

Prophylactic antibiotics for burns patients: systematic review and meta-analysis

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ABSTRACT

Objective To assess the evidence for prophylactic treatment with systemic antibiotics in burns patients.

Design Systematic review and meta-analysis of randomised or quasi-randomised controlled trials recruiting burns inpatients that compared antibiotic prophylaxis (systemic, non-absorbable, or topical) with placebo or no treatment.

Data sources PubMed, Cochrane Library, LILACS, Embase, conference proceedings, and bibliographies. No language, date, or publication status restrictions were imposed.

Review methods Two reviewers independently extracted data. The primary outcome was all cause mortality. Risk or rate ratios with 95% confidence intervals were pooled with a fixed effect model if no heterogeneity was present.

Results 17 trials were included. Trials that assessed systemic antibiotic prophylaxis given for 4-14 days after admission showed a significant reduction in all cause mortality (risk ratio 0.54, 95% confidence interval 0.34 to 0.87, five trials). The corresponding number needed to treat was 8 (5 to 33), with a control event rate of 26%. Perioperative non-absorbable or topical antibiotics alone did not significantly affect mortality. There was a reduction in pneumonia with systemic prophylaxis and a reduction in wound infections with perioperative prophylaxis. *Staphylococcus aureus* infection or colonisation was reduced with anti-staphylococcal antibiotics. In three trials, resistance to the antibiotic used for prophylaxis significantly increased (rate ratio 2.84, 1.38 to 5.83). The overall methodological quality of the trials was poor.

Conclusions Prophylaxis with systemic antibiotics has a beneficial effect in burns patients, but the methodological quality of the data is weak. As such prophylaxis is currently not recommended for patients with severe burns other than perioperatively, there is a need for randomised controlled trials to assess its use.

INTRODUCTION

Severe burns are an important health burden worldwide and affect young healthy adults and children.¹² Infections among burns patients are a major problem; the reported incidence of nosocomial infections varies at 63-240 per 100 patients and 53-93 per 1000 patient

days, depending mainly on the definitions used.^{3,4} Infections are independently associated with adverse outcomes and mortality.^{3,4} In a series of 175 patients with severe burns, infections preceded multiorgan dysfunction in 83% of patients and were considered as the direct cause of death in 36% of patients who died.⁵

In burns patients infections arise from multiple sources. Burn wounds become rapidly infected with Gram positive bacteria, mainly staphylococci, that are normal deep inhabitants of the sweat glands and hair follicles exposed by the burn.⁶ The moist, vascular burn eschar further fosters microbial growth. Gram negative bacterial infections result from translocation from the colon because of reduced mesenteric blood flow at the time of burn and subsequent insults.⁷ Furthermore, several immune deficits have been described among burns patients, including impaired cytotoxic T lymphocyte response, myeloid maturation arrest causing neutropenia, impaired neutrophil function, and decreased macrophage production.^{6,8-10} Finally, burns patients can incur hospital acquired infections common to other patients in intensive care units, including intravascular catheter related infections and ventilator associated pneumonia, with an overall incidence of infection higher than that of other patients in intensive care units.^{3,4}

Antibiotic prophylaxis reduces mortality, bacteraemia, and ventilator associated pneumonia among patients in intensive care units.^{11,12} Similarities between intensive care and burns patients suggest possibly similar benefit of prophylaxis. Both populations are critically ill, and bacterial translocation from the colon is an important source of infection, as are foreign bodies and invasive procedures. In burns patients the skin is an additional source of infection, and they have a higher degree of immunosuppression. Nevertheless, there is a broad and uniform consensus in the current literature that prophylaxis with systemic antibiotics should not be given to patients with severe burns. Recommendations for management do not address systemic antibiotic prophylaxis¹³ or explicitly state that prophylactic antibiotics are not recommended.¹⁴⁻¹⁸ The rationale given is lack of evidence, no benefit, or risk for adverse events, mainly colitis associated with *Clostridium difficile* and induction of antibiotic

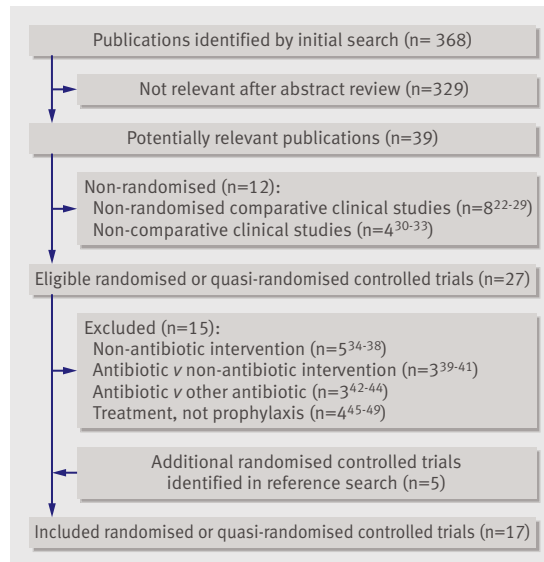


Fig 1 | Identification of studies for inclusion

resistance. Indeed, most episodes of bloodstream infection after the first week are caused by hospital-type multidrug resistant bacteria.^{4 19} Recommendations regarding perioperative prophylaxis vary and most sources recommend limited perioperative prophylaxis only for those with severe burns (>40% total body surface area).^{14 16 17}

We performed a systematic review and meta-analysis of randomised and quasi-randomised controlled trials assessing antibiotic prophylaxis for burns patients, both in the perioperative and general setting. We primarily examined the effect of prophylaxis on all cause mortality.

