

What is the Role of Prophylactic Antibiotics in the Management of Burns?

Primary Reviewers: Francis Lee, Patrick Wong, Fiona Hill ¹

Secondary Reviewer: Russell Taylor ²

¹ University of Western Australia, Perth

² Royal Children's Hospital, Australia

The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the Role of Prophylactic Antibiotics in the Management of Burns?*

The **WHO Pocketbook of Hospital Care for Children** recommends that in burns antibiotics should be administered to treat secondary infection, no mention is made of prophylactic antibiotics. (pg 242)

Introduction:

Thermal injuries are a major source of morbidity and mortality in the developing world. [1] There are over 300,000 deaths each year resulting directly from fire-related burns alone, with many more deaths from scalds, electrical and other forms of burns, for which global data are not available. [1] It has been estimated that 75% of all deaths following thermal injuries are related to infection. [2] Optimal management of burns, particularly to prevent and treat infection is therefore essential to improve outcomes. [3]

Traditionally, topical antibiotics and antibiotic-impregnated dressings have been used together with systemic antibiotics to prevent and treat infection. [4-7] However, there is a paucity of evidence to support the continued use of systemic antibiotic as prophylaxis to prevent infection following burns.

In many centres, including those in the developing world, hospitals have developed local management protocols with systemic antibiotic prophylaxis in patients who have a positive microbiological culture from a burn site in an attempt to prevent wound infection and septicaemia. [6,7]. Despite the large number of paediatric burn patients in developing countries, it is still unknown if the use of prophylactic systemic antibiotics is effective and cost-efficient in preventing infective complications. There is a lack of systematic research, standardised treatment protocols, compounded by limited resources. [8]

This review evaluates the evidence for efficacy of systemic [oral (PO) and intravenous (IV)] antibiotic prophylaxis in delaying or preventing infection of burns. This is an especially important issue for severe burns requiring operative wound debridement, surgical manipulation and skin grafting.

Methodology

Articles were identified through the Medline database using the 'Clinical Queries' framework. A broad clinical search strategy was employed using "antibiotics" AND "burns" to receive maximum yield. The Cochrane Database of Systematic Reviews, PubMed, and Medline were also hand-searched for relevant studies.

Primary outcomes assessed were efficacy of antibiotic prophylaxis, improved clinical outcomes including infection control/prevention, hospital stay, morbidity and mortality. Secondary outcomes included specific infection control/prevention e.g. Group A *Streptococcus*

(GAS) infections and comparison of swab/culture results.

Manuscripts were excluded if: (i) they were not burns-related; (ii) external body surface burn wounds were not discussed; (iii) the outcomes were related to non-clinical endpoints (such as biochemical or pharmacokinetic studies or epidemiological studies or case reports); (iv) antibiotic prophylaxis was mentioned as part of treatment regimen but its role is not further elucidated or quantified; (v) only topical antibiotics were used (the subject of an accompanying separate review) ; (vi) were experimental or *in vitro* studies; (vii) contained none or inadequate data for comparison; (viii) the antibiotics used were not related to clinical treatment; (ix) from a special population e.g. ophthalmological burns; (x) the publications were not written in English or (xi) the articles were published before 1970.

Results

Heterogeneity among studies occurred in 5 domains: (i) the use of different antibiotic prophylaxis, durations, doses and modes of administration (oral vs. intravenous); (ii) use of different antibiotic classes and preparations; (iii) non-uniform methods of outcome reporting; (iv) differing prevalence of nosocomial bacteria and background antibiotic resistance at the study site; (v) the severity of burns of patients studied and (vi) age of the study populations. However studies were not excluded if systemic antibiotic prophylaxis were implemented and discussed with good level of evidence.

The initial Medline search yielded 636 articles of which 407 were excluded after title review, 143 were excluded on basis of title and abstract review and 76 excluded based on detailed evaluation. 10 articles were found suitable for evaluation.

