

# Clinical impact of fungal colonization of burn wounds in patients hospitalized in the intensive care unit: a retrospective cohort study

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## ABSTRACT

**Background** Invasive fungal infections in burn victims significantly increase mortality and hospitalization. The effect of fungal burn wound colonization has not been established.

**Methods** All adult patients hospitalized in the intensive care unit (ICU) with burns  $\geq 10\%$  of total body surface area (TBSA) between 2005 and 2021 were included. Superficial swabs were collected whenever clinical suspicion of wound colonization was raised, and deep tissue samples were sent at any wound excision. The primary outcome was the incidence of invasive fungal infections defined as any deep tissue fungal infection or fungemia.

**Results** Of 242 patients included, 39 (16.1%) had fungal wound colonization, 22 (56.4%) with yeasts and 24 (61.5%) molds. Patients with fungal colonization had a significantly higher rate of invasive fungal infections (82.1% vs 3.9%,  $p < 0.001$ ), candidemia (15.4% vs 3.4%,  $p = 0.002$ ), as well as longer ICU stay ( $61.5 \pm 57.6$  vs  $19 \pm 40.5$  days,  $p < 0.001$ ), and higher in-ICU mortality (43.6% vs 15.8%,  $p < 0.001$ ). Survival analysis showed fungal colonization to be associated with significantly increased risk of invasive infection (aHR 25, 95% CI (9.67 to 64.62)), even when adjusted for age, TBSA, sequential organ failure assessment scores, Charlson Comorbidity Index and the presence of bacteremia.

**Conclusions** Fungal burn wound colonization is associated with increased risk of invasive fungal infections and mortality.

**Level of Evidence** This a single center, retrospective cohort study

## BACKGROUND

Burn injuries remain a complex challenge in modern healthcare, often necessitating intensive care unit (ICU) management and harboring dismal outcomes. Infections are common and significantly contribute to morbidity and mortality in this population.<sup>1,2</sup>

Interestingly, while bacterial infections of burn wounds have declined over the years, there is a reported rise in the incidence of fungal wound infections reaching a reported incidence of 6%–45% of all burn admissions with candidemia developing in up to 5% of patients with severe burns.<sup>3–6</sup> This may be explained by compromised host defenses, invasive medical procedures, and broad-spectrum antimicrobial usage, common to burn patients, all providing a fertile ground for the establishment and propagation of fungal species.<sup>7,8</sup> Studies in burn patients have linked fungal infections with worse

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While fungal burn wound infections are a major problem, we have no empirical data about the significance of superficial swab cultures and how they relate to clinical outcomes and invasive fungal infections.

## WHAT THIS STUDY ADDS

⇒ In our cohort, fungal wound colonization was associated with significantly higher rates of deep fungal wound infections and candidemia, longer intensive care unit (ICU) stay and higher in-ICU mortality.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future interventional studies could elucidate whether swab-directed antifungal treatment impacts overall prognosis.

outcomes. Fungal burn wound infections and candidemia have been associated with need for regrafting in 60%, longer length of stay, and attributable mortality as high as 33%.<sup>4,6,9,10</sup>

The higher mortality associated with invasive fungal infections in burns patients led to attempts for early diagnosis and treatment. Fungal screening assays such as  $\beta$ -d-glucan and galactomannan for early diagnosis of fungal wound infections have not shown high correlation with infection or impact on patients' outcomes.<sup>11</sup>

Amid the investigation of fungal infestation in burn wounds, a critical distinction emerges between colonization and infection. Fungal colonization, defined as the presence of fungal organisms on the burn wound surface with no deep tissue penetration, is reported in up to 90% of burn patients when routine screening is performed.<sup>10</sup> The clinical relevance of such colonization is not clear. In one large retrospective study in patients with thermal burns, fungal infection of burn wounds was independently associated with higher mortality, however, fungal colonization did not show the same association.<sup>12</sup> Conversely, in a different retrospective study, wound colonization with candida spp was found to be a significant risk factor for candidemia in burn patients.<sup>9</sup> The management of fungal colonization, in the absence of overt infection, poses a dilemma for clinicians. The indiscriminate use of antifungal agents might contribute to the development of resistance, adverse effects, and escalating healthcare costs. Striking a balance

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between proactive intervention to prevent invasive infection and exercising restraint to avoid unnecessary antifungal exposure necessitates a nuanced approach. Current clinical guidelines recommend to consider antifungal prophylaxis in selected high-risk ICU patients, however, to date, there is no recommendation specifically addressing the burn patient population.<sup>13</sup>

In this study, we aimed to assess whether fungal colonization of burn wounds is associated with clinical outcomes in patients with thermal burn wounds.