METHODS

Selection criteria

We included randomised controlled trials or quasi-randomised trials (with inadequate allocation generation methods), recruiting inpatients with burns injuries (any total body surface area or burn degree, with or without inhalation injury), regardless of publication status or language. The intervention assessed was antibiotic prophylaxis versus placebo or no treatment. Prophylaxis was defined as antibiotics administered to patients without documented infection regardless of systemic inflammatory signs, including systemic antibiotics given intravenously, orally, or intramuscularly; non-absorbable oral antibiotics; or topical (wound dressing or inhalation) antibiotics. Regimens including both systemic and non-absorbable or topical antibiotics were included in the systemic category. Antibiotics could be administered at any time after admission (“general”) or specifically targeted at a surgical procedure (“perioperative”). We excluded topical non-antibiotic antimicrobial ointments or dressings (silver with or without sulphur, iodine, or mafenide) and antifungals, unless applied identically to intervention and control arms. We excluded dose or schedule comparisons of the same antibiotics.

Outcomes

The protocol defined primary outcome was all cause mortality 100 days after randomisation. None of the studies reported 100 day data or similar, nor at another fixed point in time, and so we extracted in hospital mortality from all the studies, per protocol. Secondary outcomes included bacteraemia, pneumonia (including ventilator associated pneumonia), infection of the burn wound, length of stay in hospital, infections caused by *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and methicillin resistant *S aureus* (MRSA), resistance induction, fungal infections (fungaemia or other clinical fungal infection), and adverse events. Resistance induction was defined per protocol as clinical infection (not colonisation) caused by bacteria resistant to one or more of the antibiotics included in the prophylactic regimen. Studies, however, reported only on selected “resistant isolates” (including both clinical and colonising bacteria); these data and their definitions were extracted. Similarly, we accepted and documented other outcomes definitions used in individual studies.

Search methods

We searched PubMed (1966 to February 2009), Cochrane Library (issue 4, 2008), LILACS (1982 to February 2009), Embase (1974 to October 2009), and conference proceedings (Interscience Conference on Antimicrobial Agents and Chemotherapy 1995-2008; European Congress of Clinical Microbiology and Infectious Diseases 2000-8; Annual Meeting of the American Burn Association 2001-9; Congress of the International Society for Burn Injuries 2007; and the Annual Southern Region Burn Conference 2008-9). We crossed the words “burn” or “total body surface area or TBSA” and their MESH terms with the terms “antibiotic,” “infection”, “sepsis”, or “bacteremia”. For PubMed, this was combined with the Cochrane highly sensitive filter for randomised controlled trials.²⁰ We scanned the references of all included articles for additional studies. Authors were contacted to complement data on mortality and trial methods (one author²¹ supplied additional data on methods).

Data collection

Two reviewers (TA and AL) independently inspected each reference identified by the search, scanned full texts of relevant studies, applied the inclusion criteria, and extracted the data. Disagreements on data extraction were resolved by discussion with a third reviewer (MP). We assessed risk of bias in duplicate using domain based evaluation, classifying studies primarily according to the risk of non-random allocation of patients to the intervention arm (sequence generation) and concealment of this process (allocation concealment). These were graded as adequate, unclear, or not described and inadequate (for example, alternation, allocation by day of admission, hospital room), as recommended in the Cochrane Handbook.²⁰ We also assessed blinding and intention to treat analysis. The effect of allocation concealment on results was assessed

Table 1 | Study characteristics of trials examining prophylactic antibiotics for burns patients in general settings. Figures are means (SD or SE) or median (range) unless stated otherwise

