Positive Fungal Cultures in Burn Patients: A Multicenter Review

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Fungal infections are increasingly common in burn patients. We performed this study to determine the incidence and outcomes of fungal cultures in acutely burned patients. Members of the American Burn Association's Multicenter Trials Group were asked to review patients admitted during 2002–2003 who developed one or more cultures positive for fungal organisms. Data on demographics, site(s), species and number of cultures, and presence of risk factors for fungal infections were collected. Patients were categorized as untreated (including prophylactic topical antifungals therapy), nonsystemic treatment (nonprophylactic topical antifungal therapy, surgery, removal of foreign bodies), or systemic treatment (enteral or parenteral therapy). Fifteen institutions reviewed 6918 patients, of whom 435 (6.3%) had positive fungal cultures. These patients had mean age of 33.2 ± 23.6 years, burn size of 34.8 ± 22.7%TBSA, and 38% had inhalation injuries. Organisms included *Candida* species (371 patients; 85%), yeast non-*Candida* (93 patients, 21%), *Aspergillus* (60 patients, 14%), other mold (39 patients, 9.0%), and others (6 patients, 1.4%). Systemically treated patients were older, had larger burns, more inhalation injuries, more risk factors, a higher incidence of multiple positive cultures, and significantly increased mortality (21.2%), compared with nonsystemic (mortality 5.0%) or untreated patients (mortality 7.8%). In multivariate analysis, increasing age and burn size, number of culture sites, and cultures positive for *Aspergillus* or other mold correlated with mortality. Positive fungal cultures occur frequently in patients with large burns. The low mortality for untreated patients suggests that appropriate clinical judgment was used in most treatment decisions. Nonetheless, indications for treatment of fungal isolates in burn patients remain unclear, and should be developed. (J Burn Care Res 2008;29:213–221)

Fungal infections are a common cause of morbidity, mortality, and cost in critical care populations, including burns.[1–3] *Candida albicans* is now the fourth most common organism found in blood cultures in intensive care unit (ICU) patients.[4,5] As efforts to control these infections have intensified, isolates of resistant strains and of previously rare fungal species, including non-albicans *Candida*, and molds including *Aspergillus* have been seen with increased frequency.[6–11]

Burn patients are cited as being among the highest-risk groups for invasive fungal infections.[4,10,12–15] Burn wounds provide an ideal portal for invasive infection while also inducing substantial immune dysfunction.[14] In addition, the intensive nature of burn treatment exposes patients to multiple other risks for fungal infection, including central venous lines, urinary catheters, prolonged mechanical ventilation, and broad-spectrum antibacterial agents.[3] Data from the National Nosocomial Infection Surveillance Program demonstrated that burn patients with central venous

*See appendix for complete list of participants and institutions.

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catheters have the highest risk of candidemia of any hospitalized group.[4]

A number of problems with definition and detection make it difficult to determine the true incidence and significance of fungal infections in burn and other ICU populations. First, contamination of urine, respiratory tract, and skin by fungal organisms, particularly *Candida albicans*, can be extremely common. Clear criteria for distinguishing true infections in these settings have been difficult to define.[16–18] Consensus definitions for fungal infections have not addressed burn wounds, and sometimes rely on clinical findings (ie, fever), which may not be discriminatory in burn patients.[19] Recent specific definitions for burn wound infections rely heavily on wound appearance; fungal infections, in contrast, are notoriously difficult to diagnose on clinical evidence alone.[20] Finally, burn centers differ widely in their practices for wound care, thresholds for obtaining cultures, performance of surveillance cultures, and policies for infection control, which suggests that institutions might be expected to report widely differing rates of infection.[21]

Therefore, we thought that the magnitude of the problem presented by fungal infections in burn patients should be more clearly delineated as a first step toward developing better guidelines for surveillance and treatment. To do this, we conducted a multicenter survey of patients with positive fungal cultures to determine the incidence, severity, and consequences of these fungal organisms.