## METHODS

This retrospective cohort study was conducted in Rambam Health Care Campus, an 1100-bed academic, tertiary, and level 1 trauma center including an intensive burn unit that is an integral part of an 18-bed ICU. The Electronic Health Registry (EHR) files of all patients hospitalized in the ICU with any thermal burn injury between January 1, 2005 and December 31, 2022 were reviewed.

Included patients were those 18 years of age or older with a second-degree burn or higher of a cumulative total body surface area (TBSA) of 10% or higher that were hospitalized in the ICU in our center. We excluded patients with a lack of fully available EHR, or patients who were transferred to an ICU in another facility while hospitalized in our ICU.

Data including patients' demographics, clinical and laboratory data, microbiologic data and antibiotic and antifungal treatment were collected from the patients' medical charts. Additional data including vital signs and laboratory results on presentation were mined using the MD-Clone interface (V.3.2 or older). Machine-mined data were assessed for accuracy and relevance by the investigator reviewing the EHR. Patients were followed from admission and up to discharge from ICU. The study was reviewed and approved by the institutional ethics committee (RMB-21-0558).

As per institutional standard of care, all burn victims are hospitalized in single-occupancy chambers and treated in accordance with standard contact precautions, including gloves and disposable gowns. Standard topical wound care aims at early facilitation of autolytic debridement. Superficial exuding wounds are treated with absorbent alginate (Flaminal, Flen Health, Düsseldorf; Germany) and silver-infused dressings (Acticoat, Smith & Nephew, London, UK; and Aquacel Ag, ConvaTec, Redding, UK). Deep wounds are irrigated with Milton sterilizing fluid (1% sodium hypochlorite with 16.5% sodium chloride (Procter & Gamble, Cincinnati, OH, USA)) diluted 1:4 whenever dressing is changed. Deep wounds are surgically debrided as soon as clinical stability allows, with skin allografts or homografts implanted usually during the same operation.

Enteral nutrition is initiated as soon as possible, usually within hours from hospitalization. A team of certified dietitians estimate nutritional needs daily. Caloric intake is estimated using indirect calorimetry for ventilated patients or the Toronto equation for adult burn victims. Protein intake is maintained at 1.5 g/kg–2 g/kg of body weight. Micronutrients and trace elements are supplemented daily. Propranolol is administered, unless contraindicated, in an attempt to counteract hypermetabolism. All nutritional support is in line with the European Society for Clinical Nutrition and Metabolism guidelines for nutritional therapy in major burns.<sup>14</sup>

Swab cultures from burns are taken whenever there is a clinical impression of wound infection, for example, a new discharge or discoloration samples for pathology and cultures of deep tissue are obtained whenever burn wound excision is performed. All

samples are examined by direct smear and cultured for bacterial cultures (blood agar, CHROMagar Orientation plates and thioglycollate). In cases with suspected fungal elements seen on direct smear, swab samples are plated on CHROMagar Candida plates and tissue cultures on Sabouraud Dextrose Agar plates. All described cultures are qualitative. Blood cultures are obtained in any case of clinical suspicion of systemic infection. Blood cultures are incubated using the BD BACTEC FX system and are evaluated by direct smear when positive signals are received. If fungal elements are seen on direct smear, plating on CHROMagar Candida plates and sabouraud dextrose agar plates is performed.

Antibiotic treatment is administered to patients presenting with systemic signs and symptoms of infection, focal infection not related to the wounds or any evidence of local wound infection providing that deep tissue cultures are positive. Patients with colonization of burn wounds with no other signs of infection are not routinely covered for the bacteria isolated. Similarly, antifungal treatment is administered to patients with invasive fungal infection (isolation from any sterile site or evidence of deep tissue invasion). In cases of mere fungal colonization, the decision to administer antifungal treatment is at the discretion of the treating physician based on clinical impression of active infection. There are no institutional guidelines dictating a change in topical or surgical treatment as a result of a positive burn wound swab. No antibiotic and/or antifungal prophylaxis is routinely administered.

