FUNGAL INFECTIONS IN BURNS: A COMPREHENSIVE REVIEW

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SUMMARY. Burn wound infections remain the most important factor limiting survival in burn intensive care units. Large wound surface, impaired immune systems, and broad-spectrum antibiotic therapy contribute to the growth of opportunistic fungal species. Faced with challenging fluid resuscitation, wound excision and cardiopulmonary stabilization, mycosis in burns are likely to be underestimated. Diagnostic performance can sometimes be delayed because clinical signs are unspecific and differentiation between colonization and infection is difficult. Therapeutic measures range from infection prophylaxis over treatment with antifungal agents towards radical amputation of infected limbs. New methods of early and reliable detection of fungal organisms, as well as the use of novel antifungal substances, are promising but require wider establishment to confirm the beneficial effects in burn patients. This review aims to highlight the main important aspects of fungal infections in burns including incidence, infection control, diagnostic and therapeutic approaches, prognosis and outcomes.

Keywords: burns, burn intensive care, fungal infection

Introduction

Burn patients are exposed to a high risk of developing fungal infections, compared with other hospitalized patients.[1] Although often underestimated, invasive burn wound infections due to *Candida* spp., *Aspergillus* spp., and other opportunistic fungi are important emerging causes of late-onset morbidity and mortality in patients with major burns and severely perturbed immune systems.[2] Main risk factors that have been identified are an increase in the burned total body surface area (TBSA) and impaired immune defense. The use of broad-spectrum antibiotic substances also leads to an eradication of the natural bacterial flora and promotion of oportunistic species.[3-5] Additional predisposing factors are increased age, uncontrolled diabetes, and the presence of central venous catheters.[6]

Treatment standards and infection prophylaxis after burn center admission

After burn center admission, the patient undergoes primary wound evaluation and stabilization of vital functions. Simultaneously, measures of infection prophylaxis are initiated, including whole body cleaning, shaving, and microbial surveillance. Subsequent placement of wet and aseptic wound covers for 24 hours follows a second wound evaluation to calculate the dimensions of excision and meshgraft transplantation. Surgical excision and grafting is usually performed as soon as the patient's condition is stabilized. Depending on the depth of the wounds, excision may be tangential until adequate dermal perfusion is visible or epifascial in deep burns. Meshgraft transplantation is typically performed simultaneously, and the grafts are fixed in place with metal clamps or sutures. The grafts and the donor sites are covered with fat gauze and blankets and remain covered for 4-5 days. After another wound evaluation, either healing may be confirmed or further surgery may be planned. Each period of resuscitation, intensive care, and surgery provides a certain risk to acquire infections, including by fungal organisms, whereas the full impact of severe septic complications usually develop in the later course of burn care. Only strict and standardized hygiene regimes may support the efforts to prevent external contamination of the immune-impaired patient.

Environmental risk factors for fungal infections

Thermal injury of the skin considerably impairs the ability to regulate body temperature. Modern burn centers provide special patient rooms, so-called boxes, in which the temperature and humidity can be controlled over a wide range (between 21 and 38°C, humidity up to 60%). There is a difference in air pressure between these

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boxes and other areas of the burn unit, and the air exchange is at least 10-fold its volume per hour; microbial filters are implemented in these air exchangers. One reason for this technical expenditure is that fungal spores and other microbial species are known to spread by air exchange units.[7] In patients with large burns, additional heating lamps may be required to provide normothermia. The combination of external heat, moisturized wound covers and the wounds themselves provide a milieu that increases the risk of microbial colonization and infection, including by fungal organisms. Regular microbial surveillance and the exchange of sensitive parts, e.g., the filter membranes of the air conditioner and water connections, may identify and remove system-dependent weaknesses. Furthermore, an interdisciplinary approach including certified infection control personnel, burns and plastic surgeons, intensivists and microbiologists is required to minimize the risk of environmental contamination of burn patients.[8]

Patient-related risk factors for fungal infections

Patient-specific risk factors for fungal infections after burn injury include increasing age, >40% burned TBSA, and inhalation injury.[3,4] Further contributing factors are neutropenia and uncontrolled Diabetes mellitus.[6,9]

After burn injuries, ubiquitous *Candida* colonization of the skin and mucosal membranes of nose, throat and gastrointestinal tract likely represents a latent source of infection, especially in patients with impaired immune resistance.[2,4,10,11] Furthermore, gastric ulcers, either pre-existent or acquired during intensive care, may provide an entrance for systemic fungal organisms.[12,13]

Prior *Candida* colonization is an important risk factor for candidaemia, and the risk increases substantially with the number of colonized sites. In a study including 143 *Candida*-positive patients, 43% of patients colonized at more than three sites (and not receiving antifungal medication) developed candidaemia.[4]