METHODS

The American Burn Association has recently formed a Multicenter Trials Group (MCTG) for conducting clinical research. In 2004, members of the MCTG were invited to participate in this retrospective review of data on patients with positive fungal cultures.

Each participating institution was required to obtain the approval of their institutional review board to participate in the study. Centers were asked to review the records of all patients admitted for acute burn treatment during the period January 1, 2002 through December 31, 2003, to identify any patients who had cultures positive for any fungal species. For each patient identified, data were collected on patient demographics, mechanism and size of injury, presence of inhalation injury, medical conditions, and the number, site, and organism for each positive culture. Additional data on the presence of accepted risk factors, treatment, and outcomes were also collected. Data were de-identified before being sent to a central site for compilation and review.

Burn size was estimated by each center using a standardized Lund and Browder chart. Presence of inhalation injury was determined by each institution, but was generally defined as evidence of inflammation or carbonaceous material on bronchoscopy, or documentation of carbon monoxide intoxication, or clinical evidence of smoke inhalation by history and physical examination.

Treatment Groups

Each patient was classified based on the treatment he or she received for positive fungal cultures. Patients were classified as "untreated" if they received no systemic antifungal agents, received prophylactic nystatin (topical or "swish and spit"), and had no other manipulations (wound excision, removal of central venous catheters, etc) specifically to treat their fungal cultures. Patients were classified as receiving "nonsystemic treatment" if they were treated with other topical antifungal agents, or burn wound excision, or removal of central lines or Foley catheters specifically in response to their fungal cultures. Patients were classified as receiving "systemic treatment" if they were given enteral or parenteral antifungal agents such as Amphotericin B or Fluconazole.

Statistical Analysis

Data on each patient were entered into a spreadsheet using Excel™ (Microsoft Corp, Redmond, WA). Data were analyzed using the program SPSS™ (SPSS Inc, Chicago, IL). In the tables, data are expressed as mean ± standard deviation. However, because many of the values are not distributed normally, data were analyzed using nonparametric statistical methods (Kruskal-Wallis test for k independent samples). *P* values of .05 or less are considered significant.

RESULTS

Fifteen participating burn centers (see Appendix) contributed data on 456 patients who had one or more positive fungal cultures during the period of review. Of these, 21 cases were excluded because they were not initial admissions for acute care, or were nonburn injuries (ie, toxic epidermal necrolysis). The remaining 435 cases form the subject of this review. These cases represent 6.29% of 6918 total admissions reported by these facilities during this period. However, the incidence of positive fungal cultures varied widely, ranging between 0.7 and 24% of the patients treated at individual burn centers.

Patient Population

The study sample had a mean age of 33.2 ± 23.6 years, and 65.1% were male. Inhalation injury was present in 38.2%, and the mean burn size was 34.8 ± 22.7%TBSA, with a mean full thickness injury of 24.4 ± 23.7%TBSA. Flame was the cause of burn injury in 76% of all patients, followed by scald (15%), contact (4%), electrical (3%), chemical (1%) and "other" (1%).

As noted previously, patients were categorized by the type of treatment received for their fungal cultures as "untreated," "nonsystemic" treatment, or "systemic" antifungal therapy. Patient demographics for these groups are contained in Table 1. Groups differed in age, total and full-thickness burn size, and frequency of inhalation injury. In general, patients who received no treatment for fungal cultures were younger, had smaller burns, fewer inhalation injuries, and fewer trips to the operating room than the patients who received systemic treatment. Patients given nonsystemic treatment were younger than those given systemic treatment, and had fewer inhalation injuries, but had roughly equivalent burn sizes. Patients who received systemic treatment had more positive culture sites per patient, as well as a higher incidence of cultures that were positive for more than one fungal species.

Fungal Organisms

The frequency of fungal species in culture results is listed in Table 2. The most common organism cultured was *Candida* species, followed by yeast, *Aspergillus,* and mold. Of note is the fact that 13% of patients had positive *Aspergillus* cultures and 9% cultured mold. In this study, 116 patients (26.7%) had fungal cultures positive for more than one type of fungal organism.