Definitions:

Fungal wound colonization: any isolation of fungus from a superficial burn wound culture.

Fungal deep tissue infection: any isolation of fungus from a culture obtained from deep wound tissue (during burn excision).

Invasive fungal infection: any fungal deep tissue infection and/or candidemia during ICU admission.

ICU length of stay: number of days from admission to first discharge from ICU.

Study groups and outcomes:

Our exposure variable of interest was the presence of fungal colonization in burn wounds. Accordingly, we defined two mutually exclusive study groups by the presence or absence of fungal wound colonization (colonization and no-colonization groups). Our primary outcome was defined as the development of invasive fungal infection during ICU stay. Secondary outcomes were candidemia during ICU stay, deep tissue fungal wound infection, ICU length of stay and ICU mortality.

## Statistical analysis

Standard descriptive statistics were used to summarize population characteristics. We used a  $\chi^2$  test for categorical variables, Mann-Whitney's rank test for non-parametric variables and student's unpaired t-test for normally distributed continuous variables. Multivariate survival analysis using Cox's method was performed under the assumption of proportional hazard, with predicting variables displaying high collinearity, determined as *Pearson's*  $r > 0.7$ , excluded from the model. Mortality was considered as a competing risk. A two-sided  $p < 0.05$  was considered statistically significant for all tests. Only variables found to be significant predictors of the primary outcome on univariate analysis were included in the multivariate model. All calculations were performed using SPSS software V.29.0 (IBM, Chicago, IL).

## RESULTS

A total of 242 patients were included in the final analysis. The median age was 40 (IQR 28–57) and 56 (23%) were women.

**Table 1** Study patients' characteristics

	Not colonized N=203		Colonized N=39		Pv
Females (%)	49	(24.1%)	7	(17.9%)	0.401
Age at ICU admission (median, IQR)	40	(27.6,58)	38	(28.4,52.9)	0.338
Body mass index on admission (kg/m <sup>2</sup> )	25.3	(4.1)	26.4	(4.1)	0.137
Medical history					
Known active malignancy (%)	3	(1.5%)	2	(5.1%)	0.142
Hemodialysis prior to ICU admission	2	(1.0%)	0	(0.0%)	0.534
Diabetes mellitus	12	(5.9%)	1	(2.6%)	0.396
Chronic lung disease	1	(0.5%)	0	(0.0%)	0.661
Chronic treatment with glucocorticoids prior to ICU admission	2	(1.0%)	0	(0.0%)	0.534
Chronic treatment with other immunomodulatory medications prior to ICU admission	1	(0.5%)	0	(0.0%)	0.661
Charlson comorbidity index	3.9	(2.6)	3.4	(2.2)	0.218
Clinical characteristics on admission					
Percent of total body surface area involved (median, IQR)	<b>25</b>	<b>(18,40)</b>	<b>40</b>	<b>(25, 62)</b>	<b>0.002</b>
Facial burn involvement (%)	124	(61.1%)	27	(69.2%)	0.336
Inhalation injury (%)	62	(30.5%)	14	(35.9%)	0.509
Intubated before admission to the ICU (%)	161	(79.3%)	32	(82.1%)	0.696
Admitted to the ICU on vasoactive medications	<b>34</b>	<b>(16.7%)</b>	<b>19</b>	<b>(48.7%)</b>	<b>&lt;0.001</b>
Platelets x1000/ $\mu$ L (SD)	278.2	(126.2)	319.7	(151.7)	0.115
Bilirubin mg/dL (SD)	0.6	(1.0)	0.7	(0.7)	0.674
Mean arterial pressure mm Hg (SD)	<b>93.4</b>	<b>(19.4)</b>	<b>84.1</b>	<b>(19.4)</b>	<b>0.007</b>
Serum creatinine mg/dL (SD)	1.0	(0.7)	1.2	(0.9)	0.103
Sequential organ failure assessment score (SD)	<b>1.6</b>	<b>(1.3)</b>	<b>2.5</b>	<b>(1.7)</b>	<b>&lt;0.001</b>
Clinical course					
Surgical debridement (%)	139	(68.5%)	31	(79.5%)	0.168
Time to surgical debridement (median, IQR)	13	(3,21)	12	(4, 18)	
Skin grafting (%)	120	(59.1%)	25	(64.1%)	0.560
Time to skin grafting (median, IQR)	15	(4,24)	15	(4, 21)	

The baseline characteristics of patients included in the final analysis are presented. All grafts implanted were skin grafts. Only surgical debridement in an operating theater was recorded.  
p values below 0.05 are bolded.  
ICU, intensive care unit.

