Incidence of systemic fungal infection and related mortality following severe burns ☆

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ABSTRACT

Advancements in burn care therapy have extended survival of seriously burned patients, exposing burn patients to increased risk of infectious complications, notably fungal infections. We performed a 12-year review of autopsied patients with severe burns for the presence of fungal infection at the US Army Institute of Surgical Research Burn Center between February 1991 and November 2003. The primary goal was to identify the relationship between fungal element noted in autopsy and mortality, and to determine contributing factors that increase a patient's susceptibility to fungal infection. A total of 228 deaths (6.1%) resulted from the 3751 admissions of which 97 underwent autopsy. Fungal elements were identified on histopathology in 44% (43 of 97) of autopsied patients with an attributable mortality of 33% (14 of 43). Aspergillus and Candida were the most frequently recovered fungi, but Aspergillus was recovered in 13 of the 14 cases with fungus identified as an attributable cause of death. The most common sites of infections with attributable mortality were wounds (86%) and the pulmonary system (14%). Total body surface area (TBSA) burn and length of stay (survival after burn) were identified as contributing factors for the incidence of fungal element in autopsy on ROC curve analysis. More severely injured patients with greater %TBSA burn injury and full-thickness burns require a longer recovery period resulting in a longer hospital stay. The propensity for fungal infection increases the longer the wound is present. Therefore, the development of products to close the wound more rapidly, improvement in topical antifungal therapy with mold activity for treating wounds, and implementation of appropriate systemic antifungal therapy may improve outcome for severely injured burn victims susceptible to fungal infections.

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1. Introduction

Advances in the management of burn patients have improved overall care; however, infectious complications remain a major contributor to morbidity and mortality. Improvements in topical antimicrobial therapy, systemic antimicrobial agents, and infection control procedures have primarily focused on the management of bacterial infections. These

interventions have resulted in a decrease in bacterial infections, but fungal infections remain relatively stable [1]. Traditionally, management of fungal infections was limited because of diagnostic challenges and a limited armamentarium of antifungal agents. However, the introduction of novel and less toxic antifungals has ushered in an era of improved fungal care. It has been shown that identification of pathogens purely by histopathogic diagnosis is inadequate due to varying fungal genus and species resistance profiles to antifungals [2]. Other recent publications revealed the clinical importance of adequately managing fungal infections especially at total body surface area (TBSA) burn between 30 and 60% due to increased mortality [3,4]. However, extensive study of the attributable mortality of fungal infections has not been performed. Herein, we report a 12-year review of autopsied patients with burn injuries to identify the attributable mortality due to fungal infections and to determine the potential contributing factors that increase a patient's susceptibility to fungal infection and mortality.

2. Materials and methods

This is a retrospective medical records review of all autopsy reports from burn patients treated at the U.S. Army Institute of Surgical Research (USAISR) Burn Center at Brooke Army Medical Center (BAMC), Fort Sam Houston, TX over a 12-year period (February 1991–November 2003). Only patients with thermal burns were included in the analysis and those without autopsies were excluded. The management strategies for these patients were described previously [3]. Data obtained included cause of death, presence of fungal elements by histopathology and location, autopsy cultures, days to death after burn, age, gender, %TBSA burn, and %full-thickness burn. Patients were divided into two groups depending on the presence of fungal elements during autopsy, and then stratified by time since burn injury. The presence of fungal elements at autopsy is defined by any note of fungal elements within the autopsy report by the pathologist of record. We did not further classify the depth of fungus in the wounds. Fungal cultures were carried out as previously described [2]. Death attributed to fungal infection was based on listed cause of death in the autopsy report. Categorical values were assessed with Pearson χ^2-test, non-normal continuous variables with Mann–Whitney U-test and continuous variables with independent sample t-test. Statistical analysis involving Receiver Operating Characteristic (ROC) curves to determine the efficacy of different variables for predicting outcome were created. This study was approved by the Institutional Review Board (IRB) of BAMC and the USAISR.