Study and intervention details	Intervention duration (days)	No of patients randomised	Age (years)	TBSA (%)	3rd degree burns (%)	Inhalation injury (%)
Barret 2001 ⁵²						
Non-absorbable per nasogastric tube polymyxin E, tobramycin, amphotericin B	Until open burn area <10% TBSA	11	8 (1)	67 (6)	100	75
Placebo		12	9.4 (2)	58 (6)	100	63.6
De la Cal 2005 ⁵³						
Systemic intravenous cefotaxime + oropharyngeal paste and non-absorbable digestive administration of polymyxin E, tobramycin, amphotericin B	4	58	41.4 (17.1)	34 (21.4)	19.3 (15.3)	64.2
Placebo		59	48.2 (28.5)	37.7 (21.1)	19.0 (18.8)	68.5
Desai 1991 ⁵⁴						
Topical gentamicin 1% cream	Until wound healing	7	11.4 (1.2)	35 (7)	20 (9)	NS
No treatment		8	9.5 (1.6)	50 (6)	32 (7)	
Deutsch 1990 ⁵⁵						
Systemic and non-absorbable oral/nasogastric tube erythromycin, neomycin, nystatin	10	15	44.7 (15-79)	49.9 (22-91)	26.3 (0-75)	26.7
No treatment		12	35 (18-75)	44.9 (20-75)	26.3 (0-50)	41.7
Durtschi 1982 ⁵⁶						
Systemic intravenous or oral penicillin	5	25	31.1 (18-77)	14.9 (1-70)	NS	NS
Placebo		26	36.8 (18-66)	20 (1-91)		
Kimura 1998 ⁵⁷						
Systemic per nasogastric tube sulfamethoxazole-trimethoprim	10	21	44 (10-91)	49 (22-87)	NS	52
Placebo		19	48 (12-85)	43 (20-80)		
Levine 1978 ⁶⁵						
Inhalation gentamicin	10	12	28.1	53.8	NS	100
Placebo		18	34.3	57.6		
Livingston 1990 ²¹						
Topical neomycin and bacitracin	Until graft healing	18	<20% TBSA 46 (22); 20-40% 27 (5); >40% 49 (10)	<20% TBSA 14 (5); 20-40% 29 (7); >40% 47 (6)	NS	22.2
Normal saline		15	<20% TBSA 43 (27); 20-40% 34 (20); >40% 43 (19)	<20% TBSA 11 (3); 20-40% 28 (6); >40% 53 (16)	NS	33.3
Lowbury 1968 ⁵⁸						
Topical silver nitrate + gentamicin	Until burns had healed or were grafted	21	NS	<30	NS	NS
Topical silver nitrate		20				
Munster 1989 ⁵⁹						
Systemic intravenous polymyxin B*	7	22	34.4	29.3	NS	NS
No treatment		23	38.8	32.8		
Ugburo 2004 ⁶⁴						
Systemic oral ampicillin + oxacillin	14	21	22.9 (4.1)	41.5 (5.8)	NS	0
Systemic intravenous gentamicin+ oral erythromycin		20	24.9 (3.3)	46 (5.6)		
None		20	23.3 (3)	44.3 (6.3)		

TBSA=total body surface area; MRSA=meticillin resistant *S aureus*.

**Two sequential parts randomising patients to general systemic prophylaxis (first part) and perioperative systemic prophylaxis (second part), kept separate in our analyses.

through sensitivity analysis, with restriction of the analysis to studies with adequate allocation concealment.

Data analysis

Dichotomous outcomes (mortality, resistance development, and adverse events) are expressed per patient and count data (infections, bacteraemia) are given per patient day. Individual study results are expressed as risk ratios or rate ratios, respectively, with 95% confidence intervals. Rate ratios were calculated as the ratio of events per patient day. Results were pooled with the Mantel-Haenszel fixed effect model (Review Manager (RevMan), version 5 for Windows, Cochrane

Collaboration, Oxford). We used χ^2 test to determine heterogeneity ($P<0.1$) or an I^2 measure for inconsistency ($>50\%$).²⁰ Outcomes with significant heterogeneity were not pooled. We anticipated heterogeneity related to total body surface area and degree of burn but did not perform subgroup analyses because of paucity of trials. Analyses were stratified by antibiotic mode and intervention: systemic antibiotics (which could be administered in the general or perioperative setting), non-absorbable antibiotics, and topical antibiotics. Because of paucity of trials in each analysis, we did not use any formal method to investigate publication bias.

Table 2 | Study characteristics of trials examining systemic prophylactic antibiotics for burns patients in perioperative settings. Figures are means (SD or SE) or median (range) unless stated otherwise

Study and intervention details	Intervention duration (days)	No of patients randomised	Age (years)	TBSA (%)	Third degree burns (%)	Inhalation injury (%)
Alexander 1982 ⁵¹						
Systemic intravenous cephalothin	1	127	10.5 (0.4)	NS	NS	NS
Placebo		122	10.8 (0.4)			
Alexander 1984 ⁵⁰						
Systemic antibiotics tailored to wound cultures	1	35	NS	45.7% >30%	NS	NS
No treatment		34		38.2% >30%		
Munster 1989 ⁵⁹						
Systemic intravenous polymyxin B*	5	6	47.7	54.8	NS	NS
No treatment		11	40.6	38.4		
Piel 1985 ⁶⁰						
Systemic intravenous cephalosporin	1	25	33.6	42.6	NS	NS
Placebo		26	39.2	37		
Ramos 2008 ⁶¹						
Systemic intravenous cephalothin or antibiotics tailored to surveillance cultures	2	46	39 (21.7)	21.6 (21)	NS	NS
No treatment		44	35 (22)	27.7 (22.3)		
Rodgers 1997 ⁶²						
Systemic intravenous cefazolin	1	10	1.5	10	NS	NS
Placebo		10	1.9	11		
Steer 1997 ^{63†}						
Systemic intravenous teicoplanin	1	67 (110 episodes)	38 (23-54)	8.5 (4-18)	44	NS
Placebo		67 (110 episodes)	42.5 (26-56)	8.0 (4-16)	45	

TBSA=total body surface area; NS=not stated; MRSA=meticillin resistant *S aureus*.