Treatment-related risk factors for fungal infections

Burns may be complicated by prehospital exposure to contaminated water. Water immersion to extinquish the fire or to cool burn wounds have been described as possible source of invasive bacterial and fungal infections.[14]

Despite numerous prophylactic efforts, microbial transfer from the hospital environment or staff to burn patients is still a possibility. Incomplete or late burn wound excision increases the risk of infection, whereas too long and extensive surgery may deteriorate the patient's general condition.[3, 15] Moreover, multiple surgical sessions may be required. Large blood losses, massive transfusion, vasopressor therapy, sedation, total parenteral nutrition and renal replacement therapy further weaken immune resistance and create circumstances for possible fungal colonization and infection. Additionally, burn surgery may lead to systemic liberation of vasoactive mediators, cytokines and bacteria.[16] These stressors influence not only immune resistance but also the ability of wound healing.[17-20]

The use of fat gauze in wound coverage provides an air-sealed condition, which is another risk factor for possible treatment-related colonization of bacteria and fungi.

Certain bacteria are known to colonize burn wounds.[21-25] *Staphylococcus aureus*, *Streptococcus* spp and endogenous *Enterobacteriacae* account for early bacterial wound colonization whereas *Klebsiella* spp., exogenous *Enterobacteriacae* (e.g. *Enterobacter* spp, *Serratia* spp), *Acinetobacter* spp. and *Pseudomonas* spp. (as the most relevant species for burn wound infection) are usually confirmed in a later course of burn intensive care. Fungal colonization may occur due to delayed wound excision or due to suppression of bacterial flora after prolonged prophylactic or therapeutic antibiotic therapy.

The introduction and extensive use of topical antiseptic substances in the 1970s led to a decline in gram-negative bacterial infections in burn centers. Simultaneously, an increase in fungal infections was observed in up to 83% of the patients.[21, 26-28] Certain antimicrobial substances, e.g., tazobactam (systemic use) and nystatin (topical application) have been reported to facilitate invasive non-*albicans* Candida infections.[29-31]

Patients presenting with simultaneous inhalation injury, prolonged mechanical ventilation predispose to secondary fungal infection.[32,33] Furthermore, patients with fungal infections require longer ventilation times and intensive care treatment.[4,5]

Any catheters inserted into the body of a burn patient, e.g., tracheal tubes, central or peripheral venous catheters, gastric tubes, rectal tubes, and urinary catheters, are possible mediators of fungal colonization or infection. Therefore, their necessity and duration should be re-evaluated frequently.[1,9,34]

Diagnostic approaches for fungal colonization and infection

Clinical warning signs for fungal infections are unspecific and do not differ from infections of bacterial origin. Due to burn-wound-related permanent inflammation and consequent physiological reactions, common definitions of sepsis are not applicable to burn patients.[18,24] Furthermore, laboratory tests may have limited impact. Significant increases and declines in white blood cells and increases in C-reactive protein and in-

terleukin-6 with simultaneous low levels of procacitonin are signs of maximally activated or exhausted immune competence and may be predictors of occult fungal infection or even fungal sepsis.[13,18,19] Current diagnostic approaches for an early detection of mycosis are limited and often unreliable.[35]

Cultures

Direct confirmation of positive fungal cultures from burn wounds is the standard diagnostic approach but it may be associated with certain latency and species-dependent unreliability.[35,36] In studies evaluating independent risk factors of invasive *Candida* infections, the extent of body site colonization due to *Candida* species was recognized to be associated with consequent invasive disease. The quantification of the colonization was expressed on the Candida colonization index as a clinically relevant score. Furthermore, the Candida score that combines the clinical risk factors preceding surgery, total parenteral nutrition and severe sepsis with *Candida* multi-site colonization revealed a useful bedside scoring system to identify non-neutropaenic critically ill patients with the risk of invasive candidiasis.[4,37]

Candida and *Aspergillus* antigen test

Positive predictive values of some *Candida* antigen tests may be too low for reliable diagnostic.[38,39] In particular, Cand-Tec Candida antigen and the mannan antigen plus anti-mannan antibody measurements may have unacceptably low sensitivity or specificity. However, the (1→3)-β-d-glucan and mannan antigen may be superior biomarkers, depending on whether a sensitivity-driven or specificity-driven approach is used.[40]

Sensitivity of *Aspergillus* glactomannan immuno assays may also be low (between 0.2 and 0.55), whereas a recently developed point-of-care test for *Aspergillus* antigen based on lateral flow technology detect an extracellular glycoprotein secreted only during active fungal growth with promising sensitivity and specifity.[41,42]