3. Results

Two hundred and twenty-eight (6.1%) of the 3751 patients admitted to the burn center during February 1991–November 2003 died. Autopsy was performed on 97 of these patients (42.5%). There was no difference in age, %TBSA burn, %FTB, gender or days from burn to death between those patients who did and those who did not undergo autopsy (data not shown).
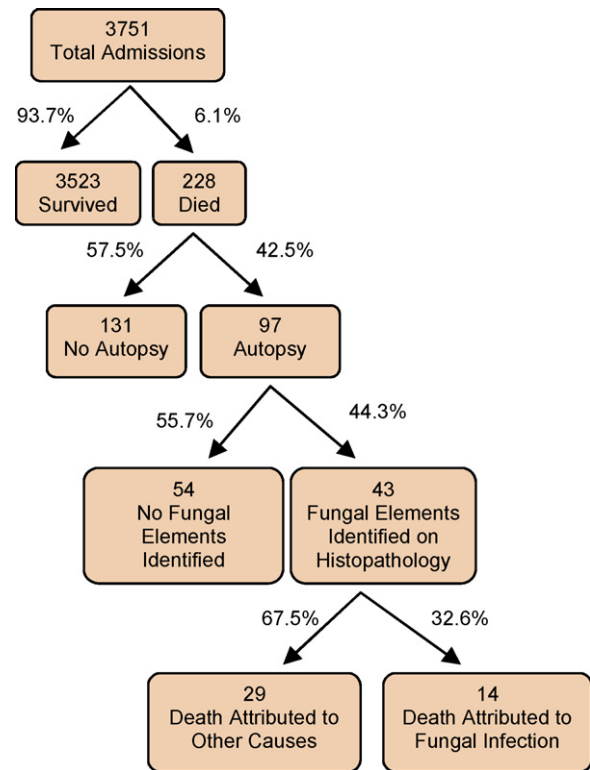

Fig. 1 – Identification of fungal infections in autopsied patients over a 12-year period (February 1991–November 2003).

Of those who underwent an autopsy, the median age was 49.0 (range, 2–95), with 27 women (28%), median TBSA burn of 57.5% (range, 1–97), and median full-thickness burn of 35.5% (range, 0–92). Identification of fungus in autopsied patients is shown in Figs. 1 and 2. There were 43 patients (44.3%) with the presence of fungal elements noted on histopathology in the autopsy report (Table 1). Death was attributable to fungus for 14 (32.6%) of these 43 patients. The median TBSA burn was 65.8% (range, 8–91.5) for those with fungal elements present in autopsy versus 45.0% (range, 1–97) for those without fungus ($p = 0.02$). The median full-thickness burns size was 44.0% (range, 0–91.5) for those with fungal elements identified on autopsy versus 32.0% (range, 0–92) for those without ($p = 0.1$). The median time to death for those without fungus identified at autopsy was 6 days (range, 0.5–89) versus 23 days (range, 1–124) for those with fungus identified ($p < 0.01$). Of those with fungus identified on autopsy, the time to death was a median of 21.0 days (range, 1–114) for those without attributable mortality from fungus and 42.0 days (range, 8–124) for those with attributable mortality from fungus ($p < 0.01$).

Fungal cultures revealed that 33 patients had *Aspergillus*, 22 patients had *Candida*, 7 patients had *Mucor*, 7 patients had *Fusarium*, 3 patients had *Alternaria*, 4 patients had *Penicillium*, 2 patients had *Cladosporium*, 2 patients had *Trichsoporon*, 1 patient had *Cryptococcus*, 1 patient had *Acremonium*, 1 patient had *Coccidioides*, and 1 patient had *Drechslera* (more recently renamed *Bipolaris*). Of those patients with fungal infections listed as one of the attributable causes of death, the anatomical sites were wound (12 cases), pulmonary system
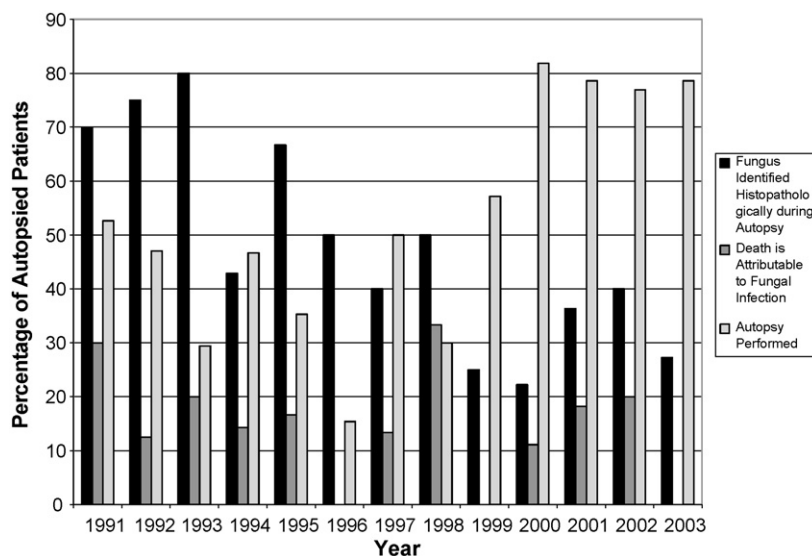
Fig. 2 – Percentage of autopsies performed each year with the presence of fungus and attributable mortality from fungal infection.

