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Antibiotic Prophylaxis in Burn Patients: A Review of Current Trends and Recommendations for Treatment

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Abstract

As nosocomial infections in burn patients are prevalent and dangerous, systemic antibiotic prophylaxis has been considered, beside other interventions. However, this kind of therapy has been questioned due to controversy related to its effectiveness and complications, such as drug toxicity and development of multidrug-resistance. This review includes evidence reported during the period 1966-2016. The quality of evidence and strength of recommendation of these guidelines are based on the GRADE system. Early post-burn prophylaxis showed no effectiveness for toxic shock syndrome or burn wound infection prevention (Grade 1C) in non-severe burn patients but it could be useful for those who had severe burns and require mechanical ventilation (Grade 2B). Perioperative prophylaxis would neither have indications for wound cleaning nor for devitalized tissue debridement of most burn patients (Grade 2B), but there is not enough evidence to make a strong recommendation to those who have extensive burns. Finally, prophylaxis could be used to prevent skin graft infections in selected procedures (Grade 2B).

Introduction

Nosocomial infections are prevalent in burn patients and reach rates of 10 to 20 per 1000 patient days in Burn Intensive Care Units[1].

Healthcare-associated Infections remain a major cause of potentially serious complications, and recurrent sepsis predisposes to multiple organ failure, lengthens hospital stays, and increases costs[2]. Therefore, improvements on infection prevention and treatment are increasingly important.

Burn patients are susceptible to infections due to epithelial barrier loss, hypermetabolic/ hypercatabolic states and immunosuppression[3]. Moreover, vital organ support requires the use of invasive procedures that undermine the body´s defense even more. As a consequence, nosocomial infection rates, including intravascular catheter-related infections and ventilator-associated pneumonia, are reflected in the literature to be higher in Burn Units than other Medical or Surgical Units[4].

As nosocomial infections in burn patients have been shown to be prevalent and life threatening, systemic antibiotic prophylaxis has been considered, beside other interventions[5, 6]. However, doubts about effectiveness and risk of complications, such as drug toxicity and development of multidrug-resistance, have made its recommendation controversial[7-9].

In order to analyze this issue, the quality of evidence and strength

of recommendation of these guidelines are based on the GRADE system and interventions are stratified according to the following subgroups: period of prophylaxis, burn severity, age and type of procedures[10].

Early Post Burn Prophylaxis

Non-severe burn patients

Toxic shock syndrome (TSS) is a rare, but life-threatening complication of early bacterial infection that could be developed following any burn size. It is mediated by exotoxin released mainly by *Staphylococcus aureus* or *Streptococcus pyogenes*. Although it can occur at any age, it is more common in children because of their immune immaturity[11]. In 2001, a single antibiotic dose protocol (Flucloxacillin) was introduced for burned children at referral emergency department with the aim of preventing TSS[12]. As not many patients presented or developed TSS during the protocol phase, therefore this study was not conclusive in showing effectiveness. Recently, Mulgrew *et al.* did not find morbidity differences in children using other prophylaxis protocols (Flucloxacillin or Erythromycin for 5 days post burn) comparing intervention cohorts from different period of time[13].

Burn wound infection predisposes the delay of epidermal maturation and the development of pathologic scars. It also leads to microorganism's invasion into the tissue layers conditioning bacteremia, sepsis, and multiple-organ dysfunction[2]. As preventing wound burn infection is essential, systemic antibiotic prophylaxis has been proposed, together with appropriate local management[5, 6]. Antibiotic prophylactic administration was widely used, particularly in children, who have high rates of beta-hemolytic streptococci carriage, until many trials highlighted its lack of effectiveness[7]. Sheridan *et al.* published in 2001 a large study in pediatrics mild burned patients, with no wound infection differences being described using either Penicillin or Erythromycin versus no antibiotics in sequential intervention periods[14]. Previously, two trials -Timmons *et al.* in children, and Durtschi *et al.* in adults- had already reported low efficacy in wound infection prophylaxis using the same antibiotics[15, 16]. Recently, Chahed *et al.* using Amoxicillin-Clavulanic or Oxacillin as prophylaxis vs no prophylaxis have also shown no wound infection shrinkage in pediatric burn patients at a prospective randomized single center trial[17].