The median TBSA for the included patients was 25% (IQR 19%–45%), 76 (31.4%) had inhalation injury, 193 (79.7%) were intubated at admission and the median sequential organ failure assessment (SOFA) score was 2 (IQR 1–2.25).

Of the 242 included patients, 221 (87.2%) had their burn wound swab cultured at least once during the hospitalization, with the first swab culture taken a median of 7 days (IQR 4–13 days). Thirty nine (16.1%) were found to have fungal wound colonization and were categorized as the fungal colonization group and 203 (83.9%) did not have fungal wound colonization and were defined as the no-colonization group.

Patients with fungal wound colonization had a significantly higher burn burden (TBSA mean difference (MD) of 14%, 95% CI (7.18 to 20.8)  $p=0.002$ ), lower mean arterial pressure on admission to the ICU (MD 9.3 mm Hg, 95% CI (2.6 to 15.9),  $p=0.007$ ), and higher SOFA scores (MD 0.9 points, 95% CI (0.4 to 1.4),  $p<0.001$ ). We had no data regarding the injury mechanism. The baseline characteristics of the two study groups are summarized in [table 1](#).

### Fungal wound colonization

For the 39 patients who had fungal wound colonization, the median time from ICU admission to first diagnosis of fungal wound colonization was 18 days (IQR 12–26). Burn wounds were colonized with yeasts in 15 (38.5%) patients, molds in 17 (43.6%) and both molds and yeasts in 7 (17.9%) patients.

*Candida albicans* was the most common isolate overall (22 patients, 41% of isolates), and *Aspergillus* spp was the most commonly isolated mold (16 patients, 41.0% of isolates). The microbiological features of the burn wound colonization isolates are detailed in [table 2](#).

### Invasive fungal infections

Overall 40 (16.5%) of the patients in our cohort developed the primary outcome of invasive fungal disease during their ICU stay, 32 (13.2%) developed deep fungal wound infections and 13 (5.4%) candidemia. Deep fungal wound infections occurred at a median of 20 (IQR 15–29) days from ICU admissions, while candidemia cases tended to occur later at a median of 26 (IQR 17–395) days from admission.

Invasive fungal infections were significantly more common in patients with fungal wound colonization compared with those with no prior colonization (82.1% vs 3.9%,  $p<0.001$ ). Similarly, both deep fungal wound infection and candidemia were significantly more common in the fungal wound colonization group (79.5% vs 0.5%,  $p<0.001$ , and 15.4% vs 3.4%,  $p=0.002$ , respectively). The study primary and secondary outcomes are further presented in [table 3](#).

[Table 4](#) summarizes the specific fungal isolates defining invasive fungal infections in each study group. Of the 32 colonized patients who developed deep fungal tissue infection, 30 (93.8%) had concordance between the fungi isolated in superficial and

**Table 2** Fungal colonization characteristics

Time from ICU admission to fungal colonization, days, median (IQR)	18	(12–26)
Yeast colonization		
<i>Candida albicans</i>	16	(41.0%)
<i>Candida tropicalis</i>	4	(10.3%)
<i>Candida parapsilosis</i>	5	(12.8%)
<i>Candida glabrata</i>	0	(0.0%)
Mold colonization		
<i>Aspergillus flavus</i>	7	(17.9%)
<i>Aspergillus fumigatus</i>	8	(20.5%)
<i>Fusarium</i> spp	12	(30.8%)
Mucormycosis	1	(2.6%)
More than one fungal isolate defining colonization	13	(33.3%)
Mixed yeast and mold infection	7	(17.9%)
Characteristics of fungal wound colonization isolates in the fungal colonization group (N=39). ICU, intensive care unit.		

deep cultures. In four patients, candida species were isolated from superficial cultures while deep cultures grew both candida species and molds, in two patients, different types of molds were isolated from the superficial and deep cultures and in one patient superficial cultures grew only molds while deep cultures recovered both molds and candida species. Of the six colonized patients who developed candidemia, four had concordance with the colonizing species, while two patients had different isolates in the wound and in the blood.

