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Routine systemic antibiotic prophylaxis for burn injuries in developing countries: A best evidence topic (BET)

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Abstract

Background—Burns are common in low- and middle-income countries (LMICs) and complicated by unhygienic conditions, malnutrition, use of high-risk homemade dressings and delayed presentation. Resultantly, use of routine systemic antibiotic prophylaxis (SAP) to prevent

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wound infection is common practice despite this intervention being abandoned in high-income countries due to increased antimicrobial resistance and non-bacterial suprainfection,

Methods—A best evidence topic (BET) was constructed using a structured protocol. The question addressed was: In LMICs, does routine use of SAP reduce burn wound infection, morbidity or mortality?

Results—From 704 retrieved records, 48 reports met criteria to be examined. Of those, 3 studies represented the best available evidence. Together, two randomized clinical trials (RCTs) and a retrospective cohort study reported no difference in the proportion of wound infection, any infection or length of hospital stay between SAP groups and controls. One RCT described a greater proportion of wounds infected with *P. aeruginosa* among SAP arms compared to controls. The studies had few participants and significant methodological weaknesses.

Conclusion—On the basis of limited, currently available evidence, the use of SAP cannot be recommended for patients in LMICs that present soon after burn injury.

Keywords

burn; antibiotic prophylaxis; developing countries; global surgery

1. Introduction

Burns are a major public health problem globally, resulting in more than 265,000 deaths and incurring 19 million disability-adjusted life years annually.[1] This burden falls disproportionately on low- and middle-income countries (LMICs), which are least equipped to provide comprehensive burn care.[2] Among survivors of initial injury, 30 – 75% of subsequent morbidity and mortality is due to wound infections.[3-5]

To date, there is no high-level evidence regarding the need for or effectiveness of systemic antibiotic prophylaxis (SAP) for burn injury in LMICs. In order to improve evidence-based decision-making, a best evidence topic (BET) was constructed according to a structured protocol.[6]

2. Clinical scenario

You work at a referral hospital in a low-income country and have admitted several patients who have sustained burns. One patient has a 10% total body surface area (TBSA) wound from a tea scald an hour ago; another has a 25% TBSA flame burn that occurred two days ago; and the third has a 2% TBSA contact burn that has been treated with a local preparation of leaves, clay and honey for a week. Remarkably, neither the patients nor their wounds appear infected. You examine the literature to determine if SAP should be provided to prevent burn wound infection.

3. Three-part question

In [LMICs], does [routine use of SAP] [reduce burn wound infection, morbidity or mortality or increase antimicrobial resistance]?

4. Search strategy

Records were retrieved from PubMed, Embase, The Cochrane Library and the World Health Organization Global Health Library using database-specific language to maximize LMIC record inclusion: “Antibiotic Prophylaxis”[MESH] OR “Anti-bacterial Agents”[Mesh] AND “Burns”[Mesh] AND (LMIC filter, Supplementary Material); ‘antibiotic’/exp AND ‘prophylaxis’/exp AND ‘burn’/exp; ‘antibiotic’ AND ‘burn’; or, ‘burn’ AND ‘antibiotic’ AND ‘prophylaxis’, respectively. No date or language restriction was used. Reference lists of relevant reports were hand searched for pertinent records.

5. Search outcome

The search returned 704 records published between 1957 and 2014. Of these, 656 records were excluded by title and/or abstract examination: 137 were not studies on burns; 127 were reviews, comments, abstracts or opinions; 98 were evaluations of intestinal decontamination or topical or perioperative antibiotic prophylaxis; 73 were in-vitro or animal studies; 72 did not have a defined exposure or control group; 56 were bacteriological surveillance; 27 were from high-income countries; 24 were pharmacological studies; and 21 were duplicates.

The remaining 48 reports were examined in full for inclusion: 25 were without a control group; 9 reported changes in antibiotic resistance over time; 7 described intestinal decontamination or topical or peri-operative antibiotic prophylaxis; 3 were from high-income countries (HICs); and one was an animal study. Three reports comparing SAP to no SAP (NP) for burn injury from an LMIC represent the best evidence to answer the question.[7-9]

6. Results

The results of the three reports, two randomized clinical trials (RCTs) and one retrospective cohort study, are summarized in Table 1.