(2 cases), abdomen (2 cases), kidney (1 case), fungemia (1 case) and diffuse granulomas from *Coccidioides* (1 case), with some patients having multiple sites. Of the 14 patients who had fungus identified as an attributable cause of mortality, *Aspergillus* was detected on culture or histopathology in 13 of 14 cases (93%) ($p = 0.02$). *Coccidioides* was found in the 14th case. Additionally, fungal pathogens identified along with *Aspergillus* in these 13 cases included *Candida* in 3 patients, *Mucor* in 2 patients, and *Fusarium* in 2 patients.

The presence of fungal elements in autopsied patients appears to increase over time as reflected in arbitrarily determined time windows after burn injury (Table 2). Specifically, the presence of *Aspergillus* and *Candida* was noted to increase over time after the burn injury ($p < 0.01$). Also, patients who survive longer after burn have a greater incidence of fungal infections contributing to death (Fig. 3). Average TBSA burn injury was also greater for patients with fungus. ROC analysis investigating the contributing factors for the incidence of fungal elements during autopsy identified TBSA burn injury and days after burn to death as significant. The area under the ROC curve for this model (Fig. 4) is 0.823 ($p < 0.01$). The following calculation provides a prediction of

fungal elements on autopsy—P(fungal elements) $= e^k/(1 + e^k)$, where $k = -2.206 + (0.021)$TBSA + (0.041) days post-burn. Age, full-thickness burn, and inhalational injury were considered but rejected by the model.

4.   Discussion

Infections remain a primary cause of morbidity and mortality in patients who are burned with fungal infections being among the main pathogens. This study reviewed 97 autopsies over a 12-year period and showed that 44% had fungal elements on histopathology. Fourteen (14%) of the 97 autopsy reports indicated fungal infections were associated with attributable mortality. *Aspergillus* and *Candida* were the most frequently recovered fungi; however, in cases where fungus was an attributable cause of death, *Aspergillus* was recovered in 13 of the 14 cases. The primary sites of infections with attributable mortality were wounds (86%) and pulmonary system (14%). The %TBSA burn injury and length of stay (survival after burn) were contributing factors for the presence of fungi and mortality due to fungus.

Table 1 – Demographics of patients with fungal elements noted on autopsy and the attributable fungal mortality				
	No fungus	Fungus	Fungus; no attributable mortality	Fungus; attributable mortality
Total	54	43	29	14
Age (year)	51 (2–95)	46 (4–91)	50 (4–91)	42 (24–67)
%Male	69	77	76	73
%TBSA burn[*]	45 (1–97)	66 (8–92)	59 (9–90)	76 (8–92)
%Full-thickness	32 (0–92)	44 (0–92)	28 (0–90)	47 (0–92)
After burn (days)[**]	6 (0.5–89)	23 (1–124)	21 (1–114)	42 (8–124)

Median (range).
[*] $p = 0.02$ between fungus and no fungus; $p = 0.04$ between no attributable mortality and attributable mortality.
[**] $p < 0.01$ between fungus and no fungus and between no attributable mortality and attributable mortality.

