THE OUTCOME OF FUNGAL INFECTIONS IN A BURN INTENSIVE CARE UNIT: A STUDY OF 172 PATIENTS

INFECTIONS FONGIQUES (IF) DANS UN CTB: ÉTUDE SUR 172 PATIENTS

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SUMMARY. Burned patients are an especially fragile population in which infections are a leading cause of death and morbidity. Fungal infections have become increasingly prevalent in Intensive Care Units (ICUs) and burn ICUs. Management of fungal colonization and infection still constitutes a challenge for clinicians. The aim of this retrospective cross-sectional study was to characterize the population of burn patients with fungal infections admitted to our Burn ICU between January 2013 and December 2015. Patients were characterized according to age, gender, date of admission and exit, type of burn, type of exit, total body surface area (TBSA) and presence of inhalation injury. Positive fungal cultures, causative pathogen and site of sampling were also registered. Statistical analysis centred around the presence of fungal infection/colonization was performed using IBM SPSS Statistics. A total of 172 patients were included, 38 (22.1%) had a positive fungal culture and of these 8 (21.1%) died. Patients with fungal infection/colonization stayed more days than those without infection. However, this tendency did not reach statistical significance when patients that died in the ICU were excluded. No relationships were found when comparing positive fungal cultures with TBSA, burn aetiology, inhalation injury or mortality. Fungal infections are a major cause of morbidity and mortality despite TBSA, burn type or presence of inhalation injury. Efforts should be made to improve management of fungal infections, especially in burn patients and other critically ill groups.

Keywords: fungal infections, incidence, outcome, burn unit

RÉSUMÉ. Les brûlés sont des patients particulièrement sensible aux infections, responsables majeures de morbidité et de mortalité. La prévalence des IF croit en réanimation, générale comme brûlologique, et la prise en charge des colonisations et infections reste un défi pour le clinicien. Le but de cette étude transversale était de préciser les caractéristiques des patients brûlés, hospitalisés dans notre CTB entre janvier 2013 et décembre 2015, ayant développé une IF. Nous avons relevé l’âge, le sexe, les dates d’entrée et de sortie, la modalité de sortie, le type de brûlure, la SCB et la présence de lésion d’inhalation. Les cultures fongiques positives, leur site et la levure isolée ont aussi été répertoriées, les études statistiques ayant utilisé SSPS Statistics (IBM). Parmi les 172 patients étudiés, 38 patients (22.1%) ont développé une IF et 8 (21.1%) en sont morts. Les patients souffrant d’une IF sont restés plus longtemps dans le service, cette constatation n’étant pas significative si les patients décédés ne sont pas comptabilisés. Nous n’avons pas trouvé de corrélation entre IF et SCB, cause de la brûlure, inhalation ni mortalité. Des efforts sont nécessaires pour améliorer la prise en charge des IF, en CTB comme en réanimation générale.

Mots-clés: infections fongiques, incidence, évolution, CTB

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Introduction

Infections are a worldwide health problem, with burned patients at a high risk of infection due to their complexity and fragility. In critically ill patients, they constitute a major cause of morbidity and mortality. In this group, infections are also a leading cause of death and morbidity, which makes burn wound infection (BWI) a major public health problem and one of the most devastating traumas.

Infections in burned patients are mainly caused by bacteria, followed by fungi and then viruses. Fungi ubiquity and widespread antibiotic use have made fungal infections an increasing problem over the past few years. This type of infection accounts for approximately 20% of all infections in Intensive Care Units (ICU), and in the burn patient scenario the situation is similar, representing 6-26% of infections according to some studies.

They usually occur around or after the second week of burn injury, in patients who have received or are taking antibiotics. These infections are also known to be associated with inhalation injury and higher burned total body surface area (TBSA), as well as with diabetes or total parental nutrition (TPN) in severely burned patients.

Despite some attention in recent years, fungal infections still constitute a challenge in burned patient management, mainly due to delayed diagnosis and difficulties in fungi culture and its sensitivity, and have been described as contributors to burn wound progression. Moreover, fungal infections are known to be associated with higher morbidity and mortality rates. Although aggressive empiric treatment is not a widespread practice, some authors proclaim it should be.