Sites of Infection

The percentage of patients with positive fungal cultures by culture site is illustrated in Figure 1. Fungal cultures obtained from the burn wound comprised over one half of all reported fungal cultures. Respiratory cultures were the second most common culture site followed by urine, blood and other. Surprisingly, fungal urine cultures occurred in only one fifth of the patients in this study. Positive fungal blood cultures occurred in nearly one of every six patients with positive fungal cultures.

One hundred sixty-eight patients (38.6%) had positive cultures from more than one site, and this differed between treatment groups. Among patients with untreated cultures, 33 patients (14.3%) had multiple sites, (mean, 1.3 ± 0.5 positive culture sites per patient), compared with 45% of nonsystemic patients (mean, 1.8 ± 0.9 sites per patient), and 40.2% of systemic patients (mean, 1.9 ± 1.0 sites per patient). These differences were all significant ($P < .05$, Kruskal-Wallis test). Patients who received nonsystemic treatment also had a higher incidence of cultures that were positive for more than one fungal species.

Risk factors for Infection

The incidence of known risk factors for fungal infection is shown in Table 3. Most patients had multiple risk factors identified, including Foley catheters, central lines, and systemic antibacterial treatment. Seventy-four percent of all patients required mechanical ventilation. Nearly one quarter of patients required total parenteral nutrition (TPN), which has widely been associated with risk for fungal infection. Surprisingly, less than 5% of patients had preinjury histories of diabetes. The number of risk factors also differed between groups; untreated patients had the

Table 1. Patient characteristics by treatment groups

	Untreated (n = 231)	Nonsystemic Treatment (n = 20)	Systemic Treatment (n = 184)	Total
Age (yr); mean ± SD*	28.3 ± 23.6	19.4 ± 21.4	40.8 ± 21.7‡§	33.2±23.6
TBSA (%); mean± SD*	27.9 ± 18.7	51.0 ± 22.0‡	41.6 ± 24.6‡	34.8 ± 22.7
Full thickness TBSA (%); mean ± SD*	17.7 ± 18.1	45.7 ± 23.9‡	30.2 ± 26.6‡§	24.4 ± 23.7
Inhalation Injury (%)†	66 (28.6)	6 (30.0)	94 (51.1)	166 (38.2)
Number of OR trips; mean ± SD	3.61 ± 3.4	10.9 ± 10.3‡	7.1 ± 5.6‡	5.4 ± 5.3
Positive sites per patient; mean ± SD*	1.3 ± 0.5	1.8 ± 0.9‡	1.9±1.0‡	1.6 ± 0.8
% Patients with >1 cultured organism†	14.3	45.0	40.2	26.7

* $P < .05$; Kruskal-Wallis test for *k* independent samples.

† $P < .05$; chi square test.

‡ $P < .05$; Mann-Whitney test (vs no treatmentuntreated).

§ $P < .05$; Mann-Whitney test (nonsystemic vs systemic).

Table 2. Fungal organisms cultured

	Untreated	Nonsystemic Treatment	Systemic Treatment	Total
Candida species*†	190 (43.6)	15 (3.4)	166 (38.2)	371 (85.3)
Unspecified yeast	42.0 (9.7)	6 (1.4)	45 (10.3)	93 (21.4)
Aspergillus†	19 (4.4)	6 (1.4)	35 (8.0)	60 (13.1)
Other mold†	14 (3.2)	4 (0.1)	21 (4.8)	39 (9.0)
Other	3 (0.7)	0 (0.0)	3 (0.7)	6 (1.4)
More than one organism†	33 (7.6)	9 (2.1)	74 (17.0)	116 (26.7)

* n (% of total patients). Some patients grew more than one organism.
† $P < 0.05$ chi-square (between all groups).

fewest risk factors per patient followed by the nonsystemically treated, with the systemically treated having the greatest number of risk factors.