*Two sequential parts randomising patients to general systemic prophylaxis (first part) and perioperative systemic prophylaxis (second part), kept separate in our analyses.

†Trial included patients before surgery (46% of episodes) or change of dressing.

RESULTS

The search yielded 368 different publications, of which 39 were potentially relevant. Twenty seven studies were excluded (fig 1). We identified five trials through reference searching and altogether included 17 studies (37 trial arms), one of which was published as an abstract.^{21,50-65} The trials were published from 1968 to 2008 and recruited 1113 patients (median 51, range 15-149). Four trials recruited children^{51,52,54,62} and the others young adults (tables 1 and 2). The mean total body surface area affected was >20% in 12 trials (>30% in nine). Most trials did not report the number of patients with full thickness burns. Twelve administered systemic antibiotic prophylaxis; six trial arms assessed general^{53,55-57,59,64} and six perioperative prophylaxis.^{50,59-63} Systemic antibiotics usually targeted Gram positive bacteria and were given for a median of 8.5 days (range 4-14) in the general setting. Two trials assessing systemic general prophylaxis and none of the trials in the perioperative setting included a non-absorbable component. One trial assessed only non-absorbable prophylaxis,⁵² three trials topical antibiotic treatment,^{21,54,58} and one trial inhalation antibiotics,⁶⁵ targeting mainly Gram negative bacteria.

Five and six trials, respectively, described adequate sequence generation and allocation concealment. Both were inadequate in three quasi-randomised trials that used alternation or hospital number for sequence generation^{55,58,59} and were not described in all other

trials (table 3 and fig 2). Patients and carers were blinded in seven trials (six assessing systemic prophylaxis). Results by intention to treat were reported in all but two trials.

Primary outcome

Nine trials reported all cause, in hospital mortality (fig 3). Systemic prophylaxis in the general setting was associated with a significant reduction in all cause mortality (risk ratio 0.54, 95% confidence interval 0.34 to 0.87, five trials, 272 patients), without significant het-

