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Review

Review

Microbiome in the setting of burn patients: implications for infections and clinical outcomes

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Abstract

Burn damage can lead to a state of immune dysregulation that facilitates the development of infections in patients. The most deleterious impact of this dysfunction is the loss of the skin's natural protective barrier. Furthermore, the risk of infection is exacerbated by protracted hospitalization, urinary catheters, endotracheal intubation, inhalation injury, arterial lines and central venous access, among other mainstays of burn care. Currently, infections comprise the leading cause of mortality after major burn injuries, which highlights the improvements observed over the last 50 years in the care provided to burn victims. The need to implement the empirical selection of antibiotic therapy to treat multidrug-resistant bacteria may concomitantly lead to an overall pervasiveness of difficult-to-treat pathogens in burn centres, as well as the propagation of antimicrobial resistance and the ultimate dysregulation of a healthy microbiome. While preliminary studies are examining the variability and evolution of human and mice microbiota, both during the early and late phase burn injury, one must consider that abnormal microbiome conditions could influence the systemic inflammatory response. A better understanding of the changes in the post-burn microbiome might be useful to interpret the provenance and subsequent development of infections, as well as to come up with inferences on the prognosis of burn patients. This review aims to summarise the current findings describing the microbiological changes in different organs and systems of burn patients and how these alterations affect the risks of infections, complications, and, ultimately, healing.

Key words: Burn, Microbiome, Skin microbiome, Gut microbiome, Lung microbiome, Multidrug-resistant organisms

Background

Burn injuries are a frequent source of morbidity and mortality worldwide. For example, in the USA alone, around half a million people have burn injuries [1]. As a matter of fact, 40 000 injured subjects are referred to an emergency department every year [1]. Moreover, as many as 75% of these patients are admitted to a specialized burn unit [1,2] and three-fourths of the deaths recorded are associated with sepsis and complications from infections in severely burned victims [2].

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As an instant systemic inflammatory response spreads throughout the body, other organs may also be affected [3]. In addition to the skin, inflammation in the lungs, liver and intestines can also be observed after burn damage [4]. Notably, in the gastrointestinal tract, burn injuries cause mesenteric vasoconstriction and produce a hypoxic environment, as shown in previous publications [3, 4]. Therefore, the reperfusion of blood to these tissues leads to a profound variation in oxygen levels, resulting in cellular stress, necrosis and, ultimately, a breakdown of the epithelial barrier. The latter is characterized by an increase in intestinal permeability and the displacement of the bacteria to the mesenteric lymph nodes [3, 4].

The risk of infection for burn patients is aggravated by additional factors such as protracted hospitalization, urinary catheters, endotracheal intubation, inhalation injury, arterial lines and central venous access [2]. Additionally, the composition and biodiversity of the microbiome can be affected by diet, environment, medication, infection, inflammation and, eventually, burn injuries as well [5–8] (Figure 1). On the first day after a severe burn, Gram-negative aerobic bacteria can fill up the gastrointestinal tract [5], leading to physiological conditions that enable opportunistic pathogens to overgrow and invade the host. Therefore, it is paramount to understand that the disequilibrium of the microbiome occurs only after a complication, such as an injury, and that commensal bacteria can play a crucial role in bacterial translocation, barrier dysfunction and sepsis. We aim to summarise the current data collected on alterations in the gut, skin and lungs, those being the most studied compartments, and how such changes can lead to the development of infections and complications while also contributing information that would aid in the healing of burn victims.

Epidemiology and risk factors for infections in burn patients

The timeline of hospital-associated infections in patients with burn injuries is completely predictable. It is frequent for skin and soft tissue infections to arise during the first week of hospitalization. Meanwhile, pneumonia, bloodstream infections and urinary tract infections tend to appear later. Accordingly, there is a clear preponderance of Gram-positive rods over Gram-negative bacteria at the early onset of infection. Nonetheless, the exact opposite can be observed later [2], which correlates with the median onset of infection, that is, 30 days after admission [9]. Therefore, the length of hospitalization is proportional to the type of bacteria isolated from the burn patient, as shown in several studies. A retrospective study conducted in a Canadian burn centre involving 125 admitted burn victims showed that *Pseudomonas aeruginosa* (*P. aeruginosa*) was rarely present within the first week of hospital admission [10]. However, the presence of *P. aeruginosa* increased to 55% of patients assessed 28 days after admission.