To evaluate the impact of fungal wound colonization on clinical outcomes, we conducted Cox's multivariate survival analyses including variables found to be significant predictors of the primary outcome (online supplemental table 1). We found a strong linear correlation between the SOFA score and both mean arterial pressure and use of pressors on admission ( $r^2=0.89$  and  $r^2=0.77$ , respectively). Accordingly, only the SOFA score was eventually entered into the model. Fungal burn wound colonization was found to significantly predict the primary outcome of invasive fungal infection (aHR 25, 95% CI 9.67 to 64.62), after adjusting for age, percent of TBSA involved by burn wounds, SOFA scores, Charlson Comorbidity Index and the presence of

**Table 3** Primary and secondary outcomes

	Not colonized N=203		Colonized N=39		P value
Primary outcome	8	(3.9%)	32	(82.1%)	<0.001
Mean days to any primary outcome (SD)	230.6	41.4	26.1	3.3	<0.001
Deep tissue infection	1	(0.5%)	31	(79.5%)	<0.001
Mean days to deep tissue infection (SD)	376.8	10	33.3	7.4	<0.001
Candidemia	7	(3.4%)	6	(15.4%)	0.002
Mean days to candidemia (SD)	237	42.2	165.9	20.2	0.003
ICU mortality	32	(15.8%)	17	(43.6%)	<0.001
Mean survival in days (SD)	210	28.1	116.1	17.7	<0.001
Median ICU length of stay in days (SD)	19	40.5	61.5	57.6	<0.001
Bacteremia	54	(26.6%)	29	(74.4%)	<0.001
The primary and secondary outcomes of both patient groups (those with and without fungal burn wound colonization) are presented. ICU, intensive care unit.					

**Table 4** Invasive fungal infection characteristics

	Colonized N=32		Not colonized N=8	
Fungemia				
<i>Candida albicans</i>	3	(9.4%)	3	(37.5%)
<i>Candida tropicalis</i>	1	(3.1%)	0	(0.0%)
<i>Candida parapsilosis</i>	2	(6.3%)	3	(37.5%)
<i>Candida glabrata</i>	0	(0.0%)	1	(12.5%)
Deep tissue yeast				
<i>Candida albicans</i>	12	(37.5%)	0	(0.0%)
<i>Candida tropicalis</i>	4	(12.5%)	0	(0.0%)
<i>Candida parapsilosis</i>	5	(15.6%)	0	(0.0%)
<i>Candida glabrata</i>	0	(0.0%)	0	(0.0%)
Deep tissue mold				
<i>Aspergillus flavus</i>	11	(34.4%)	0	(0.0%)
<i>Aspergillus fumigatus</i>	2	(6.3%)	1	(12.5%)
<i>Fusarium</i> spp.	9	(28.1%)	0	(0.0%)
Mucormycosis	2	(6.3%)	0	(0.0%)
Similar to colonization*	30	(93.8%)		
Identical to colonization†	18	(56.3%)		
Median days from ICU admission to candidemia (IQR)	59	42.75, 89.5	17	16.5, 33.5
Median days from ICU admission to deep wound infection (IQR)	19.5	14.25, 28.5	32	n/a
Microbiological characteristics of the invasive fungal infections isolates. *Similar—at least one of the colonizers was invasive. †Identical—all of the colonizers were invasive, and vice versa. ICU, intensive care unit.				

bacteremia. Of note, apart from fungal colonization, SOFA score was the only independent variable maintaining statistical significance (aHR 0.76, 95% CI (0.60 to 0.92)) in the multivariate model. Similar trends were observed for secondary outcomes including deep tissue fungal infection and candidemia. These results are presented in table 5.

With respect to the type of colonizing organism, 18 (81.8%) of the 22 patients colonized with yeasts and 21 (87.5%) of the 24 patients colonized with molds developed deep tissue infections ( $p=0.592$ ). Nine (40.1%) of the patients with yeast colonization and 12 (50%) of the patients with mold colonization died during their ICU hospitalization ( $p=0.536$ ).