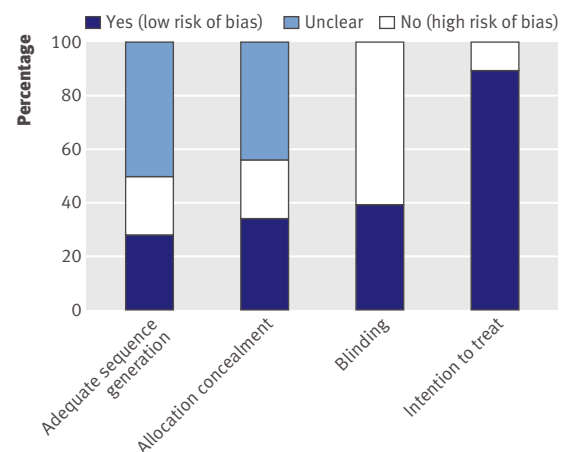


Fig 2 | Assessment of overall risk of bias

Table 3 | Methods and outcome definitions used in individual trials

Study	Allocation generation	Allocation concealment	Blinding*	Intention to treat analysis	Secondary outcomes evaluated and definitions	Resistance development/surveillance cultures†
Alexander 1982 ⁵¹	Adequate (random choice of envelopes)	Adequate (central pharmacist)	DB (placebo used, only pharmacist aware of treatment assignment)	Yes	Wound infection (discharge of pus from graft associated with graft loss); <i>P aeruginosa</i> and <i>S aureus</i> infections; hospital stay	NA. No surveillance
Alexander 1984 ⁵⁰	Unclear (not stated)	Unclear (not stated)	Open (treatment and control patients placed in different wards)	Yes	Bacteraemia; wound infection	NA. Wound and blood surveillance
Barret 2001 ⁵²	Adequate (random number chart)	Adequate (central pharmacy)	DB (placebo used, only pharmacist aware of treatment assignment)	Yes	Pneumonia (by CDC criteria or similar ⁶⁶); systemic fungal infection; hospital stay	NA. Wound, sputum, urine, blood, gastric aspirates, and stool surveillance
De la Cal 2005 ⁵³	Unclear (not stated)	Adequate (central, pharmacy and kept in sealed envelopes)	DB (placebo used, only pharmacist aware of treatment assignment) + evaluator blinded	No	Pneumonia and bacteraemia (CDC criteria ⁶⁶); wound infection (according to previously proposed criteria ⁶⁷); candidaemia; <i>P aeruginosa</i> and <i>S aureus</i> infections; hospital stay	Unrelated; ventilator associated pneumonia or bacteraemia caused by MRSA. Wound, throat, rectal surveillance
Desai 1991 ⁵⁴	Unclear (not stated)	Unclear (not stated)	Open	Yes	Wound infection (chondritis, defined); hospital stay	Related; chondritis caused by gentamicin-resistant bacteria. Wound surveillance
Deutch 1990 ⁵⁵	Inadequate (chronological alternation)	Inadequate (chronological alternation)	Open	Yes for mortality; no for secondary outcomes	Wound and fungal infection (positive wound cultures); bacteraemia; <i>P aeruginosa</i> and <i>S aureus</i> infections; hospital stay	NA. Wound surveillance
Durtschi 1982 ⁵⁶	Unclear (not stated)	Unclear (not stated)	DB (placebo used)	Yes	Wound infection (sepsis and warm, spreading, painful cutaneous erythema); bacteraemia; <i>P aeruginosa</i> , <i>S aureus</i> , and fungal infections; hospital stay	Unrelated; infections caused by gentamicin-resistant bacteria. Wound, rectal surveillance
Kimura 1998 ⁵⁷	Unclear (not stated)	Adequate (central pharmacy)	DB	Yes	Pneumonia (by CDC criteria ⁶⁶); <i>P aeruginosa</i> and <i>S aureus</i> infections	Unrelated; MRSA infections. No surveillance
Levine 1978 ⁶⁵	Unclear (not stated)	Unclear (not stated)	Single or DB (placebo inhalations used)	Yes	Pneumonia (pulmonary infiltrate); bacteraemia; <i>P aeruginosa</i> infections	NA. Blood surveillance
Livingston 1990 ²¹	Adequate (cards shuffled at assignment)	Adequate (cards placed in sealed envelopes)	Open	Yes	Wound infection (>10% graft loss and >10 ⁵ organisms/g tissue, both in non-adherent graft and recipient site; candida wound infections; hospital stay)	Unrelated; MRSA infections. Wound surveillance
Lowbury 1968 ⁵⁸	Inadequate (alternation)	Inadequate (alternation)	Open (no placebo, no blinding described)	Yes	<i>P aeruginosa</i> and <i>S aureus</i> infections	Related; infections caused by gentamicin-resistant bacteria. Wound surveillance
Munster 1989 ⁵⁹	Inadequate (randomised by hospital number)	Inadequate (randomised by hospital number)	Open (no placebo, no blinding described)	Yes	No secondary outcome	NA. No surveillance
Piel 1985 ⁶⁰	Unclear (not stated)	Unclear (not stated)	Open (intervention listed on bedside flow chart)	Yes	Bacteraemia	NA. Wound and blood surveillance
Ramos 2008 ⁶¹	Unclear (not stated)	Adequate (sealed envelopes)	Evaluator	Yes	Wound infection (graft loss with swelling, erythema, increased temperature, tenderness or purulent discharge)	NA. Wound surveillance
Rodgers 1997 ⁶²	Adequate (table of random numbers)	Unclear (not stated)	DB (placebo used, only pharmacist and one unblinded investigator in the operating room aware of treatment assignment) + evaluator	Yes	Wound infection (clinical indication of infection with positive quantitative skin, wound biopsy, or blood cultures); candida wound infection; bacteraemia; <i>P aeruginosa</i> and <i>S aureus</i> infections	NA. Wound and blood surveillance
Steer 1997 ⁶³	Unclear (not stated)	Unclear (not stated)	DB (placebo used, teicoplanin colour masked, only pharmacist aware of treatment assignment)	Yes, but analysis based on episodes	Wound infection (biopsy and quantitative tissue or skin cultures); pneumonia (respiratory infection manifested by sepsis and increase of purulent tracheobronchial secretions or worsening pulmonary gas exchange); <i>P aeruginosa</i> and <i>S aureus</i> infections; bacteraemia; candidaemia	Related and unrelated; infections caused by teicoplanin-resistant staphylococci and MRSA. Wound and blood surveillance
Ugburo 2004 ⁶⁴	Adequate (table of random numbers)	Unclear (not stated)	Open	Yes	Wound infection (clinical infection using previously proposed criteria ⁶⁸ , with histological and microbiological confirmation); <i>P aeruginosa</i> and <i>S aureus</i> infections	NA. Wound surveillance

*DB=double blind; patient and carer were blinded to treatment; NA=not assessed.

†Resistance trait and types of infections reported and relation to study drugs (related: assessment of resistance to one or more of the study drugs; unrelated: assessment of a resistance trait unrelated to the study antibiotics) and surveillance cultures reported.