The opposite could be observed for *Haemophilus influenzae*. On average, it was isolated from 36% of the patients during the first week, yet it declined to virtually zero in the following 7 days [10]. A similar increase in *P. aeruginosa* was identified in a study of 5524 burn patients from 2004 to 2013. The latter demonstrated that Gram-positive organisms tend to appear earlier when compared with Gram-negative ones [9]. Although the time of hospitalization is related to several clinical characteristics, such as burn extent and presence of inhalational injury, hospital length of stay is one of the significant risk factors for infection by multidrug-resistant (MDR) bacteria in burn victims. Infection-attributable mortality in burn patients ranges from 50 to 75% [11, 12] and infections caused by MDR bacteria increase mortality from 42 to 86% in patients with burn-related sepsis [2, 13–15].

Likewise, the risk factors for the acquisition of MDR that are usually associated with other patient populations, such as the use of urinary catheters, endotracheal tubes and other invasive medical instruments, as well as past antibiotic exposure, have also been reported for the burn group. In the previously mentioned Canadian study involving 125 patients, 6% had isolates that tested positive for MDR during the first week of hospital admittance. That percentage grew to 44% after 28 days [10]. Additionally, in a study of 5000 patients with burn injuries, the rate of infection by MDR Gram-negative bacteria demonstrated a significant rise during their hospital stay [9]. Data show that in the first 7 days after admission, the rate of *Enterobacteriaceae* was 0.04 for carbapenem-resistant *Enterobacteriaceae* (CPE), 0.26 for extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-E) and 0.52 for fluoroquinolone-resistant *Enterobacteriaceae* [9]. However, from the fourth week onwards, the rates increased to 0.82 for CPE, 0.46 for ESBL-E and 2.61 for fluoroquinolone-resistant *Enterobacteriaceae* [9]. The specific rates for MDR *Pseudomonas* spp. went up from 0.04 per 1000 patient-days during the first 7 days of hospitalization to 1.85 per 1000 patient-days from week 4 onwards [9]. The spread of antimicrobial resistance observed over the last decade may be linked to the pervasive administration of broad-spectrum antibiotics, which could endanger human health in the future [16–20]. Simultaneously, the gastrointestinal tract of the patients is colonized by resistant bacteria, taking over the living microbiota, which is one of the main risk factors for the development of infections caused by MDR bacteria such as carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp) or *Candida* spp. [21, 22]. An efficient treatment strategy to revert to healthy function might be the modulation of the gut microbiota. Burn-injured subjects are a high-risk population for infections and over-perscription of antimicrobial drugs [2, 16, 17]. The effects of antibiotics on the microbiome have been increasingly reported and the prescription of antibiotics is continuing to rise [15, 18–20]. Hence, additional investigation on the specific effect of antibiotics and the results of proliferation of MDR in the gut still needs to be conducted [2, 15, 18–20]. Understanding the complex components of the microbiome and its modification during burn trauma is one of the research highlights in this field. Given this epidemiological situation, the continuous increase of MDR

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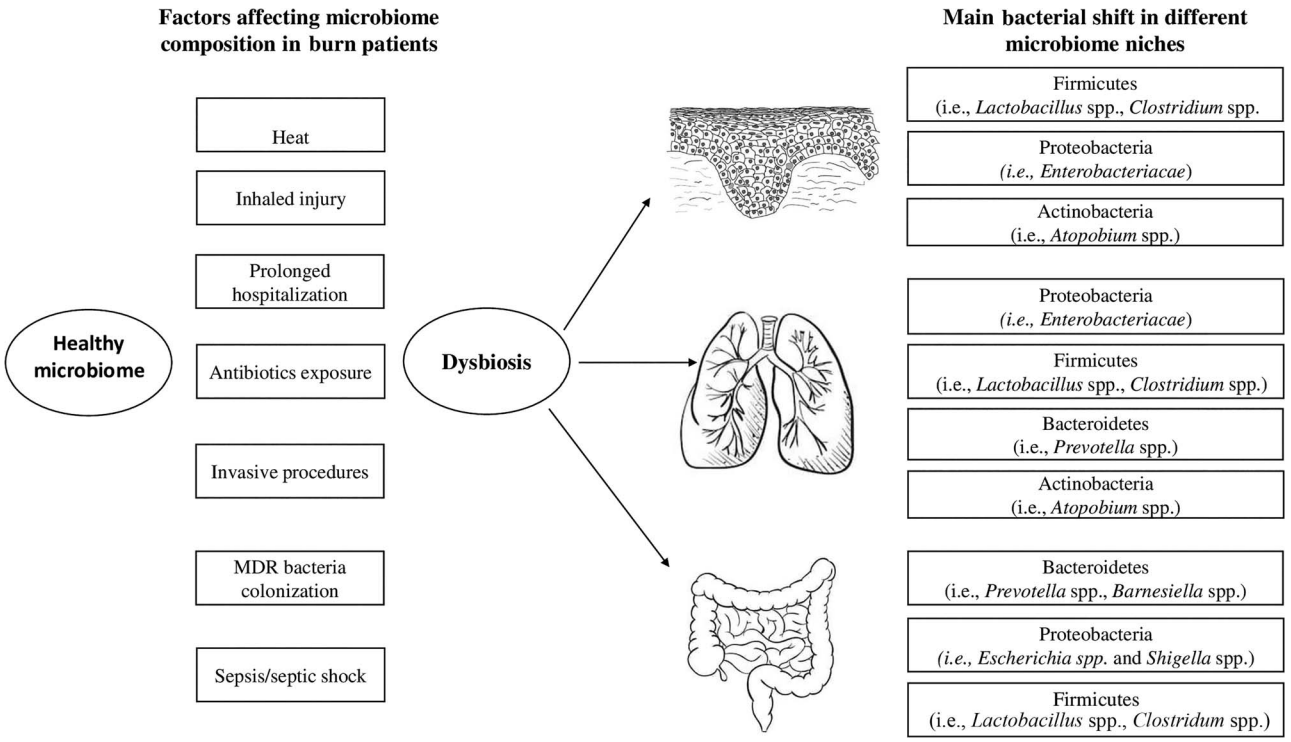