Compared with non-colonized patients, patients in the colonization group had longer ICU stay (61.5 (57.6) days vs 19 (40.5) days,  $p<0.001$ ), more days of antibacterial treatment (median 16 (IQR 10–25) vs 5 (IQR 0–16),  $p<0.001$ ), and a higher proportion of them developed bloodstream infections (26.6% vs 74.4%,  $p<0.001$ ). The in-ICU mortality was significantly higher in colonized patients (43.6% vs 15.8%,  $p<0.001$ ).

## DISCUSSION

In this study, 16% of burn patients necessitating an ICU admission went onto develop fungal burn wound colonization. Such colonization was associated with dismal outcomes, including higher mortality, longer ICU stay and significantly higher rates of invasive fungal infections, including deep wound infections and candidemia. While the association between invasive fungal infections and bleak prognosis was established in previous studies,<sup>4 6 8 15</sup> little evidence was thus far published regarding the association of wound colonization and both the hazard of invasive fungal infections and clinical outcomes.

**Table 5** Multivariate analysis

	Primary outcome				Deep tissue				Candidemia			
	HR	95% CI		P value	HR	95% CI		P value	HR	95% CI		P value
		Lower	Upper			Lower	Upper			Lower	Upper	
Fungal burn-wound colonization	25.00	9.67	64.63	<0.001	224.93	28.25	1790.96	<0.001	1.31	1.43	4.05	<b>0.01</b>
Age	1.01	0.99	1.03	0.63	0.99	0.97	1.02	0.57	1.02	0.99	1.05	0.18
Total body surface area affected (%)	1.00	0.99	1.02	0.85	0.99	0.98	1.01	0.34	0.73	0.22	2.43	0.61
Sequential organ failure assessment score	0.76	0.60	0.96	<b>0.02</b>	0.71	0.55	0.93	<b>0.01</b>	1.35	0.94	1.92	0.10
Charlson Comorbidity Index on admission	1.01	0.86	1.18	0.93	1.04	0.84	1.28	0.75	1.04	0.85	1.27	0.74

Variables found to be significant (p of 0.05 or lower) on univariate analysis were incorporated in the multivariate survival analysis as presented.

The main mechanism by which wound colonization increases the risk of invasive fungal infection is most probably direct invasion aided by the loss of physical barrier. This is supported by the high correlation between colonization and invasion isolates seen in our study. Localized immune dysfunction, caused by protracted edema, cytokine release and inflammation,<sup>1,6</sup> further promote the growth and destruction caused by the fungal pathogens. Fungal colonization itself has been shown to be recalcitrant to wound healing, further propagating local bacterial and fungal infection.<sup>3,9</sup> This could explain the significantly higher rate of bacteremia and ICU length of stay in patients with fungal wound colonization. Finally, the systemic immunosuppression of critical illness<sup>16</sup> as a contributor to fungal invasion can be seen in the strong association with SOFA scores on admission, as a measure of general burden of critical illness.

These pathophysiological pathways lend further credence to the understanding that colonization may be an important early marker of future infection, raising in turn the important question whether antifungal treatment for colonization may prevent these unwanted infectious complications. In our study, the result of colonization did not trigger a uniform initiation of antifungal therapy. This study is, therefore, not designed to answer this question and direct interventional studies are warranted.

We defined fungal colonization based on superficial swab culture results, while deep wound infection was diagnosed with biopsy culture results. Previous works have investigated the correlation between these two methods in varying types of injury, including burn wounds.<sup>17–19</sup> Compared with biopsy culture results, swab sensitivity and specificity for bacterial wound infections are reported as 90% and 60%, respectively.<sup>17,20</sup> We found no published evidence describing such metrological performance for fungal cultures. Despite our data showing high concordance between fungal isolates recovered from swab and biopsy cultures, this study was not designed to provide sensitivity and specificity data.