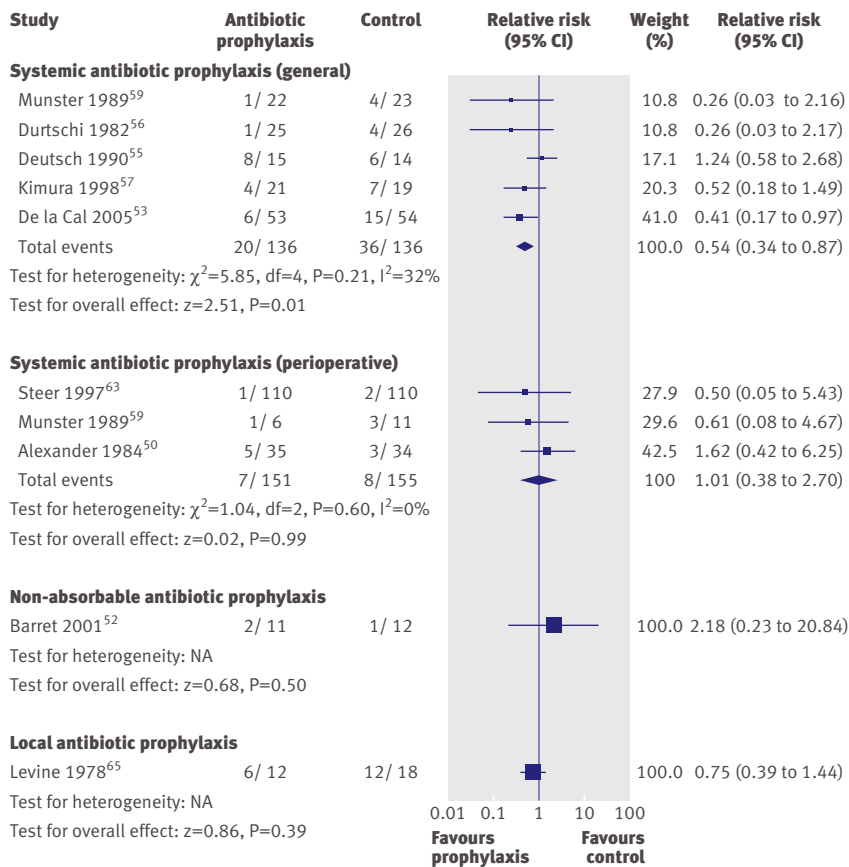


Fig 3 | All cause mortality in burns patients according to type of antibiotic prophylaxis

erogeneity ($P=0.21$, $I^2=32\%$). The corresponding number needed to treat was 8 (5 to 33), with a control event rate of 26%. The antibiotics used included cefotaxime, trimethoprim-sulfamethoxazole, penicillin, polymyxin B, and a combination of oral neomycin, erythromycin, and nystatin. The exclusion of trials with inadequate allocation concealment increased benefit (0.42, 0.22 to 0.79, three trials). There were no significant differences in mortality for perioperative non-absorbable or topical antibiotic prophylaxis.

Secondary outcomes

Outcome definitions varied between the trials; table 4 summarises the results. Seven trials comprising 4835 patient days reported on bacteraemia. One trial administering perioperative teicoplanin prophylaxis showed a highly significant reduction (rate ratio 0.26, 0.15 to 0.45),⁶³ while all other trials, including those of the general setting, showed no significant differences, both individually and pooled. Five trials reported on pneumonia (mainly ventilator associated) (103 events, 2624 patient days). Use of systemic antibiotics in the general or perioperative setting showed a significant reduction in pneumonia (0.55 (0.36 to 0.84), three trials). Eleven trials reported on burn wound infection (not colonisation) (295 events, 7357 patient days). Perioperative systemic antibiotic prophylaxis had an advantage of borderline significance (0.72 (0.52 to 1.01), four trials), while general systemic and topical antibiotics had no

effect. Most trials did not report on length of admission to hospital in a manner that could be pooled.

Microbiological assessment showed that infection or colonisation by *Paeruginosa* was not significantly different, both in trials assessing antibiotics with and without an anti-pseudomonal spectrum of coverage (1.06, 0.66 to 1.71, four trials; and 0.89, 0.62 to 1.28, seven trials, respectively). *S aureus* infections significantly decreased with anti-staphylococcal prophylaxis (0.58, 0.43 to 0.76, six trials), while the three trials assessing an antibiotic without anti-staphylococcal coverage showed an overall increase but with significant heterogeneity ($I^2=51\%$). Similarly, MRSA infections significantly decreased when anti-MRSA prophylaxis was used (0.36, 0.19 to 0.70, three trials). Fungal infections were documented more often with antibiotic prophylaxis, but without a significant difference (1.58, 0.63 to 3.99, seven trials).

While most trials performed routine surveillance cultures, at least of burn wounds (table 2), results pertaining to induction of resistance were scarce (table 3). Isolation of bacteria resistant to the study antibiotics from any site was significantly higher in the intervention arm (2.84, 1.38 to 5.83, three trials, one topical, two systemic). Three trials reported on resistant infections unrelated to the intervention antibiotic (MRSA or resistance to gentamicin), which was lower in the intervention arm (0.42, 0.18 to 0.98).

Six trials addressed adverse events comparatively, of which three reported no events. Adverse events requiring discontinuation of antibiotic treatment were specified; these consisted of rash in two trials^{51,63} and diarrhoea in one.⁵⁵ There was higher rate of discontinuation because of adverse events with treatment overall (4.97, 1.08 to 22.96). Pseudomembraneous colitis was not reported.