Outcomes

Outcome data for all patients, and for survivors, are listed in Table 4. Mortality was significant greater for systemically treated patients. Patients whose fungal cultures were untreated required fewer ventilator days and had shorter lengths of hospitalization than did nonsystemic or systemically treated groups, and this remained true when survivors were evaluated separately. When length of hospitalization was expressed as days per percent TBSA, this was significantly greater for systemically treated patients even when nonsurvivors were excluded.

Patient mortality according to organism(s) cultured is listed in Table 5. Mortality was highest for patients with cultures positive for mold followed by *Aspergillus. Candida* sp. were the most common organisms cultured, but were associated with the lowest mortality rate. Of note is the fact that patients who had positive cultures for mold had a mortality rate of 41%, whereas *Aspergillus* had a mortality rate of 25%.

A logistic regression model was used to examine factors that might have affected mortality in the study sample (Table 6). The model showed that age, burn size, and inhalation injury showed a positive correlation with mortality. Of particular interest was the fact that a positive culture of mold or *Aspergillus* was strongly predictive of death, increasing the odds ratio of death nearly 12-fold.

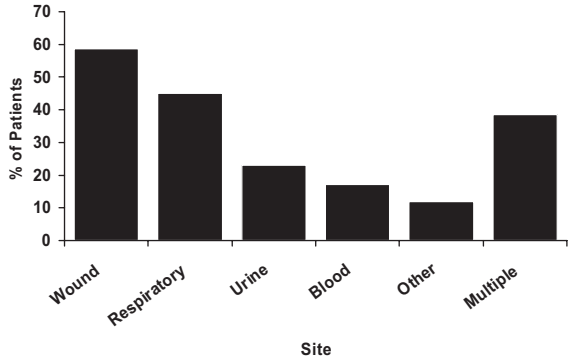

Figure 1. Sites from which fungal organisms were cultured.

Factors affecting survivor length of stay (LOS) were examined using linear regression (Table 7). In this model, total burn size and the number of positive culture sites contributed significantly to LOS, whereas age, gender, treatment group, and presence of inhalation injury did not. Although not significant, each treated fungal culture increased LOS by nearly 8 days. In our model, patients who had fungal cultures positive only for yeast had lengths of stay 21.5 days less than that of patients who had *Aspergillus* or mold cultures only.

DISCUSSION

The present review was conducted to determine the current frequency of fungal infection in burn patients. In doing so, we have confirmed a number of widely recognized observations about these increasingly common infections. However, we also anticipated that our results would illustrate problems that persist in attempting to determine either the true incidence or the consequences of these infections with accuracy, and illuminate several areas in which clinical consensus should be sought.

Fungal infections emerged as a significant clinical problem in burn patients only after the widespread introduction of effective topical antibiotics including mafenide acetate.[22] With the use of these agents, gram negative infections declined throughout the 1970s and 1980s, and fungal contamination of burn wounds became increasingly widespread, occurring in up to 85% of patients.[23] Invasive fungal infections have increased accordingly, now most often caused by previously uncommon organisms including *Aspergillus* and non-albicans *Candida*,[9,24] some of which may have been encouraged by the use of top-

Table 3. Risk factors by treatment group

Risk Factor	Untreated	Nonsystemic Treatment	Systemic Treatment	Total
Foley catheter (%)	81.0	95.0	94.0	87.1
Central line (%)	73.0	95.0	91.3	81.8
Systemic antibiotic (%)	66.7	90	91.3	78.2
Ventilator (%)	61.0	90.0	89.1	74.3
TPN (%)	15.2	20.0	32.6	22.8
Steroids (%)	10.4	10.0	17.4	13.3
Neutropenia (%)	2.6	10.0	9.8	6.0
Diabetes (%)	3.9	10.0	5.4	4.8
None (%)	6.5	0	0	3.4
No. risk factors/patient*	3.28 ± 1.7	4.4 ± 1.1†	4.5 ± 1.2†	3.9 ± 1.6

* $P < .05$ Kruskal-Wallis test for k independent samples.
† $P < .05$; Mann-Whitney test (vs untreated).

ical nystatin prophylaxis.[25,26] Fungal organisms are now among the commonest causes of burn wound infection.[11,22,27,28]