Paucity of evidence exists to support the benefit of antifungal prophylaxis administration in burn injuries. Some guidelines recommend initiation thresholds based on TBSA involvement (above 50% or 30% full thickness) as well as the presence of indwelling devices such as deep arterial or venous lines in the affected area.<sup>21</sup> Others make no specific recommendations for burn wounds but suggest antifungal prophylaxis to be reasonable in multiple and potentially infected surgical wounds.<sup>16</sup> These recommendations are based mainly on expert opinion, with no empirical data to support the effectiveness of antifungal prophylaxis. In our data set, fungal wound colonization performed better in predicting invasive fungal infection than both percentage TBSA involved and the presence of bacteremia. Hence, fungal burn colonization may be a better predictor of

invasive fungal infection optimizing the decision of antifungal prophylaxis.

Our microbiological data are in line with previous reports,<sup>4,6,15</sup> clearly indicating the highest prevalence of *Candida albicans* in both colonization and deep tissue/blood isolates, followed by *Aspergillus* spp. and then non-albicans *Candida* spp. and other molds.

Our study has several limitations inherent to its retrospective single center methodology, impairing the generalizability of our conclusions. Furthermore, our observations support the previously reported notion that patients with fungal wound colonization are sicker and hospitalized longer, suggesting that the association with clinical outcomes may represent a correlation rather than causation. Notwithstanding the innate inability of our retrospective observation to adjust for unobserved confounders, the strong relation between fungal colonization and infection, after adjustment to the most relevant confounders, seems to support at least the role of wound colonization as a harbinger of increased risk. Finally, as wound screening was not performed routinely to our patients, we may have missed some of the fungal colonization cases.

## Conclusions

Our study demonstrates a statistically significant association between fungal burn wound colonization and both invasive fungal infections and clinical outcomes such as mortality and ICU length of stay. Further prospectively randomized interventional studies are needed to elucidate the utility of antifungal therapy directed at superficial fungal burn wound isolates for decreasing such risks.

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**Data availability statement** Data are available upon reasonable request. Full unidentified data is available upon request at ostlyl@gmail.com.

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#### REFERENCES

- 1 Fitzwater J, Purdue GF, Hunt JL, O'Keefe GE. The risk factors and time course of sepsis and organ dysfunction after burn trauma. *J Trauma* 2003;54:959–66.
- 2 Jeschke MG, van Baar ME, Choudhry MA, Chung KK, Gibran NS, Logsetty S. Burn injury. *Nat Rev Dis Primers* 2020;6:11.
- 3 Branski LK, Al-Mousawi A, Rivero H, Jeschke MG, Sanford AP, Herndon DN. Emerging infections in burns. *Surg Infect (Larchmt)* 2009;10:389–97.
- 4 Ballard J, Edelman L, Saffle J, Sheridan R, Kagan R, Bracco D, Cancio L, Cairns B, Baker R, Fillari P, et al. Positive fungal cultures in burn patients: a multicenter review. *J Burn Care Res* 2008;29:213–21.
- 5 Gong Y, Peng Y, Luo X, Zhang C, Shi Y, Zhang Y, Deng J, Peng Y, Luo G, Li H. Different infection profiles and antimicrobial resistance patterns between burn ICU and common wards. *Front Cell Infect Microbiol* 2021;11:681731.
- 6 Murray CK, Loo FL, Hospenthal DR, Cancio LC, Jones JA, Kim SH, Holcomb JB, Wade CE, Wolf SE. Incidence of systemic fungal infection and related mortality following severe burns. *Burns* 2008;34:1108–12.
- 7 Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. *Clin Microbiol Rev* 2006;19:403–34.
- 8 Palackic A, Popp D, Tapking C, Houshyar KS, Branski LK. Fungal infections in burn patients. *Surgical Infections* 2021;22:83–7.
- 9 Moore EC, Padiglione AA, Wasiak J, Paul E, Cleland H. Candida in burns: risk factors and outcomes. *J Burn Care Res* 2010;31:257–63.
- 10 Horta R, Tomaz D, Egipito P, Silva A. The outcome of fungal infections in a burn intensive care unit: a study of 172 patients. *Ann Burns Fire Disasters* 2020;33:101–6.
- 11 Blyth DM, Chung KK, Cancio LC, King BT, Murray CK. Clinical utility of fungal screening assays in adults with severe burns. *Burns* 2013;39:413–9.
- 12 Horvath EE, Murray CK, Vaughan GM, Chung KK, Hospenthal DR, Wade CE, Holcomb JB, Wolf SE, Mason AD Jr, Cancio LC. Fungal wound infection (not Colonization) is independently associated with mortality in burn patients. *Ann Surg* 2007;245:978–85.
- 13 Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, et al. Clinical practice guideline for the management of Candidiasis: 2016 update by the infectious diseases society of America. *Clin Infect Dis* 2016;62:e1–50.
- 14 Rousseau A-F, Lossier M-R, Ichai C, Berger MM. ESPEN endorsed recommendations: nutritional therapy in major burns. *Clin Nutr* 2013;32:497–502.
- 15 Sharma S, Bajaj D, Sharma P. Fungal infection in thermal burns: A prospective study in a tertiary care centre. *J Clin Diagn Res* 2016;10:C05–7.
- 16 Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021;49:e1063–143.
- 17 Rondas A, Schols J, Halfens RJG, Stobberingh EE. Swab versus biopsy for the diagnosis of chronic infected wounds. *Adv Skin Wound Care* 2013;26:211–9.
- 18 Haalboom M, Blokhuis-Arkes MHE, Beuk RJ, Klont R, Guebitz G, Heinzele A, van der Palen J. Wound SWAB and wound biopsy yield similar culture results. *Wound Repair Regen* 2018;26:192–9.
- 19 Sjöberg T, Mzezewa S, Jönsson K, Robertson V, Salemark L. Comparison of surface SWAB cultures and quantitative tissue biopsy cultures to predict sepsis in burn patients: a prospective study. *J Burn Care Rehabil* 2003;24:365–70.
- 20 Gardner SE, Frantz RA, Saltzman CL, Hillis SL, Park H, Scherubel M. Diagnostic validity of three SWAB techniques for identifying chronic wound infection. *Wound Repair Regen* 2006;14:548–57.
- 21 Luo G, Tan J, Peng Y, Wu J, Huang Y, Peng D, Wang X, Hu D, Xie S, Zhang G, et al. Guideline for diagnosis, prophylaxis and treatment of invasive fungal infection post burn injury in China 2013. *Burns Trauma* 2014;2:45–52.