Histology

The histological diagnosis of burn wounds after biopsy is a reliable method to confirm fungal colonization and infection. However, due to its invasive character, this method is usually avoided and not routinely performed.[43,44]

New approaches

New diagnostic methods for an early and non-invasive detection (real-time polymerase chain reaction assays) are known, but they are not available for all fungal organisms and may not be established in every laboratory institution because of high costs.[45] These diagnostic limitations may sometimes prevent an early and appropriate antimycotic therapy.[46]

Incidence and spectrum of fungal organisms

The incidence of fungal contamination and infection in burn patients is reported to be 6.3% to 15%, although there are significant differences between individual burn centers ranging from 0.7% up to 24.1%.[3,47] This variation may be the result of different standards in the performance of surveillance cultures and may reflect differences in the frequency, quality and quantity of diagnostic efforts in suspected cases. Earlier studies confirmed much higher incidences of *Candida* infections in burn centers that performed frequent surveillance protocols compared with other burn centers.[25,48] The incidence of fungal infections in patients presenting with >80% TBSA may be lower because of other complications, e.g., uncontrollable hemodynamic instability, septic complications and multiple organ failure, which may occur earlier in the course of burn intensive care and are likely to limit survival.[2]

There is a domination of *Candida albicans* mycoses in burn centers.[1,3,11,37,41,49-52] However, there are various reports concerning the incidence and virulence of several fungal species.[35,48] In certain burn centers, an increasing incidence of invasive infections of non-*albicans Candida*, *Aspergillus* and zygomycoses has been reported.[8,39,55-58] Zygomycoses in particular, infections of saprophytic molds that typically grow in rotting organic material, may be a serious threat to burn patients. These organisms provide proteolytic enzymes, may invade healthy skin and have an angioinvasive growth pattern that may contribute to severe coagulation disorder and vessel occlusion.[59-61]

A North American multicenter analysis of 435 positive cultures from 15 burn centers reported *Candida* species in 85% of them, non-*Candida* yeast in 21%, *Aspergillus* in 14%, zygomycetes, including *Mucor* spp. in 9% and other fungal organisms in 1.4% of the cultures.[3]

Therapeutic approaches for fungal infections

For the clinical therapy of mycoses, it is important to know whether a fungal colonization or a fungal infection is involved.[52,62] In daily practice, this differentiation may be not easy because, as already mentioned, the special pathophysiology of the burn wound provides laboratory characteristics of common inflammatory response and bacteria-related infection, and, furthermore, unreliable diagnostic possibilities.

Systematic risk reduction

The most important goal in burn patients presenting with a high risk of infection is an early achievement of appropriate immune competence. This goal may be facilitated by early enteral nutrition, early and complete burn

wound excision and grafting, restrictive use of blood transfusion, early weaning from mechanical ventilation, avoidance of broad spectrum antibiotic prophylaxis, rational antibiotic therapy including de-escalation strategy and frequent re-evaluation, and restrictive use of invasive catheterization.

Antimycotic prophylaxis

Some authors recommend antimycotic prophylaxis for burn patients presenting with a > 50% burned TBSA, inhalation injury and neutropenia, although there is currently no evidence to support this strategy.[3,4] The broad and generalized use of antifungal agents in burn patients without a high risk potential may be problematic because of the possible generation of resistances and increasing costs.[36,52,63]

Antimycotic therapy

Some burn centers use topical applications of antifungal agents, e.g., nystatin, amphomoronal, and silver-containing agents. These substances may successfully treat local colonization and infection of fungal organisms that contain sterol structures in their cell membrane (*Candida albicans*) but may also hide manifest infections.[11,64-67] Furthermore, certain topical anti-infective agents may have cytotoxic effects. Therefore, their use upon meshgrafts should be restricted to avoid healing complications.

The systemic use of antifungal agents may depend on the general condition of the burn patient, the fungal species and the confirmation of fungemia[2-4,39,49] (*Table I*). Apart from established polyenes and imidazole-based azoles, new triazoles and echinocandins provide higher specificity. Limitations on the use of antifungal agents may be the development of resistances, hepato- and nephrotoxicity, the lack of rapid, reliable and precise diagnostics, insufficient tissue permeability, and limited oral or intravenous applicability.[36,38] Species-related gaps may require multiple antifungal substances.[46,69] New approaches, such as calcineurin blockers and *Candida*-secretoric aspartate protease-inhibitors are promising but still have to be clinically investigated and established.[70]

Surgical therapy

Invasive fungal infections, typically *Aspergillus* and zygomycoses, may require additional surgical exploration to limit the extension of infection, including amputation of limbs. An infection requiring surgical therapy is often associated with high mortality.[69,71,72]