Figure 1. Main changes in skin, lung and gut microbiome composition in burn patients. *MDR* multidrug-resistant

infections observed in recent years and the high infection-related mortality, it is crucial to identify patients at high risk for infections and support the creation of 'antimicrobial stewardship' programmes in this setting [16, 17].

Review

Methods

A narrative review of the available literature was performed using the PubMed database and the Cochrane library. The search terms included 'microbiome in burn patients' and 'microbiome in burn injury'. The Medical Subject Heading (MeSH) terms were as follows: 'microbiome' [All Fields] AND ('burn patients' [MeSH Terms] OR ('burn injury' [All Fields] OR 'burn' [All Fields] AND 'patients' [All Fields]) OR 'burn' [All Fields]) AND ('injury'). The defined search period from 1 September 2000 to 1 May 2020 was selected to compare studies from different periods given the changes in the microbiome and burn knowledge. Given the nature of the review, no ethics approval was required. The search was performed by two investigators (SC and TL). A total of 144 studies were identified (PubMed: 144, Cochrane: 0). Two investigators then reviewed the articles, initially by title and abstract and then in detail, using a customized data abstraction form. Studies were excluded if they had incorrect subject matter, were duplications, or were case reports, commentaries, editorials or reviews. Only studies in English were included. A total of 24 studies were identified for full-text review as they contained original data (Figure 2).

Gut microbiota in burns

Disruption of the intestinal barrier that leads to increased intestinal permeability and translocation of bacteria [21 22] or endotoxins are the frequent adverse events affecting gut colonocytes after a severe burn injury [23]. The loss of the structural integrity in the intestinal epithelial barrier may cause sepsis and subsequent multiple organ dysfunction syndromes, leading to a higher risk of mortality in burn victims [24–26]. Nonetheless, most of the supposed underlying mechanisms behind gut disruption were derived from other better investigated, critically ill populations [27, 28]. Recently, as assumed by Wheatley *et al*. in a mouse model, among predisposing factors advanced age elicits a more severe degree of gut microbial dysbiosis following cutaneous burn injury than is manifest in younger mice [23]. Clinical studies demonstrate that advanced age causes a significant increase in mortality following burn, but the role of the gut in this age-dependent susceptibility had not yet been investigated [23]. Furthermore, He *et al*. [24] reviewed the published data on intestinal barrier dysfunction in severe burn injury, focusing on extremely complex mechanisms that involve numerous signalling molecules and their related pathways. Besides heat damage, the authors explored different pathophysiological processes, such as stress, shock, ischaemia/hypoxia, inflammation, infection and surgical operation, in the early and late post-burn period [24]. The results open a new scenario for the targeted treatment of post-burn intestinal barrier dysfunction, which is theoretically multifactorial and involves multiple, extremely complex pathogenetic factors such as signalling molecules and related pathways,