Table 2 – Demographics of burn patients who underwent autopsies by day after burn				
	Days			
	0–5	6–14	15–28	>28
#Subjects	29	23	22	23
After burn (days)	2 (0.5–5)	10 (6–14)	23 (15–28)	52 (29–124)
Age (year)	58 (2–91)	49 (2–95)	48 (18–85)	38 (4–82)
%Male	66	63	73	82
%TBSA burn	58 (1–96)	41 (7–88)	59 (11–90)	63 (8–97)
%Full-thickness burn[*]	57 (0–92)	123 (0–85)	36 (3–83)	35 (0–92)
%Fungal elements present[**]	10	30	77	74
%Fungal cause of death[***]	0	9	14	43

Median (range); TBSA—total body surface area.
[*] $P = 0.05$ overall across groups.
[**] Number with fungal elements on autopsy increases as duration after burn increases ($p < 0.01$).
[***] Number of fungal deaths increases with increase in groups ($p = 0.02$).

A previous publication from this center revealed that 175 of 2651 (6.9%) patients had fungal wound infection or colonization during an 11-year period [3]. The mortality associated with fungal wound colonization was 27% compared to 76% for fungal wound infections; however, there was no attributable mortality reported. The study found that the impact of fungal infections on mortality was greatest in the 30–60% TBSA burned patients. Overall, the presence of fungal wound infection increased the mortality by an odds ratio of 8.16, which was equivalent to raising the TBSA burn by 33%. Another study by the American Burn Association's Multicenter Trials Group assessed fungal cultures in their population during 2002–2003 [4]. A total of 435 of 6918 patients (6.3%) had the presence of fungi in cultures, with *Candida* being the most commonly recovered fungus (371 patients, 85%), followed by non-*Candida* yeasts (93 patients, 21%) and *Aspergillus* (60 patients, 14%). Overall mortality was associated with increasing age, burn size, number of culture sites, and cultures positive for *Aspergillus* or other mold. The sites most commonly infected in their study were the skin followed by the lungs.

The role of fungal infections cannot be understated in a burn population, especially if *Aspergillus* is recovered, and management decisions must take into consideration the complex nature of fungal infections. A recent publication showed that histology must be augmented with culture due to inaccuracies of histology, the presence of mixed cultures, and to provide definitive identification of fungus to assist in antifungal
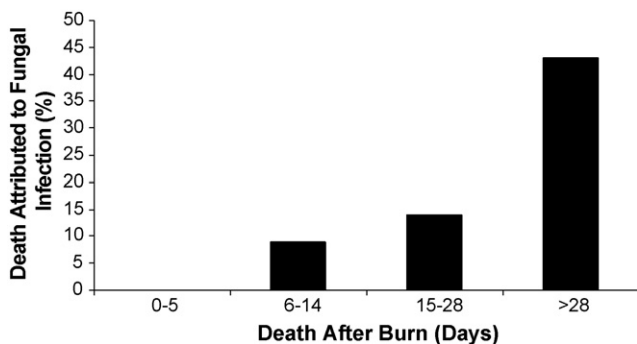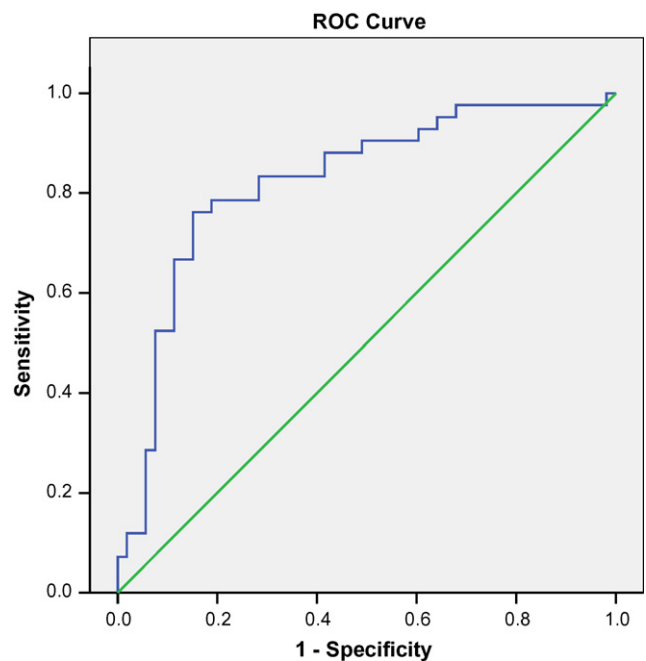

Fig. 4 – ROC Curve using %TBSA burn injury and survival time after burn to predict the presence of fungal elements during autopsy. Area 0.823 ($p < 0.01$).