The aim of this study was to determine the incidence of fungal infections in burned patients admitted to our Burn ICU between 2013 and the end of 2015, and to characterize this population.

Methods

Study design

This is a cross sectional study, done retrospectively, regarding fungal infections in burned patients admitted to a Burn ICU.

Study setting

All patients admitted to the Centro Hospitalar São João (CHSJ) Burn ICU during the years 2013-2015 have been analysed. The CHSJ Burn ICU is one of the main burn units in Portugal and is associated with the Plastic and Reconstructive Surgery Department. All data were obtained from medical records retrieved retrospectively from paper records and a computerized, hospital-wide database, during the first trimester of 2019.

Assessment and management of burn patients

In our unit, extent of burn is calculated by assessing the percentage of total body surface area (TBSA), according to the Lund and Browder chart. A patient admitted to the Burn ICU has samples collected for microbiology analysis at the moment of admission. A patient admitted to the Burn ICU has samples collected for microbiology analysis at the moment of admission. After this, every week during ICU stay blood cultures and urinary sample, skin swabs, skin biopsies or respiratory secretions are collected, depending on infection suspicion, by the clinicians.

Once blood culture results are obtained and resistance profile analysed, antibiotic or antifungal treatment is adjusted accordingly. The Burn ICU works in collaboration with a Group for Hospital Management of Infections and Treatment in order to define an appropriate treatment strategy.

Procedures

The study period was 3 years (2013-2015). Data of all patients admitted to the Burn ICU in this interval were retrieved, including age, gender and date of admission and exit, used for calculating the total time of stay in the Burn ICU.

Type of burn (6 different groups: “fire”, “chemical”, “electrical”, “scald burn” (“hot fluids”), “toxic skin syndromes” and “more than one”) and type of exit from the Burn ICU (live discharge vs. death) were recorded. TBSA and presence of inhalation injury were also registered.

Patients with toxic epidermal necrolysis (TEN) and other toxic skin syndromes, as well as those with multiple causes of burn, were excluded from the analysis.

Regarding fungal infection, patients who had at least one positive sample for fungi during their stay in the Burn ICU were identified. If a patient had more than one sample positive to fungi, only the first
isolation was registered and used in the analysis. Samples were collected when clinicians suspected infection, however colonization and infection distinction was not verified using other methods such as galactomannan or 1,3-beta-D-glucan values.

Cause of infection/colonization was also registered in 6 groups (Candida albicans, non-albicans Candida spp., Aspergillus spp., Fusarium spp., Zygomyces and Other or non-identified) and the source of the sample was also registered and grouped (4 groups: wound/soft tissues, urinary sample, respiratory secretions, blood culture).

**Statistical analysis**
Statistical analysis was performed using IBM SPSS Statistics® version 23.0, with 0.05 as a significance level. T-test was used to identify differences in age, time of stay and TBSA according to the presence of fungal infection/colonization and to mortality. Chi-squared or Fisher exact test were used to identify an association between the presence of fungal infection/colonization and the other qualitative variables. Mean and standard deviation were used for quantitative data, and absolute and relative frequencies for qualitative variables.

**Results**

**Descriptive data**

Between 2013 and 2015, one hundred and seventy-eight (178) patients were admitted to the CHSJ Burn ICU unit. Of these, 172 patients were selected for this study: 116 (67.4%) were men and 56 (32.6%) women (Fig. 1). Mean patient age was 51.65 years, ranging from 12 to 94 years (Table I).

Time of stay was on average 24 days (24.58 days) in the ICU (Table I). Forty-one (41 - 23.8%) patients had inhalation injury and 28 (16.3%) died in the Burn ICU. The most frequent cause of burn was fire (125 - 72.7%), followed by scald burns (17.4%), electrical burns (7%) and chemical (2.9%) (Fig.2). Mean TBSA was 23.18%.

Thirty-eight patients (22.1%) had a positive fungal culture in the Burn ICU, of which 21.1% (n=8) died (Table II).