Prognosis of fungal infections

An early and definitive closure of the burn wound was found to be a treatment-related positive predictor of a good outcome, implicating the great impact of thorough burn wound care after surgical therapy.[64]

In multivariate analyses, 4 parameters predicted increasing mortality due to fungal infections in burn patients: higher age, extensive percentage of burned TBSA, increasing numbers of positive cultures, and confirmation of *Aspergillus* spp. or zygomycoses.[3,73] A contamination with zygomycoses revealed a mortality of 31%, and an infection rate of 81-100%.[55,71,72,74] Furthermore, fungal infection of non-burned skin predicted mortality, independent from the extent of burned TBSA.[56]

Different sub-types of *Candida* species represent different risks in cases of infection. Compared with *Candida albicans*, non-*albicans Candida* infections may be associated with a higher mortality rate and higher resistance rates against antifungal agents, although other burn centers did not reveal these findings.[39,52,53,75,76] Recent developments of azole resistance remains a challenge in treating *Aspergillus* infections, particularly in Europe, while resistence rates are probably even underreported due to incomplete strain analysis. Direct azole resistance detection using molecular biology methods may offer more rapid analysis for clinicians, although the large number of possible resistance mechanisms contributes to very complex interaction processes.[42]

Conclusions

Fungal infections are rare but severe complications and remain a challenge in burn intensive care. Possible solutions may be the development of clinically practicable di-

Table I - Recommendations for antifungal therapy of non-neutropenic patients with Candida infection after burn injury.[25,39]

Antifungal agent[a]	Mode of application	Dosage and comments
Liposomal Amphotericin B	i.v.	5 mg/kg/day
Fluconazole	i.v./p.o.	Day 1, 800 mg/day, then 400–500 mg *C. albicans*[b]
Voriconazole	i.v./p.o.	Day 1, 6–12 mg/kg/12 h; then 3 mg/kg/12 h (creatinin-clearance ≥ 50 ml/min)
Caspofungin	i.v.	Day 1, 70 mg, then 50 mg
Micafungin	i.v.	Day 1, 100 mg, then 100 mg (>40 kg body weight)
Anidulafungin	i.v.	Day 1, 200 mg, then 100 mg

[a]Pharmacokinetic of antifungal drugs in burn patients is under-researched.
[b]Elimination half-time of fluconazole may be lower in burn patients compared to non-burn patients; clearance may be 30% higher.

agnostic methods, avoidance of broad spectrum antibiotic prophylaxis, measures to recover immune competence, and the earliest possible definitive burn wound closure. Antifungal agents should be used appropriately and targeted, keeping rising resistance rates in mind.

Key messages

- Fungal infections in burns are likely to occur in patients with large wound surfaces, impaired immune resistance, advanced age and broad-spectrum antibiotic therapy.
- Discrimination between fungal infection and colonization in burn wounds is difficult; clinical presentation is unspecific and sensitivity of diagnostic results may be unreliable.
- Recent studies report an increasing incidence of non-albicans *Candida* spp., *Aspergillus* spp., and zygomycoses including *Rhizopus* in burn units. These organisms provide higher resistance rates to antifungal substances and are associated with poor prognosis.
- Antifungal therapy includes infection control using frequent microbial surveillance, early treatment with appropriate antimycotic substances in high-risk patients and earliest possible burn wound closure.

RÉSUMÉ. Les infections de plaies des brûlures restent le facteur le plus important qui limite la survie dans des unités de soins intensifs des brûlures. Une plaie grande, une immunodépression, et une antibiothérapie à large spectre contribuent à la croissance des espèces fongiques opportunistes. Face à la réanimation liquidienne difficile, l'excision de la plaie et la stabilisation cardiorespiratoire, les mycoses des brûlures sont susceptibles d'être sous-estimées. Le rendement diagnostic peut parfois être retardé car des signes cliniques ne sont pas spécifiques et la différenciation entre la colonization et l'infection est difficile. Les mesures thérapeutiques vont de la prévention des infections au traitement avec des agents antifongiques vers amputation radicale des branches infectées. De nouvelles méthodes de détection précoce et fiable d'organismes fongiques, ainsi que l'utilisation de nouvelles substances antifongiques, sont prometteuses mais on a besoin de plus exemples pour confirmer les effets bénéfiques chez les patients brûlés. Cette revue a pour but de mettre en évidence les principaux aspects importants des infections fongiques chez les brûlures, y compris l'incidence, la lutte contre les infections, les approches diagnostiques et thérapeutiques, le pronostic et les résultats.

Mots-clés: brûlures, soins intensifs des brûlures, infection fongique

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