In the present study, 6.3% of all burn patients had at least one positive fungal culture. This is reasonably consistent with previous recent reports.[27] However, for several reasons, the true incidence of fungal contamination or infection in burn patients remains poorly delineated. First, variation in incidence between burn centers was great, ranging from 0.7 to 24.1% of patients. Burn centers differ in their policies both for performing surveillance cultures, and for obtaining site-specific cultures in cases of suspected infections. Reports from centers performing routine surveillance document a much higher incidence of *Candida* contamination.[13,20,23] In addition, fungal infections often fail to manifest specific symptoms to prompt cultures,[8] and they can be difficult to document with cultures even when suspected.[20,29,30] For all these reasons, some centers may be far more likely to detect—and report—positive cultures than others.

Compounding these discrepancies is the lack of widely accepted criteria for distinguishing invasive infections from more frequent fungal contaminants. Some recent efforts have focused on the recognition of fungemia and its appropriate treatment,[29] but less progress has been made in discriminating infections among isolates of sputum and urine, especially those caused by *Candida*.[4,16–18,31] Consensus reviews that have attempted to establish both definitions and indications for treatment of fungal infections in some patient populations have not included burn patients.[19]

In addition, the most important source of fungal infection in burn patients—the burn wound itself—

Table 4. Outcomes for all patients and survivors

	Untreated	Nonsystemic Treatment	Systemic Treatment	Total
Vent days; mean ± SD*				
All patients	13.1 ± 18.7	38.8 ± 43.1‡	37.6 ± 43.3‡	24.6 ± 34.8
Survivors	12.3 ± 18.6	38.3 ± 44.3‡	37.3 ± 45.2‡	23.2 ± 35.0
Hospital days; mean ± SD*				
All patients	45.9 ± 49.5	73.4 ± 42.0‡	73.1 ± 63.2‡	58.7 ± 57.0
Survivors	47.0 ± 51.1	74.6 ± 42.8‡	80.9 ± 67.0‡	61.4 ± 59.5
Days by TBSA; mean ± SD*				
All patients	2.4 ± 3.4	1.6 ± 1.1	2.6 ± 3.9‡	2.5 ± 3.6
Survivors	2.4 ± 3.3	1.6 ± 1.1	2.9 ± 4.3‡§	2.6 ± 3.7
Mortality (%)†	18 (7.8%)	1 (5.0%)	39 (21.2%)	58 (13.3%)

* $P < .05$; Kruskal-Wallis test for k independent samples.
† $P < .05$; chi square test.
‡ $P < .05$; Mann-Whitney test (vs untreated).
§ $P < .05$; Mann-Whitney test (nonsystemic vs systemic).

Table 5. Patient mortality and fungal organism

Organism	Number of Deaths (% of Patients With Positive Cultures for That Organism)	Percentage of All Deaths
Candida	43 (11.6)	74.1
Aspergillus	15 (25).0)	25.9
Mold	16 (41.0)	27.6
Yeast non-*Candida*	14 (15.1)	24.1
Other	1 (16.7)	1.7
Multiple organisms	25 (21.6)	43.1

has often been excluded from evaluations of fungal infections in ICU populations. Burn wounds are known to be a major risk factor for fungal infections[10,12,14,30,32]; the risk increases with burn size[33] and with delay in initial excision of the burn wound.[34,35] Our data reemphasize both the importance of the burn wound as a source of fungal infection and mortality, and the specific difficulties associated with distinguishing invasive infection in this site. Over half of the patients reviewed had fungi isolated from their wounds, and patients with positive cultures had large burns, as expected. Historically, the diagnosis of fungal burn wound infection has required histologic demonstration of fungal hyphae invading viable tissue.[36] However, many modern centers have neither the facilities nor the expertise to perform and interpret tissue biopsies routinely. Criteria for "clinician directed" diagnoses have been suggested, which may prompt clinicians to obtain cultures.[37,38] Even suspected infections can be hard to confirm with cultures, and indications for treatment remain largely empiric.[29,30]

One finding strongly supporting the existence of invasive fungal burn wound infection is fungemia. Positive blood cultures occurred in 17% (76/435) of the patients reviewed here (1.1% of the total 6918 patient screened). Other centers have reported incidences of fungemia varying from 2 to 33% of patients with positive wound cultures.[13,23,33,34] This variation reflects the documented wide variation in culturing practices among centers.[22] In addition, fungemia can occur as a primary infection, particularly associated with central venous lines, in the absence of burn wound infection. Therefore, data on positive blood cultures do not greatly help clarify which positive wound cultures were contaminants.