Non-albican Candida spp. were the most common isolated microorganisms in 20 patients (52.6%), followed by Candida albicans (15 patients - 39.5%), Aspergillus spp. (1 patient - 2.6%) and non identified agents (2 cases - 5.3%). Most fungi isolations were obtained from soft tissue samples (23 cases - 60.5%), followed by urinary samples (23.7%) and finally blood cultures and respiratory secretions samples (7.9% each) (Fig.3).
Main results

When comparing with patients with live discharge from the ICU, time of stay was lower in the patients who died in the ICU (15.04 vs. 26.43, p=0.012), while age and TBSA were higher in this group (62.07 years vs. 49.62 years and 57.26% vs. 16.51%, respectively), with all these results reaching statistical significance.

It was detected, with statistical significance, that the patients with fungal infection/colonization stayed more days than those without infection (32.76 vs. 22.25 days, p=0.031). However, when patients that died in the ICU were taken out of the analysis, the analysis was short of statistical significance, despite the same tendency being observed (32.77 vs. 24.76 days).

Regarding TBSA, there were no statistically significant differences between those with and without positive fungal cultures (Table I).

Comparing the patients with fungal infection/colonization with those without, we did not find any statistically significant differences regarding mortality or the presence of inhalation injury. However, a tendency for higher mortality was seen in those patients with fungal infection/colonization (21.1% vs. 14.9%).

Similarly, no differences between groups were found when aetiology of burn or TBSA categories were analysed. Fire burns were the most common type in both groups, and TBSA group distribution was similar regardless of the presence of fungi (Table II).

### Table I - Relation of fungal infection and mortality with age, time of stay (total and excluding dead patients) and TBSA

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
<th>Fungal Infection</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>with</td>
<td>without</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td>Mean</td>
<td>51.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>19.94</td>
</tr>
<tr>
<td><strong>Time of Stay</strong></td>
<td></td>
<td>Mean</td>
<td>24.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>21.95</td>
</tr>
<tr>
<td><strong>Time of Stay (excluding patients dead on ICU)</strong></td>
<td>Mean</td>
<td>26.43</td>
<td>32.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>20.63</td>
</tr>
<tr>
<td><strong>TBSA</strong></td>
<td></td>
<td>Mean</td>
<td>23.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>23.23</td>
</tr>
</tbody>
</table>

### Table II - Relation of fungal infection with mortality, inhalation injury, aetiology of burn and TBSA categories

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Presence of Fungal Infection</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>with</td>
<td>without</td>
<td>with</td>
</tr>
<tr>
<td><strong>Fungal Infection</strong></td>
<td></td>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
<td>(22.1%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>134</td>
<td>(77.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged</td>
<td>144</td>
<td>(83.7%)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>28</td>
<td>(16.3%)</td>
<td></td>
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<tr>
<td><strong>Inhalation Injury</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No inhalation injury</td>
<td>131</td>
<td>(76.2%)</td>
<td></td>
</tr>
<tr>
<td>Inhalation injury</td>
<td>41</td>
<td>(23.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Aetiology of Burn</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fire</td>
<td>125</td>
<td>(72.7%)</td>
<td></td>
</tr>
<tr>
<td>Electricity</td>
<td>12</td>
<td>(7.0%)</td>
<td></td>
</tr>
<tr>
<td>Chemical</td>
<td>5</td>
<td>(2.9%)</td>
<td></td>
</tr>
<tr>
<td>Scald</td>
<td>30</td>
<td>(17.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>TBSA (categories)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30%</td>
<td>122</td>
<td>(70.9%)</td>
<td></td>
</tr>
<tr>
<td>30 - 59%</td>
<td>25</td>
<td>(14.5%)</td>
<td></td>
</tr>
<tr>
<td>≥ 60%</td>
<td>18</td>
<td>(10.5%)</td>
<td></td>
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<tr>
<td>missing</td>
<td>7</td>
<td>(4.1%)</td>
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Discussion

Extensive thermal injury, seen in burned patients admitted to an Intensive Care Unit, results in severe cardiovascular, end-organ perfusion and immune derangement, known as burn shock. These patients exhibit a clinical picture marked by systemic inflammation, described as systemic inflammatory response syndrome (SIRS), mostly caused by the tissue damaged by the burn. Immunosuppression is associated with the next phase following SIRS. This facilitates pathogen colonization and infection. Infection may lead to sepsis, a major cause of morbidity and also mortality, accounting for the majority of deaths in burn patients.