The Cochrane Database of Systematic Reviews was hand-searched using the terms “Antibiotic Prophylaxis [MeSH]” AND “Burns [MeSH]”. Of the 10 articles found, 2 paediatric trials [8,9] and 1 adult trial [10] were included. Medline yielded a further 23 articles after a search for “Antibiotic Prophylaxis” AND “Burns” of which 6 met inclusion criteria. Of these, 3 had already been found by the Cochrane search and the other 3 paediatric trials were included in this review. [11-

13] PubMed *Clinical Queries* was interrogated through the MeSH database using “Antibiotic Prophylaxis [MeSH]” AND “Burns [MeSH]”. Of 24 articles identified, 10 met inclusion criteria of which 6 had been found in the previous searches.

The combined search yielded 10 relevant articles which included 4 individual randomised controlled trials (RCTs), 4 prospective cohort studies, 1 prospective and 1 retrospective case-control study. Three contained purely paediatric data, 2 contained purely adult data and 4 had mixed population data.

Of the 10 studies which met the search criteria, 3 were performed in developing country hospitals. 2 studies showed continued benefit from routine systemic antibiotic prophylaxis [12,15] while the other 8 concluded that there is no advantage in this practice. [8-11,13-14,16-17]

Specific antibiotics used prophylactically differed considerably between trials. Choices of antibiotics included penicillin [13,17], ampicillin [8,11], dicloxacillin [17], cloxacillin [8], erythromycin [8,16,17], gentamicin [8], cefazolin [9], cephalothin [15], cephadrine [17], piperacillin [14], tazocin [11], amikacin [14], teicoplanin [10], flucloxacillin [12], 2nd generation cephalosporins [11] and clarithromycin.[11]

Data from adult studies

A RCT (n=61) in Lagos, Nigeria found that systemic antibiotic prophylaxis had no effect in controlling burn wound infection in patients managed on surgical wards. [8] The prophylaxis of ampicillin, cloxacillin, erythromycin or gentamicin had no significantly beneficial effect on the prevention of colonisation/infection of burns nor on the time to colonisation or infection.. Furthermore, the findings indicated that antibiotic prophylaxis may be deleterious, favouring the growth of *Pseudomonas aeruginosa* in burn wounds. [8] The methodology of this study was sound and relevant to developing countries. However it did not contain paediatric data and did not use standardised antibiotic regimens.

An RCT performed in UK on 134 adults compared bacteriological response and clinical outcomes between burns patients who received teicoplanin versus placebo.[10] While there was

significant difference in wound culture results, with the antibiotic group significantly having less episodes of peri-operative Gram-positive bacteraemia [8 cases (7%) versus 51 cases (46%)] ($p < 0.001$), clinical outcome was similar in both groups ($p=0.7$). The study concluded that postoperative recovery was not affected by the prophylactic prevention of Gram-positive bacteraemia. [10] However due to the small sample size and location, it was difficult to determine if the conclusion can be extrapolated to a developing world hospital.

The available adult data do not support the use of antibiotic prophylaxis in burns management. It is unclear if these adult data can be readily extrapolated to paediatric patients.

Data from paediatric studies

A small RCT ($n=23$) in Philadelphia, USA investigated the effectiveness of antibiotic prophylaxis at the time of surgical burns wound debridement or grafting. [9] Patients with burns surface area (BSA) $<35\%$ received either cefazolin or placebo while patients with BSA $>35\%$ received either cefazolin or antibiotics targeted against burn culture results. The study endpoints were clinical outcomes and surveillance cultures. This study reported that prophylactic cefazolin did not influence outcome in patients with either with BSA $<35\%$ or BSA $>35\%$. [9] However, this is a relatively old partially-blinded RCT performed more than 10 years ago with a small sample size, and only the abstract was available for consideration. The weight that can be given to the conclusions is therefore limited.

A retrospective case-control study ($n=77$) from Turkey compared 47 patients who received prophylactic antibiotics (tazocin, 2nd generation cephalosporins and clarithromycin) with 30 patients received no prophylaxis. [11] Wound infection rates were very similar in the two groups and of the 8 patients with clinical sepsis, all but one of them were from the group who received antibiotic prophylaxis. [11] However, in this retrospective study, the decision of prophylactic antibiotics may have been biased by factors including worse severity of burns, younger age, delay in hospital admission or worse clinical presentation. This is a well-written, relevant study but still lacks adequate scientific persuasion, uniformity of antibiotic choice and

has methodological issues and relatively poor power.

