PERINEAL DIAGNOSTIC MICROBIAL SWABS AS A PREDICTIVE PARAMETER IN PEDIATRIC BURN INJURY

INTÉRÊT DE L'ÉVALUATION DU MICROBIOTE PÉRINÉAL CHEZ LES ENFANTS BRÛLÉS

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SUMMARY. The aim is to evaluate the predictive usefulness of perineal diagnostic microbial swabs (PDMS) which will identify an enteric reservoir as possible source of concomitant wound infection following scald burn injury in infants. Perineal swabs were taken on admission of infants presenting with scald burn injury along with a standardized protocol of initial sterile surgical field cleansing and dressing. Complicated (CC) and uncomplicated (UC) clinical cases were discriminated based on parameters of significant microbial burn wound colonization, such as onset of fever, white blood cell count (WCC), C-reactive protein (CRP) and a concomitant need for surgical wound revision with/without guided antibiotic therapy. Relative risks (RR) / odds ratios (OR) based on microbial swab results were calculated related to anticipated wound infection. We found PDMS to be an independent predictive parameter for clinically relevant microbial wound colonization in pediatric patients (n=274; age 2.81±2.69). Most importantly, we show that in patients with initial total burn surface area (TBSA) >5%, clinically relevant burn wound infection requiring intervention can be predicted from initial perineal swab results with ORs ~10fold. Infants presenting with scald burn injury are exposed to a relevant risk of wound infection emanating from a unique microbial enteric reservoir, even with initial surgical decontamination and sterile dressing protocols, warranting further hospitalization. Based on our findings we suggest PDMS as a useful additional predictive parameter to (i) characterize the relevant enteric microbial reservoir and (ii) direct further therapeutic measures with the aim of preventing complicated wound infections, including preemptive aseptic wound dressings, guided antibiotic therapy and surgical wound revision.

Keywords: pediatric scald burn injury, Suprathel® wound dressing, enteric microbial reservoir/microbiome, wound infection

RÉSUMÉ. *Cette étude a pour but d'évaluer l'intérêt de la surveillance par écouvillonnage du microbiote périnéal comme reflet du microbiote digestif, susceptible de contaminer les brûlures par ébouillantement chez l'enfant. Le prélèvement était réalisé à l'entrée des enfants par ailleurs bénéficiant d'un traitement standard de pansements stériles. Les brûlures étaient considérées comme compliquées devant un syndrome septique (fièvre, hyperleucocytose, augmentation de la CRP) d'origine locale (nécessité de pansement chirurgical) et l'antibiothérapie pouvait être guidée par le prélèvement initial. Nous avons calculé risque relatif et Odds Ratio d'infection de brûlure selon le résultat de l'écouvillonnage, qui s'est avéré, quand il est positif, multiplier par 10 le risque d'infection locale. Les enfants ébouillantés ont un risque d'infection par bactéries d'origine digestive clairement augmenté en cas de colonisation périnéale, même avec des pansements réalisés en conditions stériles. Nous suggérons donc la réalisation d'une cartographie bactérienne périnéale initiale chez ces patients afin d'évaluer le risque d'infection locale et de guider le traitement (type de pansement, antibiothérapie, pansement chirurgical).*

Mots-clés: *enfant, brûlure, ébouillantement, pansement, Suprathel®, microbiote digestif, infection*

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Introduction

Scald burn injury unintentionally acquired in a domestic setting is common among preschool infants, and although reliable epidemical data is limited,[1-4] pediatric scald burns usually constitute a substantial burden to burn centres.[5,6] Moreover, it appears that in the majority of cases, the extent of burn injury does not necessarily trigger referral to specialized burn centres according to respective national guidelines and aspects of health care infrastructure.[7-11] On the other hand, criteria related to the severity of burn injury which would warrant specialized care, such as burn surface area (BSA), burn depth or anatomical location are usually based on existing classification systems in adult burns. Here, standardized care should include concepts of adequate pain management, volume resuscitation and surgical wound treatment.[12]