As severe infections are uncommon in mild to moderate burn patients and systemic antibiotic prophylaxis did not seem to affect the outcome, there is no current evidence to support its indication. Although most of the reported trials have low quality score, the lack of prophylaxis effectiveness was consistent across them. Consequently, not using prophylactic antibiotics in this group should be considered as a strong recommendation (Grade 1C).

Severe burn patients

Multiple infectious sources can be identified in patients with major thermal injury and include central venous and arterial catheters, urinary catheters, ventilator support, as well as the burn wound itself.

Burn wound infections are closely related to morbidity and mortality in severe burn patients. Thus preventing or delaying them is a desirable goal. Ugburo *et al.* conducted a prospective randomized trial in adult patients, where 3 groups were assigned; one without antibiotics, another with ampicillin/cloxacillin within the first 6 hours and a third one with erythromycin/gentamycin after the 3rd day and for 2 weeks. It was reported a great incidence of heavy colonization after the third day post burn. Systemic antibiotics neither prevented burn wound infection nor delayed colonization or infection occurrence. Otherwise, this study showed that the use of systemic antibiotics could be dangerous because it might favor the growth of microorganisms of difficult eradication, such as *P. aeruginosa*[18].

In severe burn patients, endotoxemia has been documented since early stages of burn originating in the burn wound or the intestinal tract. Subtherapeutic doses of Polymyxin B have been reported to bind endotoxin. Two studies assessed Polymyxin B as systemic intravenous prophylaxis during early post burn period. One of them assessed the effect of immunological support, with Immunoglobulin G (IVIG), plus endotoxin binding, with Polymyxin B, in severe burn at two pediatric burn centers during a period of five years[19]. Patients from Hospital A were treated with IVIG and low-dose Polymyxin B, whereas patients from Hospital B were not. Outcome analysis had several limitations because of intercohort basal differences among hospitals. In spite of this, they described differences in sepsis episodes per patient (1.2 vs 1.9, p= 0.01) and hospital stays (77.1 vs 103.8 days, p= 0.04), but they did not find differences in mortality.

The other study compared only systemic Polymyxin B versus placebo in a prospective randomized trial at adult population[20]. Although it showed a reduction on endotoxin levels either in perioperative or post burn injury, the data was not strong enough to assess important clinical impact.

Another potential source of infection in severe burn patients is gastrointestinal tract. Translocation of bowel microorganisms due to increased intestinal permeability has been associated to burn wound colonization and infection[21]. In 1990 Deutsch *et al.* used erythromycin plus non absorbable gastrointestinal antibiotics -Neomycin and Nystatin- in order to decontaminate the digestive tract and prevent wound infections. They showed not only lack of effectiveness, but risk due to an earlier *P. aeruginosa* wound colonization[22]. Furthermore, intolerance was

reported, being diarrhea the most common complication that forced treatment suspension. In 2005, another article with selective digestive decontamination (SDD) in burn patients was published[23]. In this study, de la Cal *et al.* combined non-absorbable antibiotics to decolonize the mouth and the gastrointestinal tract, with intravenous third generation cephalosporin in Intensive Care Burn Unit. Strikingly, a reduction mostly at primary endogenous infections (caused by microorganisms that were carried in throat and/or gut upon admission), was shown. In this trial, treatment with SDD was associated with a significant reduction of early pneumonia and mortality. Pneumonia has been described as one of the most common causes of nosocomial infection in severely burned patients, and with an attributable mortality rate of between 20% and 50%[24].

As many centers in Japan had high incidence of methicillin-resistant *Staphylococcus aureus* ventilator-associated pneumonia, systemic prophylaxis (Trimethoprim – Sulfamethoxazole) was used at Burn Center. In this trial, Kimura *et al.* reported early pneumonia decrease and trend towards reducing mortality[25]. Recently, Tagami *et al.*, analyzing a Japanese database, described beneficial effects of antibiotics prophylaxis in a subgroup of severe burn patients who required early mechanical ventilation (28-day in-hospital mortality)[26].