A prospective cohort study ($n=50$) in Belfast, UK aimed to assess whether prophylaxis with a single dose of a systemic antibiotic prevented the occurrence of toxic shock syndrome (TSS). [12] 78% of patients received antibiotic prophylaxis while the remaining 22% received antibiotic treatment later if clinically indicated. 6% developed septicaemia of which 4% were from the group receiving prophylaxis but there were no cases of TSS in either group. The results suggested that a single dose flucloxacillin prophylaxis may indeed have a role in prevention of TSS. [12] This study is specific and detailed in its clinical outcomes but lacks power to address the stated rare outcome effect.

A large retrospective case-control study ($n=917$) in Boston, USA aimed at preventing GAS infections by comparing routine infection surveillance data on burn patients cohorts admitted during two periods - 1992-1994 and 1995-1997. [13] In total 543 and 435 children were admitted and studied, respectively. The first cohort received antibiotic prophylaxis while the second cohort only received specific antibiotic treatment when sensitivities were known after screening cultures. There was no significant difference in patients developing GAS infections between both cohorts ($P=0.71$). It was concluded that routine antibiotic prophylaxis of burn wounds in children was not effective in reducing the incidence of GAS wound infection if children underwent both early excision of deep burns and screening cultures. [13] This study has a large paediatric population but suffers from the retrospective methodology and geographical variation.

Mixed adult and paediatric studies

A large prospective cohort study ($n=1213$) in Kuwait studied the efficacy of antibiotic prophylaxis against GAS infections by investigating a mixed age cohort of burns patients ranging from 15 days to 93 years old (mean=23 years) over a 5 year period. [14] Overall only 14 (1.1%) of the 1213 burn patients acquired streptococcal infections of which only one third were due to GAS. The study concluded that the low incidence of GAS in burns patients did not warrant penicillin prophylaxis in the first five post-burn days. [14] This study was adequately powered but suffers from short follow-up (5

days), poor level of evidence, selection bias and uncorrected confounding factors such as age, socioeconomic status, topical antibiotic use and no uniform systemic antibiotic use.

An RCT (n=249) in Ohio, USA compared the effectiveness of prophylactic cephalothin (n=127, mean age 10.5+/-0.4 years) versus placebo (n=122, mean age 10.8+/-0.4 years) with operations using skin grafts for reconstruction following burns injury over a period of 25 months. [15] Prophylaxis was effective in reducing infection (0.8% versus 5.7%, p<0.03), reducing graft loss (99.89% versus 84.75%, p<0.02) and shortening hospital stay (12.38 days versus 13.66 days, p=0.02). This study concluded that antibiotic prophylaxis does reduce infection rates in graft operations. However, this is an old study (published in 1982) which does not address the issue of antibiotic prophylaxis for burn wounds at first presentation and does not discuss the early burns sepsis normally experienced by burns victims. Also, this is a developed nation study and includes confounding factors e.g. different burn wound thickness, different graft size and thickness.

A prospective cohort study (n=294) from Yale, USA compared wound infection rates in outpatient burns patients (ranging from 2 to >60 years old) treated with prophylactic systemic antibiotics in the emergency department (n=133) against patients with similar burns but received no prophylaxis (n=161). There was no significant difference in the infection rates between the treated and untreated patients (3.8% versus 3.1%, p>0.75). [16] The authors agreed that prophylactic systemic antibiotics did not reduce the risk of wound infections. As this is an old (1985) observational cohort study focused on outpatient treatment with a 46% patient loss to follow up and poor epidemiological evidence, it can be argued that the study needs better methodology to be convincing.