Overall, treatment regimens related to pediatric scald burns appear to differ significantly between burn centres but share a common feature of (i) microbial decontamination initially and (ii) prevention of clinically relevant wound colonization during wound healing.[3,13] In our burn centre, we commonly opt for an initial superficial surgical cleansing of partial thickness burn wounds in combination with a sterile wound dressing technique for scald burns of >5% BSA and/or affected face, hands, feet or joints. We use Suprathel®[14] synthetic biodegradable sheet for initial wound onlay based on a well published rationale[15,16] opposed to well accepted alternatives such as Biobrane®,[17] MepilexAg®[18] or silver sulfadiazine-based ointments.[19,20] Also, we avoid performing autologous split thickness skin graft (STSG) as primary intent with scald burns.

Scald burn injury will typically result in superficial partial thickness burn injury that in the majority of uncomplicated cases (UCs) does not require skin grafting. Here, proper wound care will typically result in uneventful healing within 10 to 14 days without significant complications, such as clinically relevant microbial infection or scar formation requiring surgery.[21] Conversely, misjudgment of depth and complications such as serious bacterial infections in unison with local deterioration of burn wounds requiring secondary surgical intervention such as tangential excision techniques followed by skin grafting will occur in a minority of complicated cases (CCs). Said complications can be hard to predict only based on the initial presentation of burn wound patterns, but both BSA and deferred bacterial wound colonization as a precondition of outright infection appear to be the most relevant contributing factors in these cases.[22] However, both the necessity and efficacy of prophylactic antibiotic treatment of pediatric patients with relevant BSA burn injury has been under debate due to a lack of conclusive evidence,[22-28] with most studies concluding that only confirmed infections, not mere microbial colonization of wounds, should be treated with antibiotics.[24,29] This restrictive concept of a prophylactic use of antibiotics in pediatric burn patients is well linked to the observation that a rather broad spectrum of bacteria is capable of effective wound colonization, potentially but not necessarily followed by subsequent wound infection. However, bacterial species most commonly encountered in pediatric burns include Staphylococcus, Enterobacter, Pseudomonas, Escherichia coli and Klebsiella spp.,[24,25,30] but these are far from exclusive.

In order to improve the management of anticipated complicated clinical cases of burn injury in infants related to wound infections, which are difficult to predict for said reasons, we hypothesized that an enteric reservoir was most relevant for subsequent wound colonization in the context of a standardized initial surgical cleansing and a 'sterile field' wound dressing.

The main purpose of the presented work was to correlate initial microbial swab results of the perineal region, thus identifying the specific enteric reservoir, along with other parameters of scald burn injury in infants in order to identify predictors of relevant clinical complications related to microbial colonization of burn wounds.

Materials and methods

Data acquisition

Prospective data acquisition was performed for children (2.95 age ± 2.96 SD, median = 2 years; n = 284) hospitalized within 24h following scald (hot water, tea, coffee) burn injury that was considered

partial thickness during initial surgical wound surface cleansing under general anesthesia. Non-scald burns and burns with any indication of even a partial area full thickness/third degree initial burn, as well as children with pre-/coexisting medical conditions related to infectious disease such as upper airway infection, enteritis, otitis or pre-existing fever, were excluded from the study. With these exclusion criteria, children per se did not require prolonged mechanical ventilation or ICU care intervals and thus sex, overall TBSA or initial resuscitation volumes were not considered to be relevant confounders opposed to what would be expected in patients with severe burn injury as defined by e.g. the ABSI or PRISM scoring systems.[31]

Definitions of burn degree

Most relevant for the purpose of this study was an accurate clinical evaluation of partial thickness/second degree/II° burn injury. Based on current concepts of both research[32] and clinical guidelines[33-36] of e.g. the American Burn Association (ABA), the European Burns Association (EBA) or the German Society for Burn Treatment (DGV) a further distinction of the term *partial thickness* is advocated. Here, a partial thickness burn which extends through the epidermis and into the upper dermis, also referred to as papillary region, is considered superficial or IIa°, clinically apparent as blister formation with a hyperemic wound bed and intact pain sensation. Conversely, a hypoemic wound bed with reduced pain sensation is an indicator of a deep or IIb° partial thickness burn injury. Although an accurate distinction between IIa°/superficial second degree vs. IIb°/deep second degree is debatable, most burn surgeons consider it useful in order to predict aspects of spontaneous healing intervals or a likelihood for a need of secondary skin grafting or scar formation. Since a prolonged interval of spontaneous wound reepithelialization is likely to increase the risk of complications related to microbial wound colonization, we included IIa° vs. IIb° burns as parameters of this study.