DISCUSSION

The pooled evidence in our systematic review shows a significant decrease in all cause mortality with systemic antibiotic prophylaxis for 4-14 days among patients with burns (mostly severe), with a number needed to treat of 8 (5 to 33). Systemic prophylaxis was associated with a reduced rate of pneumonia and, when administered perioperatively, with a reduced rate of burn wound infections. Resistance of bacteria to the antibiotic used for prophylaxis increased. Our findings are based on a few small trials and in most randomisation methods were unclear or clearly inadequate. These results stand in contrast with the current consensus regarding antibiotic prophylaxis for patients with severe burns.¹⁴⁻¹⁸

Comparison with studies conducted in intensive care units More evidence on the effects of antibiotic prophylaxis is available from studies on other critically ill patients in intensive care units. In this setting prophylaxis with non-absorbable or topical (oropharyngeal) antibiotics aims to decontaminate the digestive tract of Gram negative bacteria, *S aureus*, and candida. Most trials assessing antibiotic prophylaxis in intensive care

Table 4 | Secondary outcomes in burns patients according to antibiotic treatment

Outcome	No of trials	Rate ratio (95% CI)	Heterogeneity	
			χ^2 P value	I ²
Bacteraemia*				
Systemic general	4 ^{53 55 56 62}	1.30 (0.91 to 1.85)	0.56	0%
Topical, inhalation	1 ⁶⁵	0.92 (0.39 to 2.16)	—	—
Wound infection				
Systemic general	5 ^{53 55 56 62 64}	1.13 (0.82 to 1.55)	0.92	0%
Systemic perioperative	4 ^{50 51 61 63}	0.72 (0.52 to 1.01)	0.17	40%
Topical	2 ^{21 54}	1.49 (0.67 to 3.34)	0.83	0%
Pneumonia				
Total systemic	3	0.55 (0.36 to 0.84)	0.28	21%
Systemic general	2 ^{53 57}	0.52 (0.33 to 0.83)	0.12	58%
Systemic perioperative	1 ⁶³	0.71 (0.23 to 2.23)	—	—
Non-absorbable	1 ⁵²	2.70 (0.11 to 66.10)	—	—
Topical, inhalation	1 ⁶⁵	1.00 (0.42 to 2.37)	—	—
<i>P aeruginosa</i> infections				
Total	12	0.95 (0.71 to 1.27)	0.94	0%
With anti-pseudomonal activity	4 ^{55 58 64 65}	1.06 (0.66 to 1.71)	0.97	0%
Without anti-pseudomonal activity	7 ^{51 53 56 57 62-64}	0.89 (0.62 to 1.28)	0.61	0%
<i>S aureus</i> infections				
With anti-staphylococcal activity	6 ^{51 57 58 62-64}	0.58 (0.43 to 0.76)	0.72	0%
Without anti-staphylococcal activity	3 ^{53 55 56}	1.70 (1.09 to 2.64)	0.13	51%
Fungal infection				
Total	7	1.58 (0.63 to 3.99)	0.56	0%
Antibacterials and antifungals	3 ^{52 53 55}	1.26 (0.26 to 6.14)	0.49	0%
Antibacterials without antifungals	4 ^{21 56 62 63}	1.78 (0.56 to 5.59)	0.34	11%
Resistance development†				
Resistance trait related to prophylaxis	3 ^{53 54 63}	2.15 (1.25 to 3.70)	0.50	0%
Resistance trait unrelated to prophylaxis	3 ^{21 56 58}	0.42 (0.18 to 0.98)	0.70	0%
Adverse events requiring discontinuation‡				
Total	3	4.97 (1.08 to 22.96)	0.41	0%
Systemic general	1 ⁵⁵	13.10 (0.65 to 265.42)	—	—
Systemic perioperative	2 ^{51 63}	2.99 (0.47 to 19.02)	0.32	0

*With systemic prophylaxis in perioperative setting, one trial⁶³ showed highly significant advantage with prophylaxis (0.26, 0.15 to 0.45), while other⁵⁰ showed no difference (1.16, 0.79 to 1.70), thus this category was not pooled and nor was overall assessment of systemic antibiotic prophylaxis.

†Risk ratios shown.

units, however, also used broad spectrum systemic antibiotics for the first few days. The full (systemic plus non-absorbable) selective digestive decontamination regimen achieves a larger reduction in mortality (odds ratio 0.71, 0.61 to 0.82) than the non-absorbable intervention alone (0.94, 0.71 to 1.24).^{11 69} Selective decontamination regimens reduce mainly Gram negative infections,⁷⁰ and induction of resistance has not been shown in trials conducted in low resistance settings.¹² In the trials that assessed burns patients, systemic antibiotics alone were used in all the perioperative trials and some of the general prophylaxis trials. A recent trial, independently showing a reduction in mortality and ventilator associated pneumonia, used the full selective decontamination regimen.⁵³ *S aureus* infections were reduced with prophylaxis in the perioperative setting. Considering similar risk factors for intensive care and burns patients, the unique susceptibility of burns patients to infections caused by skin flora, and the available evidence, it seems that the

optimal regimen for prophylaxis among burns patients would be a full selective decontamination regimen including systemic and non-absorbable antibiotics. Antibiotics targeting Gram positive bacteria might be of added value perioperatively after discontinuation of the systemic antibiotic.