Fig. 3 – Fungal infections contributing to death in autopsied patients based on survival time after burn.

selection [2]. All fungi are not susceptible to the traditionally used antifungal agent amphotericin B [2,3]. This is true even within the genus of *Aspergillus*, as *Aspergillus terreus* is innately resistant to amphotericin B [5]. Alternative agents are now available to treat fungal infections including the newer azoles (voriconazole and posaconazole) and the echinocandins (anidulafungin, micafungin, and caspofungin). These agents all have their own strengths and weaknesses which include their available formulations (oral or intravenous), their toxicity profiles, efficacy, and drug–drug interactions. Although topical therapy is often implemented in the management of burn wounds, the current topical therapies do not have adequate antifungal activity for *Aspergillus* or other molds [6,7].

The findings in this study on the role of %TBSA with prolonged hospital stays predicting infection emphasizes the

role of adequate infection source control. Early excision has become the standard of care in most burn units; however, the evidence supporting this management strategy is limited. A recent meta-analysis reviewed this literature indicating that in patients without inhalation injury there is a reduction in mortality and duration of hospitalization [8]. The role of early excision and coverage of wounds might be even more important in the prevention of fungal infections because of the challenges with diagnosis and the lack of adequate topical therapies. This study shows that those whose wounds remain open for prolonged periods seem to be at greater risk of fatal fungal infections, not only in the wounds but also in the lungs. This observation intimates that more rapid wound closure, perhaps with alternative technologies, might decrease these risks.

Although this study includes 12 years of burn patient care, there are only 97 autopsies reviewed which included 43% of the patients who died. However, the patients who underwent autopsies at the USAISR are reflective of the entire population that died. Another limitation of this study is the lack of correlation with clinical therapy around the time of death. Further analysis is needed to evaluate the role of therapy including topical agents, systemic antimicrobial agents, and surgical interventions including timing of excision and wound coverage. Finally risk factors that have been reported in other surgical patients need to be investigated in this patient population including age; duration, timing, and spectrum of antimicrobial therapy; ongoing abdominal process; diabetes; nutritional support; steroids; glucose control; immunosuppression; and severe head injuries [9,10]. These analyses should be carried out in prospective controlled trials.

In conclusion, fungal infections were noted to have attributable mortality in this autopsy series of burn patients. The presence of greater %TBSA burn injury and length of stay are important predictors of fungal infections and attributable mortality from fungus. Improved diagnostic strategies and therapies are needed in the care of fungal infections to improve the outcome for severely burned victims.

REFERENCES

[1] Becker WK, Cioffi WG, McManus AT, Kim SH, McManus WF, Mason AD, et al. Fungal burn wound infection: a 10-year experience. Arch Surg 1991;126:44–8.

[2] Schofield CM, Murray CK, Horvath EE, Cancio LC, Kim SH, Wolf SE, et al. Correlation of culture with histopathology in fungal burn wound colonization and infection. Burns 2007;33:341–6.

[3] Horvath EE, Murray CK, Vaughan GM, Hospenthal DR, Wade CE, Holcomb JB, et al. Fungal wound infection (not colonization) is independently associated with mortality in burn patients. Ann Surg 2007;245:978–85.

[4] Ballard J, Edelman L, Saffle J, Sheridan R, Kagan R, Bracco D, et al. Positive fungal cultures in burn patients: a multicenter review. J Burn Care Res 2008;29:213–21.

[5] Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008;46:327–60.

[6] Wright JB, Lam K, Hansen D, Burrell RE. Efficacy of topical silver against fungal burn wound pathogens. Am J Infect Control 1999;27:344–50.

[7] Monafo WW, West MA. Current treatment recommendations for topical burn therapy. Drugs 1990;40:364–73.

[8] Ong YS, Samuel M, Song C. Meta-analysis of early excision of burns. Burns 2006;32:145–50.

[9] Dean DA, Burchard KW. Fungal infection in surgical patients. Am J Surg 1996;171:374–82.

[10] Burchard KW, Minor LB, Slotman GJ, Gann DS. Fungal sepsis in surgical patients. Arch Surg 1983;118:217–21.