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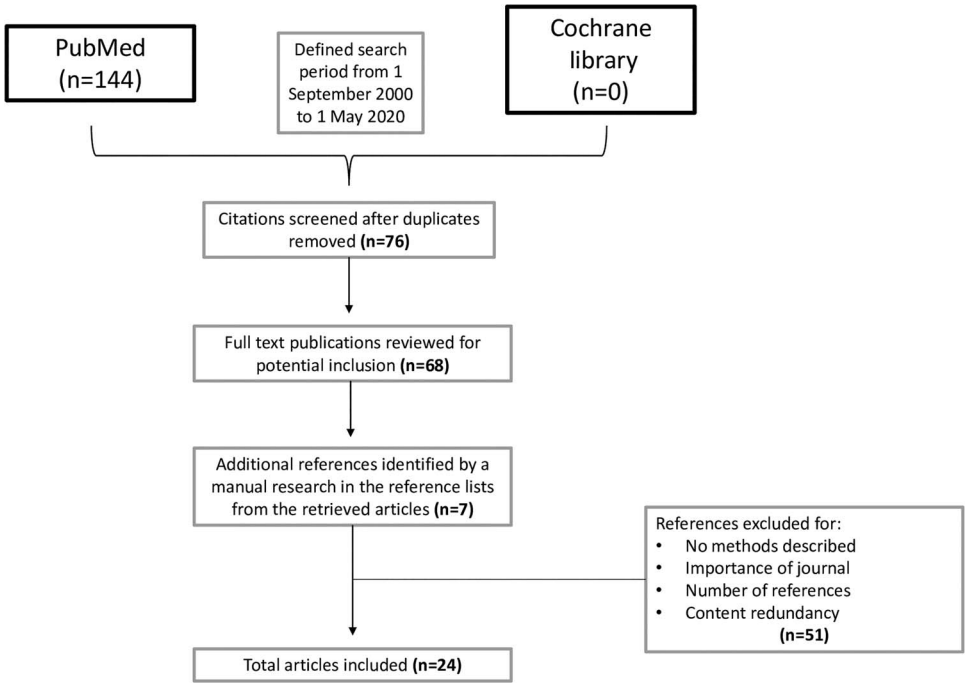


Figure 2. Literature narrative review flowchart

thereby requiring a tailored approach in the future [24]. Some authors [29–32] have explored the gastrointestinal microbiome during the early stages of burn injury. Their studies described an increase in gut dysbiosis that suggested a decrease in some probiotic microbes, such as butyrate-producing bacteria, while some potentially pathogenic bacteria flourished. These authors reported an abundance of Proteobacteria, flanked mostly by an increase in *Escherichia* spp. and *Shigella* spp. and a decrease in the Firmicutes/Bacteroidetes levels in early post-burn stage [29–32] (Figure 1).

Lactobacillus spp., like other lactic acid bacteria (i.e. *Bacillales*, *Sporolactobacillus*), have been associated with the production of short-chain fatty acids (SCFAs; i.e. acetate, propionate, butyrate, isobutyrate and isovalerate), which are the primary energy substrates for colonocytes [33] and may help regulate epithelial barrier function, mucosal immune systems and inflammatory responses [34, 35]. Moreover, the luminal content of SCFAs significantly decreases after a severe burn, suggesting loss of epithelial integrity and immune homeostasis [34, 35]. Although the mechanisms underlying the decrease in SCFA contents have not yet been precisely defined, data suggest that a decrease in Firmicutes/Proteobacteria levels leads to an increase in SCFA contents [34, 35].

Zhang *et al*., have investigated in a mouse model the role of *Clostridium butyricum* (*C. butyricum*) and its production of butyrate in burn injury [36]. *C. butyricum* and butyrate are beneficial for the homeostasis of intestinal microflora, and both decrease during burn injury and their levels were negatively correlated with gut permeability [36]: in concluding, authors have described that oral administration of *C. butyricum* significantly alleviated intestinal permeability.

Dynamic changes in gut bacteria biodiversity were reported in five patients with severe burn [37]. In the four survivors, after an initial decrease of probiotic microbes, an increase in mostly obligate anaerobes and *Bifidobacterium* was displayed compared with the non-survivor. Furthermore, the relative abundance of potentially pathogenic bacteria (i.e. *Pseudomonas* and *Candida* spp.) was higher in the non-survivor patient [37]. Similarly, Wang *et al*. investigated the dynamic changes of the gut microbiome 6 weeks after a severe burn and explored its association with enteral nutrition (EN) [38]. After detecting gut dysbiosis, this condition gradually resolved and EN was associated with the rapid promotion of gut homeostasis in patients that tolerated EN well. Shimuzu *et al*. [37], as supported by Wang et al. [38], highlighted the usefulness of understanding gut flora and its dynamics to establish, albeit not directly, prognosis in severe burns.