A retrospective cohort study (n=269) from the UK reviewed cohorts of burns patients over a period of 4 years (1979-1982) where prior systemic prophylaxis (erythromycin) was stopped and *Streptococcus pyogenes* infections were monitored. It was recorded that 9 patients (3.3%) were found to have *Streptococcus pyogenes* infections and all recovered after appropriate antibiotic treatments were given. It was further argued that since the actual infection rates were very low, targeted use of systemic prophylaxis to

high-risk burns patients would be more beneficial than blanket prophylaxis which would increase bacterial resistance and economical burden while causing more antibiotic-related side effects. [17] This cohort study may not be relevant to current developing countries and lacks good methodology as it has no matching control group, no statistical significance comparison, no follow-ups and has no epidemiological data.

Discussion

Systemic prophylactic antibiotics in burns patients have traditionally been used in four clinical settings: (i) early administration of anti-streptococcal drugs to prevent burn wound cellulitis, (ii) oral and enteral administration of antibiotics to prevent bacterial infection, (iii) peri-operative administration of antibiotics, and (iv) administration of broad-spectrum antibiotics pending return of culture information in febrile or hypotensive patients. [18]

The available data from adult [8,10], paediatric [11,12] and mixed population [14-17] studies have demonstrated that systemic antibiotic prophylaxis in burns patients have no role in the prevention of bacterial infections. Moreover, GAS infection in burns patients is infrequent and is not further reduced by prophylactic antibiotics, providing those who had GAS on admission or subsequent surveillance cultures were treated appropriately. [13] Furthermore, peri-operative antibiotic prophylaxis did not decrease the incidence of graft or donor site infection. [9] Children with significant burns often have moderate fever in the absence of infection [19] and in this circumstance, administration of broad-spectrum antibiotics is not appropriate and moreover injudicious use of broad-spectrum antibiotics will increase bacterial resistance and may ultimately worsen outcomes in previously uninfected children. [18] The available data do not indicate that judicious use of antibiotics in febrile paediatric victims is incorrect. In established burns wound sepsis, targeted antibiotic usage may be helpful to eradicate the bacteraemia/septicaemia and reduce mortality rates. [18]

The role of early debridement and/or skin grafting cannot be underestimated in the management of paediatric burns. An RCT (n=344) compared survival rates of burns victims who received

either early excision or topical antimicrobial therapy with skin grafting after spontaneous eschar separation. Mortality from burns without inhalation injury was decreased by early excision from 45% to 9% in patients who were 17 to 30 years of age ($P < .025$). [20] A retrospective study in 1988 ($n=1674$) investigated the mortality of children with burn injuries and found that mortality was substantially reduced through the use of prompt eschar excision. [21] These studies demonstrate the benefits in survival and length of hospital stay that can be achieved with the practice of early excision in paediatric burns.[20,21]

There has also been a paucity of evidence on the relevance of post-operative antibiotics use in the management of paediatric burn patients and with the lack of support of the role of prophylactic antibiotic in the surgical management of paediatric burn patients [15-20], there seems to be a diminishing role of peri-operative antibiotic use.

However, it has been difficult to compare data from developed and developing countries due to geographical variation, complications in extrapolating adult data into paediatric population and challenging to draw conclusions due to variations in drug choices/doses/duration in all the studies included. Also, the presence of other confounding factors including differing universal precautions [19], other concurrent illnesses, variations in nutritional and hydration status, availability of resources and inconsistent practice in individual hospitals [22] add to the complexity of the situation. There is a paucity of high quality evidence for systemic antibiotic prophylaxis for the management of paediatric burns in the developing world that needs to be addressed.

Summary

The available evidence does not support the role of systemic antibiotic prophylaxis in the management of paediatric burns. This review also highlights a lack of a comprehensive evidence to address the pressing issue of whether prophylactic systemic antibiotics should be used in the management of burns in children.

With the present body of evidence, further studies of established and novel topical antimicrobial agents (other than topical antibiotics) are

warranted to reduce colonisation and infection rates. While the limited available evidence do not support prophylactic systemic antibiotics in burn management, further adequately powered RCTs in developing countries may be warranted to address this issue definitively.

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