At this point we can conclude that systemic antibiotics in patients with severe burns and high risk of pneumonia may be indicated. However, trials neither showed an agreed antibiotic scheme nor evaluated consistently antimicrobial related risks, thus making a strong recommendation not possible (Grade 2B).

Perioperative Prophylaxis

Perioperative prophylaxis is also a controversial issue, particularly in severe burn patients who require multiple surgical procedures over several weeks in order to remove devitalized tissue, to prepare the wound bed and to perform the split-thickness skin graft to heal the burn wound.

Wound cleaning or debridement

Even though bacteremia could be released by any wound intervention, those most prone to suffer it are: extensive burn, late post burn procedure, heavy colonized or infected wound and aggressive surgical procedure[27].

In order to restrain prophylaxis recommendations, Mozingo *et al.* described a group with low risk of perioperative bacteremia which included patients with burns involving less than 40% of total burn surface area and procedure done during the first 10 post burn days[28]. This criteria could exclude to great number of burn patients from prophylaxis, but this trial was not designed to evaluate prophylaxis efficacy in those with higher risk. In 1985, Piel *et al.* showed that bacteremia incidence lessened using cephalosporins, only in extensive burns[29]. Later, Rodgers *et al.* also described that cephalosporins were not useful during procedures with non-extensive burns[30]. Steer *et al.* also published a significant reduction in perioperative bacteremia rates using Teicoplanin as prophylaxis in 1997, although no differences in clinical post-operative complications (fever with rigors, hypotension or severe sepsis) were observed. Most of them were non-severe burn patients[31].

Therefore, available evidence does not allow recommending the use of prophylaxis for wound burn cleaning or debridement. Nevertheless, there is not enough support to make any recommendations in severe burn patients who require aggressive procedures (Grade 2B).

Skin grafting

Skin grafting represents the most rapid and effective method for closure of excised full-thickness burns. This procedure may be unsuccessful because of numerous reasons, especially those that prevent temporary anchors to the wound bed, like hematoma, seroma, graft displacement or poor recipient site (poor vasculature or bacterial infection)[32].

In 1990, Livingston *et al.* showed the efficacy of local antimicrobial agents to improve graft takes in early tangential excision followed by skin grafting. Neomycin plus Bacitracin was as effective as silver nitrate and more effective than Ringer Lactate for non-extensive burns, but the antibiotics were associated with rapid emergence of drug-resistant organisms whereas silver nitrate was not[33].

Systemic prophylaxis to prevent skin grafted infections was reported in many trials. In 1982, Alexander *et al.* addressed the efficacy of cephalothin for prophylaxis of skin grafting procedures in reconstructive surgery. In this trial, antibiotic prophylaxis was effective in reducing infections, graft loss and hospital stays[34]. However, skin graft was placed over surgical wound instead of burn wound, with a considerable lower density of wound bacterial colonization.

Few trials have evaluated the efficacy of systemic antibiotic prophylaxis for skin grafting surgeries in acute wound burns. Alexander et al, in 1984, showed no differences in graft takes with or without antibiotics[35]. A few years later, Griswold *et al.* reported less donor site infection and a tendency to reduce skin graft infection in those who received antibiotics, in a retrospective study[36]. Another study described a non-significant skin graft infections reduction associated to Teicoplanin use, but few procedures were included[31]. Ramos *et al.* described a significant skin graft loss shrinkage when prophylaxis was used. In this study, half of the burn wounds were colonized before grafting[37]. No other clinical outcome was assessed.

We conclude that while prophylaxis might be effective in preventing graft loss due to infection, its clinical relevance in acute burns is not clearly demonstrated. Hence, systemic antimicrobial prophylaxis for perioperative skin grafting should be considered as a weak recommendation. (Grade 2B)

Conclusion

Systemic antibiotic prophylaxis during early post-burn period would not have indication in most burn patients but it could be useful in patients with severe burns and requirement of mechanical ventilation. Perioperative prophylaxis during resection of devitalized tissue would not have indications in most burn patients. However, there is not enough evidence to make a recommendation on extensive burns. Finally, prophylaxis could be useful for the prevention of split-thickness skin graft infection in selected procedures.

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