Interestingly supportive care, such as EN, and its role in the microbiota are studied as part of burn-related research. Moreover, the swine model of McIntyre *et al*. described the role of fluid resuscitation on gut microbiome [39]. High fluid resuscitation seems to have the ability to reverse the rise of potentially pathogenic organisms such as *Proteobacteria* and ease the growth of beneficial bacteria such as *Bacteroides* in this preliminary study [39].

Lung microbiota in burns

Inhalation injury is present in ~10–20% of all burn traumas [40]. It predisposes the patient to secondary pneumonia and acute respiratory distress syndrome and often requires mechanical ventilation [41]. Currently, very little is known

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about airway microbiota after burn and inhalation injury [42].

A recent publication by Walsh *et al*. [43] evaluated lung microbiome composition in 48 burn patients with inhalation injury who developed early hypoxaemia compared with patients without hypoxaemia [44]. The authors described that hypoxaemic patients had an enrichment of facultative anaerobes such as *Streptococcaceae*, *Enterobacteriaceae* and *Staphylococcaceae* (32%, 27% and 83%, respectively) in comparison to aerobes and strict anaerobes [43]. Hypoxic conditions may also favour *Prevotella melaninogenica* (*P. melaninogenica*) enrichment, which is part of the healthy microbiota [45–46]. However, several studies indicate that *P. melaninogenica* could also play a non-beneficial role under certain conditions, as demonstrated in intubated cystic fibrosis patients [47]. Although the results cannot be unambiguously interpreted due to the low number of patients analysed and the possibility of nosocomial acquisition of these pathogens at admission, such preliminary findings may support the need for a longitudinal study to identify the burden and the relevance of the changes mentioned above [43, 45] (Figure 2).

Skin microbiota in burns

The cutaneous microbiome provides many niches in which large populations of microbes are subjected to a myriad of ecological pressures (i.e. temperature, pH). These communities are directly related to the ability to maintain skin barrier function and encourage inflammation, homeostasis and wound scarring [48–50]. Shortly after burn injury, the skin undergoes an excessive activation of the cutaneous and systemic immune responses, targeting commensal and invading pathogens alike [51]. Specific resident commensal microbes, mostly in the phyla *Actinobacteria* (i.e. *Proprionibacterium* spp.) and Firmicutes (i.e. *Staphylococcus* spp.), may boost skin homeostasis. A recent study observed that a lower abundance of *Proprionibacterium* spp. is correlated with a higher risk of pneumonia and wound infections [52–54].

Furthermore, Plichta *et al*. reported an enrichment in thermophilic and halophilic bacteria such as *Aeribacillus*, *Halomonas*, *Caldalkalibacillus* and *Nesterenkonia* [51]. The latter are typically isolated from soil and water samples [55–57] and a direct correlation between these taxa and the development of pneumonia in the burn population has been established. Thus far, it is unclear if the enrichment of these taxa could be partially due to the exposure of the patient to water sources outside of the hospital setting, such as during debridement with tap water. Regardless, this could be a promising microbiome-based morbidity index that may help stratify patients at admission according to their specific colonizing microbiome.

A small Asian study [58] evaluated the skin microbiome of recently healed burn wounds, i.e. 3 months after the incident, which comprises the late phase of recovery from a burn injury. Comparative microbiome analysis did not detect any considerable fluctuations in microbial abundance or composition when comparing samples from the wound scars and the unaffected skin of these burn patients [58]. Likewise, they did not find any compelling temporal dynamics in microbial abundance or diversification in the burn samples. Curiously, contrary to early reports on the antibiotic-treated gut microbiome, when the skin microbiome was exposed to antibiotic pressure, it showed an increase in bacterial diversity and uniformity when compared with the control subjects [58–61]. However, the samples from the burn patients harboured more Firmicutes than those from the control patients (Figure 1).

There is a consensus that the microbial composition of skin wounds impacts wound healing, but conclusions are conflicting [62]. Delayed wound healing in mice was supposed due to dynamic changes and dysbiosis in the microbiome and to the effect of oral antimicrobials [63], while other authors assumed an enhanced wound-healing in the absence of commensal skin microbiota [64]. Furthermore, Sanjar *et al*. have described skin microbiome changes over 11 days following thermal injury [61] with reduced bacterial richness, altered bacterial genes and associated predicted functions within bacterial communities [61]. In an *in vivo* study, Liu *et al*. have confirmed a lower community richness with dysbiosis in burn scars that persist after healing, despite that these changes and their impact on the rate of wound healing were not explored [58]. In conclusion, there remains a considerable knowledge gap in understanding connections between the microbiome and wound healing in burn injuries [61, 62].