Surgical standard care

A combined superficial debridement/scrubbing of skin, e.g. with removal of blisters as well as an antiseptic treatment of surgical fields was performed using sterile gauze compresses soaked with octenisept® [Schuelke & Mayr GmbH, Germany] (per 100g solution: octenidine dihydrochloride 0.1g, 2-Phenoxyethanol 2.0g) according to manufacturer instructions and scientific evidence related to the treatment of burn wounds.[37] This was followed by a rinsing step with sterile saline (0.9%) solution before the application of Suprathel® [PMI - PolyMedics Innovations, Germany],[14,15] a biodegradable synthetic copolymer foil. Finally, a protective dressing was applied consisting of an overlay with Jelonet® [Smith & Nephew plc, UK] sterile paraffin tulle gauze dressing, followed by a layer of sterile gauze compresses.

Post-surgical standard care

Along with the initial surgical procedure, wound and non-invasive perineal diagnostic microbial swabs (PDMS) were taken with approval of the competent institutional ethical commission upon admission and consistently on day 2-5 following hospitalization if microbial wound colonization was suspected upon dressing check-ups. Additional wound swabs were taken whenever outright wound infection was clinically apparent. The latter mandated, among other things, a timely complete removal of the Suprathel®. With no sign of complications, patients were discharged within 2.79 days ± 1.13 SD. During hospitalization, patients were evaluated daily for signs of relevant microbial wound colonization based on the following parameters: (i) gross clinical wound aspect e.g. smell, color of secretions, (ii) microbial wound follow-up swabs, (iii) fever, (iv) white cell blood count (WCC), (v) c-reactive protein (CRP). Here, a diagnosis of wound infection, opposed to colonization, warranted a pathological aspect of all listed parameters. Opposed to uncomplicated cases (UCs), complicated cases (CCs) warranted repeated aseptic wound decontamination under anesthesia with/without the need for additional antibiotic treatment. Conversely, UCs did not require further specific treatment other than superficial dressing changes performed with sterile gauze compresses. Standard nursing care of infants included cleansing of the perineal area with a soapy solution following bowel actions and removal/renewal of stool contaminated gauze material if necessary.

