.

Literature on wound management is sparse. As regards wetting sutures, previous studies have compared standard management (keeping wounds dry) with washing with soap and water in the first 48 hours after minor skin excisions or compared standard management with early showering after more major surgery.^{2–4} These relatively few published studies suggest that getting sutures wet does not increase the infection rate. However, numbers of patients studied have been small, and only one previous study was randomised. No previous studies have been done in the general practice setting.

As regards uncovering sutures, some evidence shows that no difference exists in the incidence of infection between wounds left without dressings and those covered with a dry dressing in the early postoperative period.^{5–8} Again, no previous studies have been done in a general practice setting.

As the two factors, wetting and uncovering, are difficult to separate in the immediate postoperative period, we decided to

assess these factors together. We proposed to look at the effects of allowing patients to uncover and wet their wounds during the first 48 hours after minor skin excision, hypothesising that infection rates would be non-inferior compared with a control group following the dry wound management recommendations.

Methods

Study design

This was a randomised controlled, multicentre trial involving patients presenting for minor skin excisions.

Setting and participants

Sixteen general practitioners from four practices in the Mackay area, tropical North Queensland, Australia (latitude 21° south; inhabitants of Mackay area approximately 75 000) participated. The general practitioners were a self selected group who attended a monthly evidence based medicine meeting. Data collection took place from October 2004 to May 2005. We invited consecutive patients presenting for minor skin excisions to take part in the trial. Practice nurses were responsible for recruiting patients and collecting data. We collected demographic information on all patients, as well as clinical information on the presence or absence of diabetes or any other important medical condition (such as peripheral vascular disease, anaemia, or chronic obstructive pulmonary disease). We used a body site map to define excision sites. At the end of the study we asked practice nurses to re-examine computer records to fill in any missing data. The principal researcher visited participating general practitioners and practice nurses to provide training and ensure that recording was standardised.

We gave all participating patients an information sheet and asked them to give signed consent. We gave written instructions on postoperative wound care to patients who consented to participate.

Eligibility criteria

All patients who presented to a participating general practitioner for "minor skin excision," except for skin excisions on the face, were eligible to participate in the study. We excluded patients who were already taking oral antibiotics, for whom oral or topical antibiotics were clinically indicated immediately postoperatively, or who were on immunosuppressive drugs. Further exclusion criteria were lacerations, having a flap or two layer procedure (tying a "bleeder" did not count as two layer), excision of a sebaceous cyst, and skin excision on the face. We made these exclusions in an attempt to standardise the type of wound being studied and reduce the number of confounding factors.

Research

Surgical wound management protocol

A workshop attended by participating general practitioners developed guidelines to ensure that excisions were managed in a standardised manner. The following procedure was agreed: skin preparation (normal saline); usual sterile technique (standard precautions), including sterile gloves; local anaesthetic (type and volume recorded); suture material—nylon (size recorded); no antibiotics, either topical or oral (if required, or already prescribed, exclude from study), topical antiseptics (such as betadine or alcohol), or antiseptic washes or medicated soaps; dressing type—melolin and tape, removal of sutures, according to site (back = 10 days, all other sites = seven days).

Intervention

We gave patients oral and written instructions on postoperative wound management (fig 1). We asked the “dry” group to leave the dressing on and keep it dry for the first 48 hours, then to bathe and undress as normal until the sutures were taken out. We asked them to avoid using antiseptic washes or soaps.

We asked the wet group to take the dressing off within the first 12 hours and then bathe as normal until the sutures were taken out. We felt that patients should leave the surgery with a dressing to absorb immediate bleeding, but we also felt that defining an exact time to remove the dressing would be unrealistic, we considered “within 12 hours” to be a reasonable request. We also asked them to avoid using antiseptic washes and soaps.

Clinical outcomes

A practice nurse or doctor assessed wounds for infection on the day of removal of sutures, or sooner if the patient re-presented with a perceived infection. We adapted our definition of wound infection from standardised surveillance criteria for defining surgical site infections developed by the Centre for Disease Control's national nosocomial infection surveillance system (back).¹ The primary researcher briefed all participating doctors and nurses on the definition of infection, and we also gave them written information.