Table 6. Logistic regression model for mortality

Variable	Odds Ratio	95% Confidence Interval
Age (5-year intervals)	1.08	1.05–1.11
% TBSA (5% intervals)	1.03	1.01–1.06
Inhalation injury	2.55	1.09–6.00
Positive mold culture	11.99	2.37–60.71

Table 7. Survivor hospital length of stay

Variable	Estimate	*P*
Age	0.15315	.1996
% TBSA	1.16392	<.001
Inhalation injury	11.65152	.0548
Number of sites	9.28258	.0126
Number of treated infections	7.75113	.0704
Positive yeast cultures	−21.4631	.0382

Linear regression model ($R^2 = .37$).

In addition to the burn wound, we also confirmed the ubiquity of other risk factors for opportunistic infection, similar to those seen in ICU residents, cancer patients, and transplant recipients. These factors include neutropenia, systemic steroids, central venous access,[39] TPN, hemodialysis, diabetes mellitus, and urinary catheterization.[40] Although the incidence of preburn diabetes was low in our patients, burn-associated hyperglycemia increases the risk of fungal infections; the two conditions may perpetuate each other.[41] The frequent and prolonged administration of broad-spectrum antibacterials such as carbapenems, vancomycin, and aminoglycosides has been linked to fungal infections in burn and other populations,[3,30,40] and, along with central venous catheters, have helped extend the risk of fungemia to groups that have not historically been considered high risk. Almost every patient in our study had more than one of these factors, and they were more common in patients who received systemic treatment. Most of these treatment-related factors are widespread in critical care, and may have served largely as surrogates for critical illness, which in some cases could have been caused by fungal infection. Even so, we were surprised to note that so many of the patients reviewed were receiving TPN or systemic steroids. This may reflect a more widespread "real world" use of these modalities than would be presumed from current recommendations. Alternatively, use of these agents may serve as a marker for unusual severity of illness that prompted clinicians to obtain fungal cultures.

We asked participating centers to indicate what treatment, if any, patients were given for their positive cultures. Over half the patients received no

specific therapy; these patients were younger and had smaller burns than the patients who received systemic antifungal treatment. A few patients had nonsystemic treatment, consisting of removal of suspicious devices or burn excision. We did not ascertain the indications for treatment where it was provided. Although diagnostic criteria for many types of infection have been published,[42] their relevance to burn patients is sometimes limited, and even some well-developed indications (for ventilator-associated pneumonia, for example) are known to be imprecise. Clinical judgment is necessary in deciding to treat any positive fungal culture, even from blood. It was thus impossible to know how appropriate these therapeutic decisions were. However, despite the wide variation in incidence of fungal cultures between centers, the difficulties in discriminating true infections, and the subjective nature of treatment decisions, the significantly lower mortality rate for untreated patients could be interpreted as evidence that clinicians treated most patients appropriately. Patients who received systemic treatment had a higher number of culture-positive sites, which is not surprising given that this is a commonly used indication for treatment. They also had more risk factors for infection, which may have translated to more places from which positive cultures could be obtained. Similarly, their increased incidence of inhalation injury and prolonged duration of ventilatory support almost certainly resulted in more and longer courses of antibacterial treatment, because pneumonia remains a major source of bacterial infections in burn patients,[43,44] and thus increases the risks of secondary fungal respiratory infections. The significantly longer LOS among systemically treated patients helps confirm their more serious illnesses.