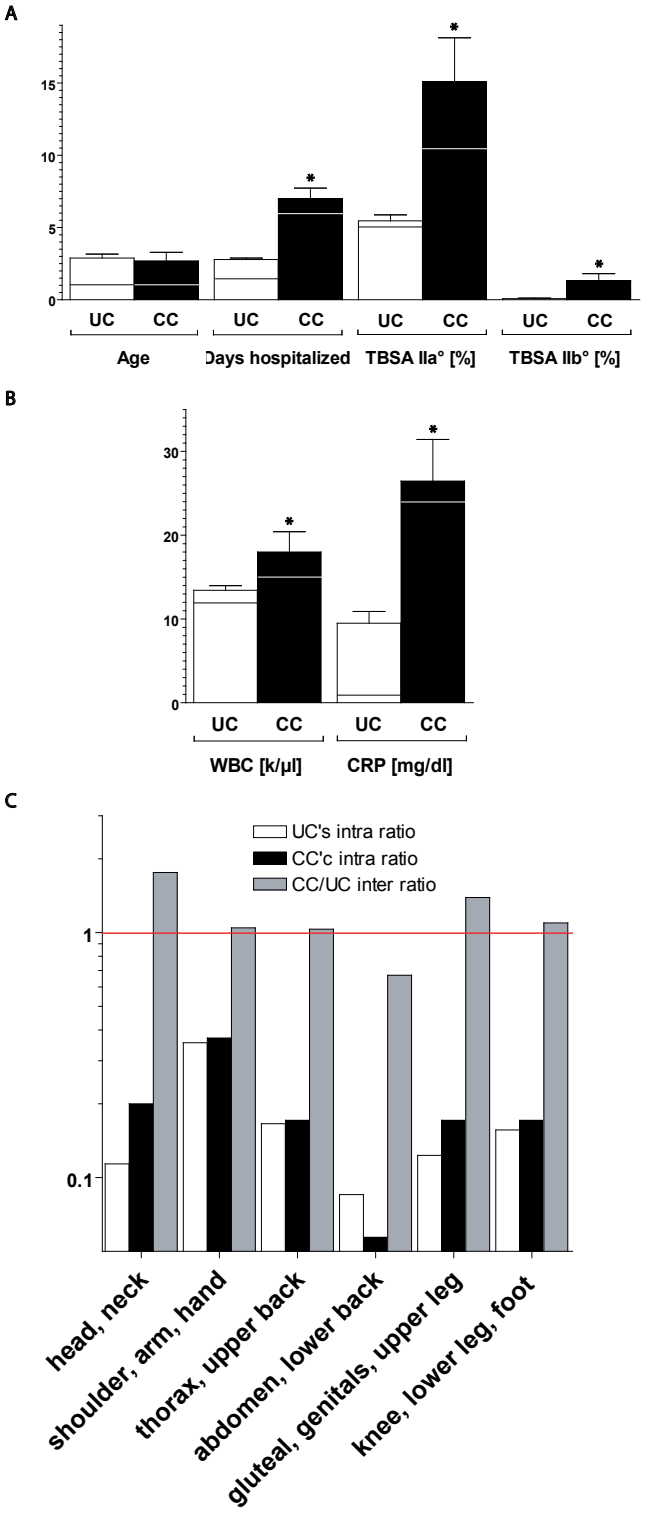
Statistical analysis

Results are presented as mean ± SD. Data analysis was performed using Prism®4.0 (//www.graphpad.com/) and Excel - Microsoft® software. Predictive measures related to diagnostic microbial perineal swabs were described as odds ratios (OR) or relative risk (RR) based on feasibility. We assumed statistical significance for a probability value $p \leq 0.05$ with a 95% (1,96 coefficient) confidence interval (CI) calculation. In addition, pair wise comparisons of nominal variables were performed using chi-squared (χ^2) McNemar-test for independence applied with an error $\alpha_{0,05}$ ($\chi^2=3.84$).

Results

Hospitalized cases of scald burn injury which mandated repeated surgical intervention due to signs of clinically manifest wound infection required on average a >2-fold hospitalization time (7.17 days ± 3.13 SD; 2.69 age ± 2.44 SD, median = 2 years for complicated cases) not related to age differences, compared to uneventful cases (UCs). However, with complicated cases (CCs) showing a ~ 3-fold BSA affected with IIa° scald burn compared to UCs, BSA was clearly a predictive factor for anticipated relevant wound colonization leading to infection. CCs also clearly evidenced a IIb° component of burn injury compared to UCs (*Fig. 1A*). Regarding standard laboratory testing, CCs on average demonstrated significantly higher levels of white blood cell counts along with C-reactive protein (CRP) as to be expected by definition (*Fig. 1B*). However, based on laboratory testing alone, we saw a significant bias with clinical decision-making in various cases where a transient leucocytosis with or without fever or an isolated rise in CRP levels did not match clinical wound aspects or sterile wound swab results. In these cases no other obvious clinical focus of infection was evident, e.g. otitis, laryngitis, epiglottitis, enteritis.

In order to discern a possible impact of burn affected anatomical sites on the risk of early onset wound infection, we also looked at the relative anatomical site-of-burn distribution both in the UC and CC group as well as CC/UC but did not find evidence of a significant predictive value (*Fig. 1C*).