Sample size

We calculated sample size on the basis of a pilot study done in February to June 2004 and involving 543 patients, which showed an overall infection rate of 5.7%. On the basis of a projected infection rate of 5%, we decided that an increase in incidence of infection of 5% would be clinically significant. To come to this conclusion with statistical confidence, a power of 80%, and a significance level of 0.05 using a one sided equivalence test of proportions, we needed a total of 357 patients in the intervention group and 357 patients in the control group.

Randomisation

All patients provided written informed consent before enrolling in the study. After agreeing to participate, patients were

randomised by picking a ball out of a hat. The practice nurses chose this method of randomisation because of its ease and acceptability. The practice nurses enrolled patients and assigned participants to their groups. No blinding took place.

Statistical analysis

We based all analyses on the intention to treat principle. We used χ^2 tests to assess differences between categorical variables and unpaired *t* tests to compare numerical and categorical variables. To determine non-inferiority, we calculated the one sided 95% confidence interval of the difference in infection rates and compared it with the maximum allowable difference of 5%. We considered *P* values less than 0.05 to be statistically significant.

Results

Practice and study characteristics

Participating general practitioners were younger (median age 44) and more predominantly female (64%) than average for Australian general practitioners (median age category 45-54; 32% female). Of the total of 1247 patients who attended for skin excisions during the collection period from October 2004 to May 2005, we excluded 377 patients (table 1).

No significant differences existed in the age ($P=0.87$) or sex ($P=0.89$) of participating and non-participating patients. Of the remaining 870 patients, 450 patients were randomised to the intervention (wet) group and 420 to the control (dry) group. A total of 13 patients were eventually lost to follow-up. Follow-up was completed in 857 (98.5%) randomised patients (fig 2).

Baseline data

We found no significant differences between the intervention group and the control group at baseline (table 2).

Infections

Infection occurred in 74 (8.6%) of the 857 excisions. The intervention group had an infection rate of 8.4% compared with 8.9% in the control group. The one sided 95% confidence interval of the difference of the two proportions was ∞ to 0.028, so the non-inferiority side was lower than 0.05, the maximum allowable difference. We therefore concluded that the intervention group was not inferior to the control group with respect to the resulting infection rates ($P<0.05$).

Discussion

Our results indicate that patients can uncover and occasionally wet stitches in the first 48 hours after minor skin excisions without increasing the incidence of wound infection. The overall incidence of infection in our study was higher than we expected from our pilot study or from published literature looking at simi-

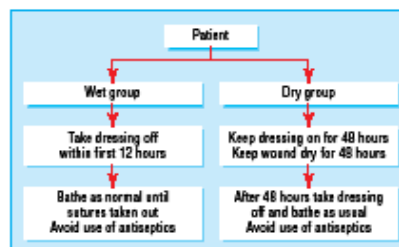


Fig 1 Wound management protocol in wet (intervention) and dry (control) groups

Research

Table 1 Reasons for exclusion of patients

Reason	No (% of 1247 eligible patients)
Refused	87 (5.4)
Forgot*	16 (1.3)
Not returning for removal of suture**	5 (0.4)
Face	256 (20.5)
Biopsy	10 (0.8)
Flap	17 (1.4)
Immunosuppressed	1 (0.1)
Antibiotics	5 (0.4)
Total	377 (30.3)

*The practice nurse forgot to invite these patients to participate.
 **These patients knew that they would not be able to return for removal of sutures.

lar cohorts,^{9,10} although exclusion of facial excisions from our study, which may have a lower incidence of infection, may have falsely raised our overall incidence of infection.

The study did have several limitations. Various characteristics influence the occurrence of infections, and, although we recorded information on as many variables as possible, ensuring that baseline data were comparable proved difficult. For example, we had inadequate data recorded on suture size and occupation, so we could not compare these factors. Also, the prevalence of diabetes and of other medically important conditions was probably under-recorded, and power to analyse these subgroups was limited. In addition, we did not record smoking, which may be a risk factor for surgical site infection.¹¹

The diagnosis of infection, although done using guidelines, is subjective and has previously been shown to have inter-observer and intra-observer variation.¹² The definition we used is the most widely implemented standard definition of wound infection.¹² Although we asked for recording of patients' compliance at the end of the trial, no recorded instances of non-compliance occurred, which may have been because of inadequate reporting; lack of compliance could also be subjective. We had no reported incidences of patients refusing their allocated intervention, but this could have been because of incomplete reporting rather than perfect compliance. Patients in the intervention group were asked to "bathe as normal" after removal of the dressing, but they did not record the number of episodes of wetting.