## The clinical impact of fungal colonization of burn wounds in patients hospitalized in the intensive care unit - a retrospective cohort study

### Supplementary material

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## Supplementary Table 1 - Univariate analysis

Presented are the univariate Hazard Ratios for the Primary Outcome calculated based on

Univariate analysis

	Hazard Ratio	lower 95% CI	upper 95% CI	<i>p value</i>
Gender	0.77	0.37	1.57	0.47
<b>Age</b>	1.00	1.00	1.01	<b>0.01</b>
<b>Total Body Surface Area of burn (%)</b>	1.02	1.01	1.03	<b>0.01</b>

Facial involvement of the burn wound	0.82	0.43	1.57	0.56
Inhalation Injury	1.62	0.86	3.05	0.14
Was the patient intubated upon ICU admission	0.49	0.23	1.03	0.06
Was the patient in need of vasopressors upon admission to the ICU	1.00	0.99	1.02	0.68
Active malignancy past 6 months	1.00	0.99	1.02	0.65
Diabetes Mellitus	0.40	0.06	2.94	0.37
Body Mass Index upon ICU admission	0.99	0.92	1.06	0.76
Were broad spectrum antibiotics administered during ICU stay	1.24	0.48	3.21	0.65
Were Carbapenems administered during ICU stay	1.00	1.00	1.00	0.92
<b>Was the burn wound colonized</b>	<b>16.06</b>	<b>7.05</b>	<b>36.60</b>	<b>0.001</b>
Bacteremia during ICU stay	1.14	0.96	1.35	0.16
Need for supplementary O2 upon ICU admission	1.00	0.69	1.46	1.00
SpO2 upon admission	0.94	0.84	1.04	0.21
Platelet count upon admission	1.00	1.00	1.00	0.05
Total Bilirubin upon admission	1.01	0.75	1.35	0.98
MAP upon admission	1.13	0.96	1.34	0.15
SCr upon admission	1.18	0.90	1.54	0.24
<b>Sequential Organ Failure Assessment Score upon admission</b>	<b>0.98</b>	<b>0.97</b>	<b>1.00</b>	<b>0.04</b>
<b>Charlson Comorbidity Index upon admission</b>	<b>1.97</b>	<b>1.01</b>	<b>2.71</b>	<b>0.05</b>