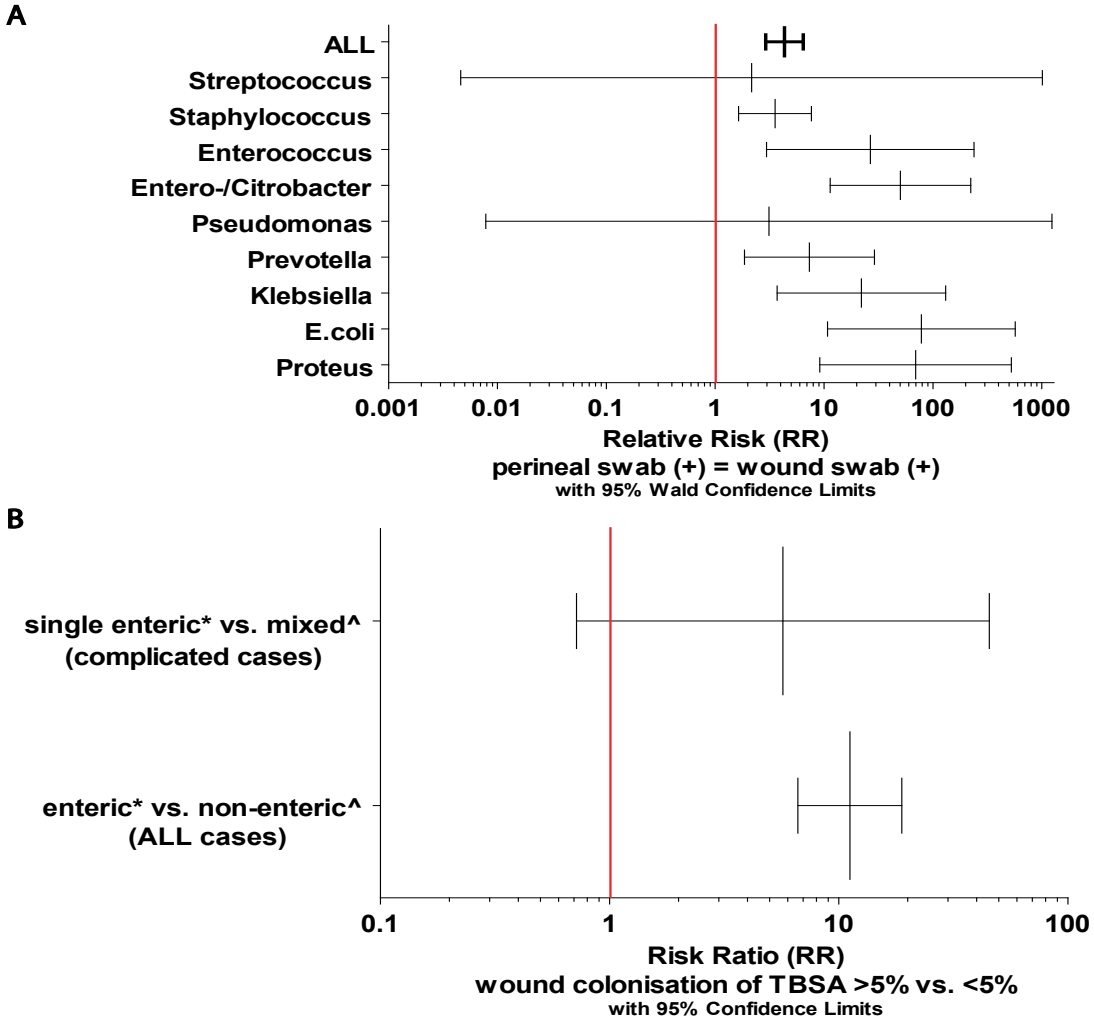
As a consequence of relevant bacterial colonization with symptoms of wound infection, complicated cases (CCs) varied significantly opposed to uncomplicated cases (UCs) in various clinical parameters, including (A) total body surface area (TBSA) of both IIa° and IIb° scald burn injury or (B) white blood cell count (WBC) and C-reactive protein (CRP). However, age as well as (C) the anatomical distribution pattern of burns were not a distinguishing hallmark of CCs vs. UCs. (shown: mean/median ±SD; * $p \leq 0.05$; odds ratio=OR significant with confidence interval ≠ 1)

Fig. 1 - Characterization of uncomplicated vs. complicated cases related to scald burn injury in infants

Another major incentive to perform this study was to discern a reliable correlation of initial perineal diagnostic microbial swab (PDMS) results following pediatric scald burn injury with wound swabs later on.