Chahed et al. performed a single-blind RCT in Monastir, Tunisia to assess whether SAP prevents any infection (e.g. wound, bacteremia, urinary tract) in children. They concluded that there was no benefit to the use of SAP compared to NP.[8] Eighty patients who presented within 48 hours of burn injury were randomized into three groups: i) 25 patients in SAP1, ampicilline-clavulanic acid; ii) 20 patients in SAP2, oxacilline; or iii) 35 patients in NP. There was no evidence for a reduction in any infection with SAP use (SAP1 20% with infection; SAP2 15%; NP 23%; p=0.70).

This study had methodological flaws. First, there was no mention of allocation concealment, randomization strategy, reason for the markedly different number of patients in each group, placebo-control, characteristics between the groups, intention to treat analysis, follow-up characteristics or adverse events related to antibiotic use. Second, biopsies were only done for clinical signs of infection (i.e. not on pre-selected intervals, leading to an unknown degree of measurement bias) and wound infection alone was not an outcome. Lastly, patients with long pre-hospital times were excluded; such exclusion prevents

generalizability to patients with longer pre-hospital times and greater risk of wound infection after admission.[10]

Ugburo et al. performed a RCT in Lagos, Nigeria. The authors concluded that there was no difference in time to wound infection with or without SAP; however, there was an increase in *P. aeruginosa* among infected wounds after SAP use.[7] Patients presenting within 24 hours of burn injury were randomized into three arms: i) SAP1 with ampicillin and cloxacillin (21 patients); ii) SAP2 with erythromycin and genticin (20 patients); and iii) no SAP (NP; 20 patients). Wounds that showed signs of infection were biopsied for histopathological assessment and culture. Time to wound infection and proportion of wounds infected with *P. aeruginosa* and other organisms were measured. There was no difference in time to wound infection between the three groups (5.7 ± 1.7, 5.8 ± 1.6 and 5.6 ± 1.9 days for SAP1, SAP2 and NP, respectively; $p>0.05$). However, there was evidence that treatment with erythromycin and genticin resulted in more wounds infected with *P. aeruginosa* compared to controls (53% in SAP1; 63% in SAP2; 43% in NP; $p<0.05$). Conversely, *S. aureus* was not isolated from SAP1 wounds, compared to 6 and 7% in SAP2 and NP wounds, respectively ($p<0.05$).

This trial also had methodological weaknesses that preclude assessment of its validity and generalizability. First, there was no mention of allocation concealment, blinding, or intention to treat analysis. Second, biopsies were not performed on pre-selected intervals. Next, the study did not report the number of infections in each group, follow-up characteristics or any adverse events related to antibiotic use. Finally, patients were excluded if they presented more than 24 hours after burn injury. Given these shortfalls, the results do not allow strong recommendations to be made regarding SAP for the management of burns in LMICs.

The third study, performed by Ergün et al., described a retrospective pediatric cohort from Izmir, Turkey.[9] This study concluded that there was no difference in wound infection between patients who did and did not receive SAP. All records of children treated for burn injury over two consecutive years were reviewed. Records were excluded if more than five days had elapsed since burn injury or wound infection was present on admission. Wound infection was defined as a positive wound culture with clinical signs of infection without another obvious source. Wound infections and length of hospital stay (LOS) were examined. Of the 47 patients that received SAP, 10 patients (21%) developed wound infections; 30 patients did not receive SAP and 5 of them developed wound infection (17%). There was no difference in wound infection between the two groups ($p>0.05$). Although LOS was significantly longer in the SAP group (21.7 ± 16.4 days vs 13.5 ± 10 days in the NP group; $p<0.05$), this was confounded by a significantly greater burn size (mean burn size in the SAP group was 18 vs 10% TBSA in the NP group; $p<0.05$).

In addition to the selection bias evidenced by the larger burn size in the SAP group, interpretation and generalization of the results is difficult due to several other reasons. The antibiotic regimens used in the SAP group were not standardized and only children were examined. Additionally, most children underwent early excision and grafting, an intervention that is rarely performed in resource-limited settings, which limits the generalizability of this study; instead, wounds are most often managed open and allowed to

heal secondarily, which have have significant negative impact on wound infection rates and survival.[2, 11-13]

7. Discussion

The best evidence available does not support use of SAP for burn patients in LMICs. However, each of these studies has significant methodological weaknesses that hamper the ability to answer the question dutifully, including: inadequate reporting of RCT methodology, small numbers of patients, exclusion of longer pre-hospital times, variation in antibiotic regimens and lack of a standardized wound infection definition.