Burn wounds provide an optimal environment for bacterial growth, due to deficient perfusion and nutrient rich conditions. Normally, colonization ensues by environment, gut and oropharyngeal track pathogens, being gram positive bacteria the first to colonize followed by gram negative bacteria. Colonization by fungi usually occurs later on.

The incidence of fungal infection/colonization was 22.1%, which is similar to other studies around the world with fungal infection incidences ranging from 26% to 44%, but contrasting with other works with incidence ranging from 6% to 10%, including a multicentre American Burn Association review (ABA). Fungal infections have become increasingly prevalent following broad-spectrum antimicrobial use and given the ubiquity of fungi and fragility of burned patients. Most frequently, fungi come from the environment as burn patients roll on the floor to extinguish flames, use running water to wash chemical and fire burns and use contaminated bandaging left open to the air. Other environmental foci described are air conditioning vents and floor drains. Often infection arises from the patient’s own flora.

Fungal infections are associated with high morbidity and mortality rates in burned patients, regardless of TBSA, inhalation injury or age, as described in other works. Despite this, we did not find statistical significance between positive fungal cultures and mortality.

This study detected, with statistical significance, a higher time of stay among the patients with fungi positive cultures, as has also been seen in other studies. When patients who died in the ICU were taken out of the analysis, this relation did not reach statistical significance. The timing of infection by fungi may explain this, as some studies have shown that fungal infection commonly appears after 2 - 4 weeks of hospitalization. Patients who died shortly after admission to the ICU might not have had the time to get infected by fungi.

Most commonly, according to some literature, fungal isolation is obtained from wound/soft tissue samples, followed by urinary samples and respiratory secretions and lastly from blood cultures. This pattern meets our findings regarding sample sites. We also found Candida spp. to be the most common pathogens causing fungal infection/colonization, which was also reported in multiple studies.

Some studies described an association between TBSA and fungal infection, with mainly TBSA between 30% and 60% being associated with higher fungal infection rate. Our findings do not support this association, with no statistically significant relation being found between fungi presence and TBSA (either normal and grouped).

The management of fungal infections presents a challenge. The diagnosis of fungi colonization and infection is not easy as routine culture techniques require around 7 to 14 days and venous blood culture sometimes fails to reflect the fungal agent. This leads to a delay in treatment initiation and complicates fungal infection management. Antifungal treatment itself is rendered difficult by toxicities and limited treatment options. Fluconazole is the most common antifungal agent: other azoles, amphotericin B and echinocandins are other options. Wound closure with autographs and early burned tissue debridement remain the most successful treatment options.

Although this study includes a database of 172 patients, a bigger population could have been used, expanding the time of study, which could reveal other findings that our study fell short of demonstrating. Better differentiation of colonization and infection should have been used in order to demonstrate a stronger correlation between analysed variables and fungal infection. Temporal recording of fungal infection diagnosis in the Burn ICU would have shown some interesting data regarding fungal infection tim-
ing in hospitalized patients. Moreover, more variables such as treatment agent and patient risk factors (e.g. diabetes mellitus, heart failure, autoimmune diseases, etc.) that were not analysed because of lack of data may be important to better understand and characterize fungal infections in burned patients.

Conclusions

Despite not reaching statistical significance as in other works, a tendency for higher mortality among patients with fungi positive cultures was seen. Fungal infection/colonization did not seem to be related to TBSA, burn type or presence of inhalation injury. Diagnosis and treatment of fungal infections have a lot of setbacks that make it difficult to approach this important problem. This emphasizes the need for better tools (for early diagnosis and treatment agents) for fungal infection management, especially in critically ill groups such as burn patients, as it represents a high burden problem in this group.

BIBLIOGRAPHY


Conflict of interest. All named authors hereby declare that they have no conflicts of interest to disclose.