Here we saw significant, group independent relative risks (RR) for initial PDMSs to match wound swabs of typical enteric origin ranging from ~ 8-fold for Prevotella spp. to ~ 800-fold for E. coli and Proteus spp.. In contrast, bacteria not commonly associated with the enteric microbiome such as Streptococcus spp. or debatable Pseudomonas spp. showed no significant correlation (*Fig. 2A*). We concluded that bacteria of typical enteric origin are most relevant for secondary wound colonization in a clinical setting characterized by an initial sterile surgical surface-debridement and sterile dressing of scald burns in pediatric patients.

We also aimed to clarify whether the initially estimated affected BSA is also a critical contributing factor related to secondary wound colonization from an enteric reservoir. Here we saw a RR for the enteric microbiome ~ 10-fold increased opposed to non-enteric bacteria with a TBSA >5% (*Fig. 2B*). For complicated clinical cases (CCs) this appeared also to be the case if a mixed wound colonization with both bacteria of

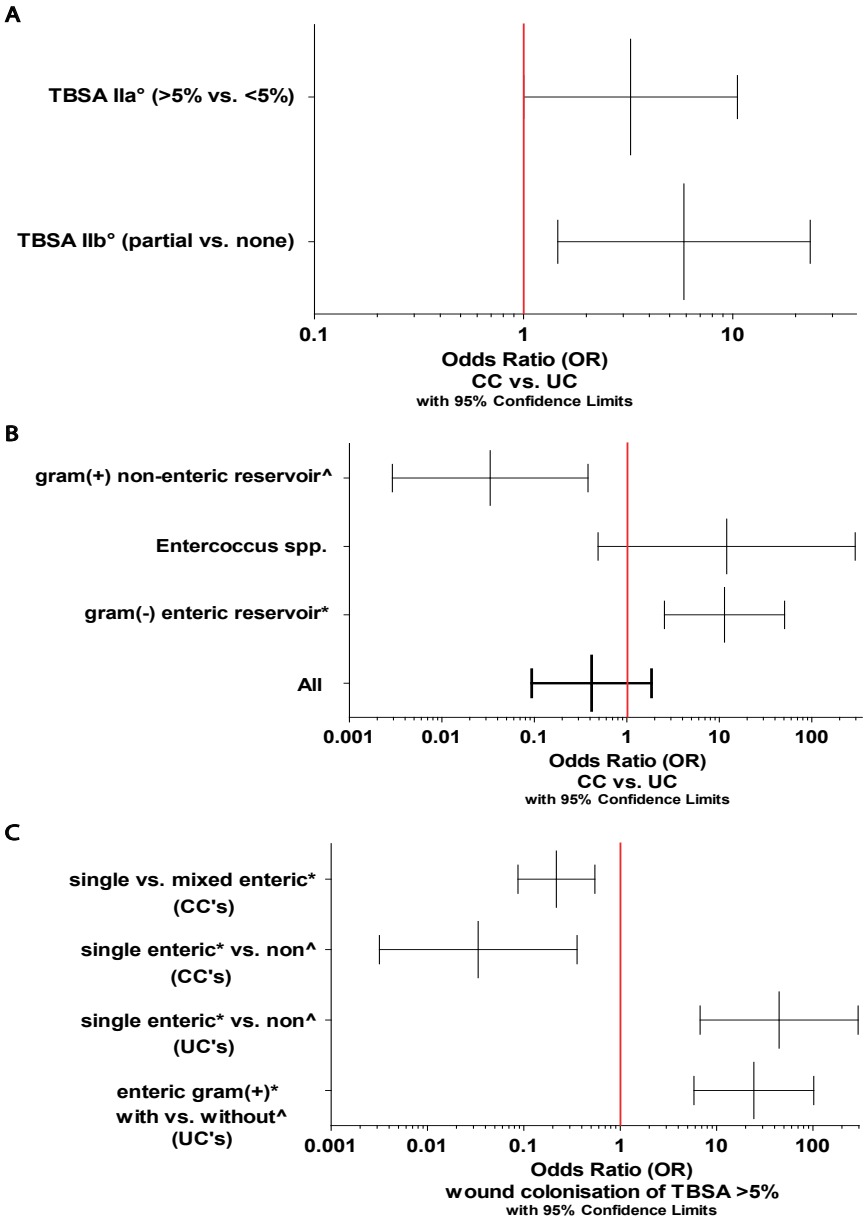


(A) Relative risk (RR) of matching perineal and burn wound microbial swabs. (B) With a TBSA >5%, infants showed an increased RR for wound colonization from an enteric reservoir. For complicated cases, wound infection with additional non-enteric bacterial strains (mixed) did not appear to add significantly to the overall RR. Thus, a comparison between initial perineal diagnostic microbial swabs (PDMS) and the colonization of burns over the course of hospitalization with various bacterial strains suggests PDMSs as a useful predictive parameter for complicated wound colonization during the initial hospitalization interval of infants following scald burn injury >5% TBSA (RR significant with confidence interval ≠ 1)

Fig. 2 - Relative risk-related diagnostic microbial swabs and an anticipated colonization of burn wounds from an enteric reservoir

alleged enteric and non-enteric origin occurred.

With the eminent role of the identified enteric reservoir for subsequent wound colonization we finally evaluated whether knowledge of the enteric reservoir would be helpful in predicting relevant burn wound colonization leading to clinically relevant infection. We confirmed that both an affected TBSA >5% as well as a IIb° burn component are indeed correlated with a ~ 2- and ~ 5-fold