In LMICs, burns are complicated by less hygienic conditions, malnutrition, frequent use of high-risk homemade dressings, long pre-hospital times related to significant barriers to burn or surgical care and open wound management.[14-18] Resultantly, burn wound infections are more common in LMICs than HICs and systemic antibiotic prophylaxis (SAP) remains a standard component of burn care in developing countries.[5, 7, 19-23]

However, a meta-analysis of studies from HICs reported that the risk of burn wound infection was no different in patients that received systemic antibiotic prophylaxis SAP and those that didn't.[24] Similarly, sepsis, bacteremia, LOS and mortality rates were similar regardless of SAP use.[24] In addition, HIC studies demonstrated that SAP increases the incidence of antibiotic resistance and non-bacterial suprainfections.[25] As a result, routine use of SAP in HIC burn centers is no longer recommended.[24, 26, 27]

8. Clinical bottom line

On the basis of currently available evidence, the use of SAP cannot be recommended for patients that present soon after burn injury in LMICs. Given the large and increasing burden of burn injury in LMICs, robust studies to generate evidence-based guidelines for essential burn care are urgently needed.[1]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Systemic antibiotic prophylaxis for burns is common practice in LMICs
- Evidence from HICs suggests that this practice is ineffective, and potentially harmful
- Limited evidence from LMICs does not support routine systemic antibiotic prophylaxis

Table 1

Best evidence studies for the routine use of systemic antibiotic prophylaxis for burns in low- and middle- income countries

Author, date; country	Patient group	Study type; level of evidence	Outcomes	Key results	Comments
Chahed et al. 2014; Tunisia	80 pts aged 3 months to 15 years, presenting **within 48 hours** of injury (mean TBSA 26%); **SAP1** (ampicilline - clavulanic acid) = 25; **SAP2** (oxacilline) = 20; **NP** = 35	Single-blind, prospective, randomized clinical trial; Level II	Any infection (SAP1 vs SAP2 vs NP)	Any infection: SAP1 5 pts (20%); SAP2 3 pts (15%); and NP 8 pts (23%) **(*p*=0.70)**	This single-blind RCT showed no evidence for a reduction in any infection with the use of SAP. There was no mention of allocation concealment or intention to treat analysis. Clinicians were not blinded to SAP use. Biopsies were only done for clinical signs of infection (i.e. not on pre-selected intervals) and wound infection was not examined as a specific outcome. The study did not report patient characteristics to evaluate adequacy of randomization, the reason for markedly different numbers of patients in each group or follow-up characteristics. Patients with long pre-hospital times were excluded.
Ugburo et al. 2004; Nigeria	61 pts with burn presenting **within 24 hours** and without inhalation injury (mean TBSA 44%); **SAP1** (ampicillin & cloxacillin) = 21; **SAP2** (erythromycin and genticin) = 20; **NP** = 20	Prospective, randomized clinical trial; Level II	Time to wound infection (SAP1 vs SAP2 vs NP); Proportion of infected wounds with *P. aeruginosa* or other organisms isolated	Days to wound infection: SAP1 5.70 ±70, SAP2 5.75 ± 1.62 and IO 5.6 ± 1.90 **(*p*>0.05);** *P. aeruginosa* isolated: SAP1 = 53% **(*p*>0.14)**, SAP2 69% **(*p*<0.001)** and NP 43%.	This RCT showed no evidence for a reduction in wound infection with use of prophylactic antibiotics. However, there was an association between SAP2 use and more frequent infection with *P. aeruginosa*. All groups were treated similarly and robust methods for wound infection diagnosis were used. There was no mention of allocation concealment, blinding, or intention to treat analysis. Biopsies were only done for clinical signs of infection, not on preselected intervals. The study did not report number of infections in each group or follow-up characteristics. Patients with long pre-hospital times were excluded.
Ergün et al. 2004; Turkey	77 pts under age 9 years, presenting **within 5 days** of injury (mean TBSA 14.9); **SAP** (mixed agents) = 47; **NP** = 30	Retrospective cohort study; Level IV	Wound infection (SAP vs NP); LOS (SAP vs NP)	Wound infection: SAP 10 pts (21%) vs 5 pts (17%) **(*p*>0.05), t**here was no correlation with infection and day of admission **(*p*>0.05)**; LOS: SAP 21.7 ± 16.4 days and NP 13.5 ± 10 days (*p<0.05;* see comment).	This retrospective cohort study showed no evidence for a reduction in wound infection with use of SAP. The results are confounded by: a larger TBSA in the SAP group (mean 17.8 vs 10.4 in the NP group; p<0.01), which confounds LOS; antibiotic agent(s) used was not standardized; and, the definition of infection was a positive wound swab culture and foul smelling fluid or discoloration and clinical signs of infection. Patients were excluded

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