It is also unknown how either the emergence or the perceived threat of fungal infections has affected current practice in burn care. We polled contributors to this study regarding some of their antibiotic-usage practices, and received responses from 10 of the 15 participants. Nine responders felt that Sulfamylon™ cream or solution was ineffective against fungal isolates; only two centers avoided use of these agents for that reason, but 9 of 10 stated that they switched to other topical agents when fungi were cultured from burn wounds. None of the centers indicated that they routinely used antibiotic prophylaxis in the early postburn period, though most (8/10) used transient antibiotic prophylaxis perioperatively.

However, these data could also permit alternative interpretations. For example, it is impossible to determine whether patients received systemic treatment because they had serious (and correctly diagnosed) fungal infections, or because their overall more serious condition made clinicians more likely to include antifungal treatment in a "shotgun" approach to therapy. One disturbing finding from this review is the apparently inconsistent response to cultures of *Aspergillus* and other mold. Our data confirmed previous observations that, whereas *Candida* is a frequent cause of burn wound contamination,[37] and by far the most common fungal isolate from patients of all types,[4] the finding of mold or *Aspergillus* is far more ominous. These organisms and more commonly cause invasive infection[27,37] In a review of 2114 patients from the Brooke Army Burn Center, fungi caused 67% of invasive burn wound infections; *Aspergillus* and *Fusarium* caused 68% of these infections.[27] In the present study, a finding of *Aspergillus* or other mold in any site was associated with an almost 12-fold increase in mortality. Thus, the finding of these organisms in any culture should reasonably be considered an indication for aggressive treatment. With this information in mind, it is concerning that slightly less than half the mold and *Aspergillus* cultures reported in this review (43 of 99 cultures) occurred in patients who were not reported as having received systemic treatment. These and other findings certainly fail to demonstrate that current treatment algorithms are optimal.

It is clear that fungal isolates continue to be seen in burn patients with regularity, and they contribute significantly to morbidity and mortality in patients with major burns. We expected to use the results of this review as a starting point both for defining indications for diagnosis and treatment of fungal infections in burn patients and in designing multicenter trials to collect prospective data on this problem. We are continuing to review these data in an attempt to "drill down" on more specific questions. For example, do positive blood cultures, or cultures of mold or *Aspergillus*, mandate treatment? When can cultures of *Candida* from urine or sputum be ignored? Most importantly, can routine prophylaxis be designed which will reduce the incidence of these infections with acceptable complication rates? Ideally, this experience should stimulate the creation of uniform criteria for diagnosis and treatment of fungal isolates, which can then be evaluated prospectively among participating burn centers in the hope of reducing the consequences of these serious infections.

APPENDIX

Facilities and investigators participating in the project

Institution	Location	Investigator(s)	Coordinators
Akron Children's Hospital Burn Center	Akron, OH	Rose Baker, RN	
Bothin Burn Center, Saint Francis Memorial Hospital	San Francisco, CA	Paula C. Fillari, RN	
Emmanuel Hospital Burn Center	Portland, OR	Nathan Kemalyan, MD	Lorraine Donison, RN
Maricopa County Burn Center	Phoenix, AZ	Daniel Caruso, MD	Karen Richey, RN
North Carolina Jaycee Burn Center	Chapel Hill, NC	Bruce Cairns, MD	Mary Kessler, RN
St. Elizabeth's Hospital	Lincoln, NE	David Voigt, MD	Paul Edwards
Shriners Burn Center, Northern California	Sacramento, CA	David Greenhalgh, MD	Johanna Sanders, RN
			Mary Beth Lawless, RN
University of California, Davis, Burn Center			
Shriners Burn Center, Cincinnati	Cincinnati, OH	Richard Kagan, MD	Judy Nelson, RN
University of Cincinnati Burn Center			
Shriners Burn Center, Boston	Boston, MA	Robert Sheridan, MD	Joan Weber, RN
University of Iowa Burn Center	Iowa City, IA	Lucy Wibbenmeyer, MD	Ingrid Newell, MD
University of Montreal Burn Center	Montreal, Canada	David Bracco, MD	Rule Soueida
University of Utah Burn Center	Salt Lake City, UT	Jeffrey Saffle, MD	Linda Edelman, RN
US Army Institute of Surgical Research	San Antonio, TX	Leopold Cancio, MD	Nancy Molter, PhD