respectively increase of wound infection (*Fig. 3A*). Most importantly, we saw that among CCs, gram negative (-) enteric bacteria such as Proteus or E. coli spp. were ~ 10-fold more likely to be present on burn wounds opposed to UCs, whereas Enteroccous spp. appeared to be 'less-pathologic' in terms of causing clinically relevant infection. Our finding of a negative correlation in CCs for bacterial colonization not commonly associated with an enteric reservoir clearly demonstrated that an initial sterile surgical decontamination of burn wounds was indeed effective (*Fig. 3B*).



(A) Odds ratios (ORs) in a CC vs. UC group for a clinically relevant wound colonization entailing from an assumed enteric or non-enteric microbial reservoir. (B) ORs related to wound infections in CCs caused by bacteria of enteric and non-enteric origin or a combination of the two differ significantly from ORs related to mere wound colonization in UCs with >5% TBSA. (OR significant with confidence interval ≠ 1; enteric reservoir* = Proteus spp., E. coli spp., Klebsiella spp., Entero-/Citrobacter spp., Enterococcus spp.; non-enteric reservoir^: Staphyloccus spp., Streptococcus spp., Pseudomonas spp.)

Fig. 3 - Odds ratio related to an enteric microbial reservoir entailing burn wound infections

Thus, 'knowing the unique individual enteric reservoir' by means of a PDMS early on along with affected TBSA appears to be a powerful predictive indicator for anticipated wound infection in pediatric scald burns.

Discussion

Scald burn in preschool children is a common occurrence in emergency departments both in developed and under-developed countries, warranting specialized surgical and pediatric treatment. Major concerns of treatment relate to highly dynamic pathophysiological aspects of burn injury ranging from adequate fluid resuscitation, pain management, prevention of hyperthermia and the evaluation of tissue swelling and ischemia in an acute phase. Secondary complications related to the ischemic and dysfunctional 'zone of stasis' within heat-injured but viable tissues as well as opportunistic microbial wound colonization are paramount aspects of a subacute phase in burn injury, dictating a further need for surgical intervention such as repeated cleansing, a debridement of deeper skin and subcutaneous layers, followed by skin grafting and ultimately any long-term sequelae to scarring.