Definition of surgical site infection

- Infection must be within 30 days of excision
- There must be purulent discharge from the wound, or
- The general practitioner must diagnose a wound infection, or
- The general practitioner starts antibiotics
- Stitch abscess must not be counted as an infection

Table 2 Baseline comparison of intervention (wet) and control (dry) group. Values are numbers (percentages) unless stated otherwise

	Wet (intervention) (n=450)	Dry (control) (n=420)	P value
Mean (SD) age (years)	55.9 (16.6)	56.5 (16.2)	0.58
Male patients	249 (55)	206 (50)	0.08
Mean (SD) days to removal of sutures	8.6 (2.2)	8.6 (2.2)	1
Presence of diabetes	9 (2)	14 (3)	0.2
History of other medical condition*	8 (2)	10 (2)	0.5
Treated with 1% lignocaine adrenaline	435 (97)	411 (98)	0.3
Excision of skin cancer	294 (65)	289 (69)	0.3
Excision at lower limb	112 (25)	106 (25)	1

*Chronic obstructive pulmonary disease (n=6), anaemia (1), "aspirin" (2), "steroids" (3), "warfarin" (2), ischaemic heart disease (1), and peripheral vascular disease (1).

Although we were mainly interested in the wetting of sutures in the immediate postoperative period, separating this factor from uncovering and removing the dressing was difficult in practice, so we measured the two factors together.

Some limits to generalising these findings exist. The general practitioners involved were younger and more predominantly female than the average Australian general practitioner.¹³ The population of Mackay is slightly older and has a lower median household income than the Australian population as a whole.¹⁴ Mackay is a provincial town in tropical North Queensland. The climate is hot and humid, with the mean daily maximum temperature ranging between 24.2°C and 30°C during the summer months, and a relative humidity of 75-79%.¹⁵ These tropical conditions may increase sweat production and produce damp dressings, which might reduce the effectiveness of wound dressings as a potential barrier against exogenous bacteria.¹⁶⁻¹⁸ This would make the dry and covered control group more prone to infection in a tropical environment. Our findings may therefore not be generalisable to a temperate climate where dressings are less likely to become damp. Our results are encouraging, however, and studies in temperate climate should be considered.

Contributors: CH conceived and designed the study and analysed and interpreted the data. FB did the sample size calculation and statistical analysis. ER, SB, RB, MC, RS, and DG contributed to the design of the study. All authors contributed to the manuscript. CH is the guarantor.

Funding: Research was funded by a novice research scholarship from the primary health care research and development fund. The authors' work is independent of this funding.

Competing interests: None declared.

Ethical approval: Approval number H1902 granted by James Cook University ethics committee.

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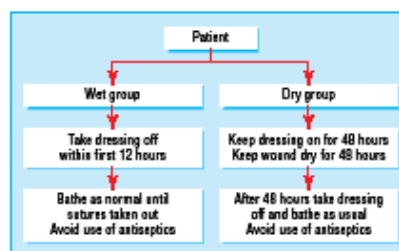


Fig 2 Flowchart of enrolment, randomisation, and follow-up of patients

Research

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What is already known on this topic

Guidelines instruct that surgical wounds closed primarily should be kept dry and covered for 48 hours

Sparse evidence suggests that wetting and uncovering sutures makes no difference to infection rates

What this study adds

Wetiting and uncovering sutures in the first 48 hours after minor excisions did not increase the infection rate

**APPENDIX 20.
HOW TO DISSECT SURGICAL JOURNALS: VII –
COMPARING OUTCOMES**

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**APPENDIX 21.
HOW TO DISSECT SURGICAL JOURNALS: IX –
SAMPLE SIZE**

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