Strengths and limitations of study

We included systemic, non-absorbable, and topical antibiotics to inspect the effects of each separately and to fully appraise their combined effect on resistance induction. We included all types of burns, although the question of prophylaxis applies mainly to patients with severe burns. Most trials recruited patients with burns over more than 20% of total body surface area, and the mortality rate of the control group was 25% in trials that assessed general systemic prophylaxis and 17% in all trials reporting on mortality (fig 3). The paucity of trials precluded separate analyses for patients with severe or full thickness burns only.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antibiotic prophylaxis reduces all cause mortality among patients in intensive care

Current guidelines for management do not recommend systemic antibiotic prophylaxis for burns patients, stating lack of evidence for efficacy and induction of antibiotic resistance

WHAT THIS STUDY ADDS

In burns patients systemic antibiotic prophylaxis administered in the first 4-14 days significantly reduces all cause mortality by nearly a half; limited perioperative prophylaxis reduces wound infections but not mortality

Topical antibiotic prophylaxis applied to burn wounds, commonly recommended, had no beneficial effects

The methodological quality of the evidence is weak, however, so a large, robust randomised controlled trial is now needed

Included trials span a long period, starting before 1968 and the last published in 2008. During this period advances in support and surgical treatment and changes in antibiotic treatment and resistance have occurred, limiting the validity of the pooled evidence. Randomisation methods were inadequate (quasi-randomisation) in three trials, and most others did not report the methods used. Although exclusion of the quasi-randomised trials did not reduce the effect on mortality, results should be interpreted with caution. Finally, although we performed a comprehensive search, we cannot be sure that we did not miss unpublished trials or older trials that were not labelled as randomised. The paucity of trials in each category precluded the assessment of publication bias.

Implications for practice

Infections are the leading cause of death in patients with severe burns, even given contemporary resuscitation protocols and surgical techniques.⁵ The onset of infection is difficult to pinpoint because patients with severe burns often present with systemic inflammatory signs and shock. Inhalation injury masks the appearance of pneumonia. This difficulty has been addressed by the American Burn Association's consensus definitions for sepsis, designed specifically for burns patients.⁷¹ Even with improved definitions, it is difficult to ensure early appropriate antibiotic treatment for these patients; thus the appeal of antibiotic prophylaxis. In hospitals, burn units have notoriously been known as a source for outbreaks of multidrug resistant bacteria. Historically the appearance of MRSA and multidrug resistant *Pseudomonas* and *Acinetobacter* species were linked to burn units⁷²⁻⁷⁴ and more recently vancomycin resistant *Enterococcus* species and *S aureus*.⁷⁵⁻⁷⁶ Thus, the fear of further induction of resistance with antibiotic prophylaxis is real. Weighting a survival benefit against possible harm to future patients through cross infection with resistant strains is difficult. Most clinicians would probably opt for the individual's immediate gain. The reduction in mortality shown in the current analysis, however, needs to be confirmed in a larger contemporary trial.

Implications for further research

Future trials should assess a full selective decontamination regimen including systemic and non-absorbable antibiotics. The duration of the systemic component can probably be limited to the first four days, similar to the regimen used in the most recent trial and in trials in the intensive care unit.^{12,53,77} Limited perioperative prophylaxis targeting Gram positive bacteria can be considered. Optimal resuscitation protocols and local care should be provided uniformly to both arms to assess the added benefit of antibiotic prophylaxis to current best practice.¹⁴⁻¹⁸ Special attention should be drawn to infection control practices during the trial to avoid cross infection between the trial arms. Contemporary methods used in multicentre trials should ensure adequate sequence generation and allocation concealment. Although randomised controlled trials might not be the optimal platform to assess development of resistance (randomised patients are in the same unit and the timeframe is inadequate),⁷⁸ special attempts should be placed on documenting the effect of prophylaxis on colonisation (using surveillance cultures) and clinical infections caused by multidrug resistant bacteria. Other adverse effects including *C difficile* colitis and fungal infections should be addressed. Ultimately, however, a patient's survival incorporates both ill effects and the benefit of prophylaxis and is the goal of managing burns patients. The current analysis (26% mortality in the control arm and relative risk of 0.54) suggests that an individual multicentre trial can be powered to assess all cause mortality as the primary outcome (about 200 patients per arm for a power of 80%). In hospital mortality among burns patients is highly variable; a fixed point in time relevant to the assessment of benefit and harm should be used.

In summary, we have shown a discrepancy between current guidelines for management of burns patients recommending against antibiotic prophylaxis and the evidence showing a reduction of about 50% in all cause mortality with systemic antibiotic prophylaxis. Given the paucity and limitations of the available evidence, this should serve mainly as an urgent call for a large randomised controlled trial.

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