Current & future perspective

In recent years, an increased incidence of infections caused by MDR bacteria has been reported in several burn centres [11, 12, 16, 17, 63]. MDR infections lead to a progressive reduction of therapeutic options and a potential delay in obtaining appropriate antibiotic therapy, which is usually associated with increased mortality. [11, 12, 16, 17, 63]. This overuse and misuse of antibiotics is accompanied by a broad spectrum of changes involving burn-injured subjects, including the resident microbiome at different sites [15, 18–22]. Burn injury itself leads to a disruption of the intestinal barrier, leading to increased intestinal permeability and translocation of bacteria or endotoxins [23–25]. Gut dysbiosis, decrease of probiotics and alteration in the relative abundance of potentially pathogenetic bacteria may appear from the early to the late stages after burn injury [23–25]. Theoretically, the gut may become an entrance for pathogenetic strains, leading to burn-related sepsis, which is often due to colonizing MDR bacteria. Some authors [29–32] interestingly reported, during the early stage of burn injury, a gut increase of gram-negative bacteria, notably *Escherichia* spp. and *Shigella* spp., well-known agents of bloodstream infections in burn units [64, 65]. Gut dysbiosis seems to be strictly related to *C. butyricum* viability and its product butyrate, and their levels were negatively correlated with gut permeability [36]. Moreover, intestinal barrier dysfunction more exactly derives from a multifactorial complex in which other factors should be considered for a holistic, therapeutic approach, as assumed by

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He *et al*. [24]. Recently, a particular focus on the role of supportive care (e.g. EN, probiotics, fluid resuscitation, antimicrobial therapies) and their link with dynamic microbiota changes have enabled us to discover gut bacteria biodiversity in severe burn patients: probiotics supplementation [36], high fluid resuscitation [39] and prompt enteral nutrition [37, 38] may be beneficial for gut homeostasis in hospitalized patients. On the lung microbiome side, very little is currently known about airway microbiota after burn and inhalation injury. Despite that, an episodic enrichment of facultative anaerobes (notably *Staphylococcaceae*) in hypoxaemic-scalded subjects has been observed [43, 45, 46]: preliminary data need to be validated in a longitudinal study but could open important perspectives also in antimicrobial stewardship programmes within burn units [66, 67]. The composition of skin microbiota could be a promising precocious index that may help stratify patients at admission according to their specific colonizing microbiome based on the increase in correlation between the decrease (e.g. *Proprionibacterium* spp.) or the abundance (e.g. thermophilic and halophilic bacteria) of some species and the increased risk of pneumonia or wound infections [51, 55–57]. Interestingly, reduced bacterial richness and dysbiosis seems to persist after healing, as assumed by Liu *et al*. [58], and thermal injury alters even the functional level of bacterial communities. The effects of burn injury on skin microbiome have not been fully elucidated [61, 62, 68, 69]. Furthermore, it is still unclear how the microbiome composition may interfere with wound healing, but it certainly appears that there is a deep bond between the two that requires to be studied further [61, 62, 68, 69].

Conclusions

Fluctuation of the human microbiota is directly linked to health issues and medical conditions. There are plenty of approaches to balance the composition of the microbiota. Therefore, targeting the microbiota has been suggested as an advanced method to confront different medical conditions. Some basic questions still need to be answered to fully understand the microbiota complexities from a therapeutic perspective, particularly in burn patients. Further characterization of the mechanisms by which stress-induced molecules influence microbial proliferation and metabolism is necessary to identify the changes in the microbial phenotypes that directly influence the host's innate immune responses required for optimal healing. Knowledge of the microbiome and its functions may help individualize medicine in the preventive or curative setting. Targeting or rehabilitating the microbiome may be an efficient therapeutic strategy in the near future.

Abbreviations

CPE: Carbapenem-resistant *Enterobacteriaceae*; CP-Kp: Carbapenemase-producing *K. pneumoniae*; EN: Enteral nutrition; ESBL-E: Extended-spectrum β-lactamase-producing *Enterobacteriaceae*; MDR: Multidrug-resistant; SCFAs: Short-chain fatty acids

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Authors' contributions

SC, TL and FGDR conceived the study. FDR supervised the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

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