In our study we aimed to clarify a possible benefit in identifying early on a highly variable enteric reservoir in pre-school patients presenting with scald burn injury. Based on the observation that despite a thorough initial sterile surgical surface debridement of scald burn wounds followed by a standardized dressing regime using Suprathel® foil, clinically relevant wound infection still occurred in a pediatric subpopulation with a higher percentage of affected BSA. Here, wound infection appeared to be mostly associated with bacterial isolates of typical enteric origin. Thus, as means of identifying an enteric microbiome relevant for concomitant burn wound infection, we opted to perform perineal diagnostic microbial swabs (PDMS) upon admission. The underlying rationale here was that enteric bacteria which are able to dominate perineal skin flora in a context of continuous skin contamination due to bowel movements would be most relevant for possible subsequent burn wound colonization. Here it is important to note that we found a great variety of enteric bacteria, (i) in part rather common and similar to adult enteric flora such as Enterococcus spp. (gram (+); *phylum:* Firmicutes > Bacilli), (ii) in part common in children although uncommon in adults such as Prevotella spp. (gram (+); *phylum: Bacteroidetes*) or E. coli spp. (gram (-); *phylum: Proteobacteria*), or (iii) in part less common or of rarity even among pediatric populations such as Citrobacter spp., Moraxella spp., Peptostreptoccus spp., Clostridium spp., Acinetobacter spp., Arthrobacter spp. among others. Of note, we did not consider Pseudomonas spp. to be of primarily enteric origin since perineal swabs were consistently negative, even in a few cases of wound infection later on. Conversely, Pseudomonas spp. has a proven ~5% enteric prevalence highly relevant for severe burn injury seen in adults. Thus, the stated variety of the microbiome in pediatric patients that varies significantly from the adult enteric microbiome, especially before two years of age, is another argument in favor of PDMS.[38]

Our findings strongly support the notion that under a treatment protocol that provides an initial microbial decontamination of burn wounds, the enteric reservoir, as opposed to other intrinsic (skin, oral, respiratory tract) or extrinsic (environment) factors, becomes most relevant for subsequent wound colonization with or without outright infection. We also showed that with a certain threshold of affected BSA e.g. > 5% BSA, enteric bacteria are very likely to successfully colonize wounds. Whether this will result in outright infection is obviously dependent on more than one additional factor, of which a IIb degree burn component appears to be one. This may be due to a significantly delayed wound reepithelialization or a more prolonged soft tissue ischemia. Conversely, based on a current scientific understanding reflected in the literature, we did not consider a mechanism of bacterial enteric translocation[39,40] relevant for the purpose of the study. The latter has been suggested in the context of a dysfunctional innate immunity combined with a loss of enteric barrier function in allowing enteric bacteria to contaminate burn wounds via the hematogenic route at a relatively early stage following severe burn injury, but data both from clinical studies

e.g. related to selective digestive decontamination[41,42] as well as animal-based models e.g. developed by the authors[43] remain inconclusive.

One important finding was that gram (-) bacteria with flagella such as Proteus spp. or E. coli spp. appear to be most effective in wound colonization and subsequent infection, whereas Enterococcus spp. was also commonly found in wound swabs but were unlikely to cause outright infection e.g. with fever and rise of WCCs.

Most significantly, we were able to demonstrate that odds ratios for selected bacteria of enteric origin causing subsequent infection were ~10-fold increased in patients with an affected BSA >5% and thus predictive. Of course we saw wound colonization and even several CCs of non-enteric origin such as with Streptococcus spp. and Staphylococcus spp.. However, most likely due to the initial treatment protocol with sterile surgical field dressing application, these cases were only a fraction (< 1/10) of observed CCs.

Overall our data strongly suggests microbial swabs taken from the perineal region early on following scald burns in infants to be a useful clinical predictor of relevant microbial wound colonization and/or outright wound infection later on under a standardized treatment regime characterized by initial surgical surface debridement and a sterile wound dressing.

Conclusion

We recommend performing perineal diagnostic microbial swabs (PDMS) along with any treatment regime aimed at an initial wound decontamination of pediatric burn patients upon admission in order to identify patients with a heightened risk of secondary wound infection, allowing for e.g. a guided antibiotic therapy or a change in planned outpatient check-up intervals.

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