REFERENCES

1. Rentz AM, Halpern MT, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. Clin Infect Dis 1998;27:781–8.
2. Swoboda SM, Merz WG, Lipsetta PA. Candidemia: the impact of antifungal prophylaxis in a surgical intensive care unit. Surg Infect (Larchmt) 2003;4:345–54.
3. Cochran A, Morris SE, Edelman LS, Saffle JR. Systemic *Candida* infection in burn patients: a case-control study of management patterns and outcomes. Surg Infect (Larchmt) 2002;3:367–74.
4. Jarvis WR. Epidemiology of nosocomial fungal infections, with emphasis on *Candida* species. Clin Infect Dis 1995;20: 1526–30.
5. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309–17.
6. Trick WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. Clin Infect Dis 2002;35:627–30.
7. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. Clin Infect Dis 2004;38:161–89.
8. Holzheimer R, Dralle H. Managment of mycoses in surgical patients—review of the literature. Eur J Med Res 2002;31: 200–26.
9. Krcmery V, Barnes AJ. Non-albicans *Candida* spp. causing fungaemia: pathogenicity and antifungal resistance. J Hosp Infect 2002;50:243–60.
10. Fridkin SK, Jarvis WR. Epidemiology of nosocomial fungal infections. Clin Microbiol Rev 1996;9:499–511.
11. Nash G, Foley F, Goodwin M, Bruck H, Greenwald K, Pruitt BA Jr. Fungal burn wound infection. JAMA 1971;215: 1664–6.
12. Gelfand JA. Infections in burn patients: a paradigm for cutaneous infection in the patient at risk. Am J Med 1984;76: 158–65.
13. Ekenna O, Sherertz RJ, Bingham H. Natural history of bloodstream infections in a burn patient population: the importance of candidemia. Am J Infect Control 1993;21:189–95.
14. Esposito S. Immune system and surgical site infection. J Chemother 2001;13(Spec 1):12–6.
15. Charles PE, Doise JM, Quenot JP, et al. Candidemia in critically ill patients: difference of outcome between medical and surgical patients. Intensive Care Med 2003;29:2162–9.
16. el-Ebiary M, Torres A, Fabregas N, et al. Significance of the isolation of *Candida* species from respiratory samples in critically ill, non-neutropenic patients. An immediate postmortem histologic study. Am J Respir Crit Care Med 1997;156: 583–90.
17. Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis 2000; 30:14–8.
18. Lundstrom T, Sobel J. Nosocomial candiduria: a review. Clin Infect Dis 2001;32:1602–7.
19. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34:7–14.
20. Petri MG, Konig J, Moecke HP, et al. Epidemiology of invasive mycosis in ICU patients: a prospective multicenter study in 435 non-neutropenic patients. Paul-Ehrlich Society for Chemotherapy, Divisions of Mycology and Pneumonia Research. Intensive Care Med 1997;23:317–25.
21. Hodle A, Richter K, Thompson R. Infection control practices in US burn units. J Burn Care Res 2006;27:142–51.
22. Wheeler MS, McGinnis MR, Schell WA, Walker DH. Fusarium infection in burned patients. Am J Clin Pathol 1981;75: 304–11.
23. Law EJ, Kim OJ, Stieritz DD, MacMillan BG. Experience with systemic candidiasis in the burned patient. J Trauma 1972;12:543–52.
24. Mousa H, Al-Bader S, Hassan D. Correlation between fungi isolated from burn wounds and burn care units. Burns 1999; 25:145–7.

25. Desai MH, Rutan RL, Heggers JP, Herndon DN. *Candida* infection with and without nystatin prophylaxis. A 11-year experience with patients with burn injury. Arch Surg 1992; 127:159–62.
26. Dube MP, Heseltine PN, Rinaldi MG, Evans S, Zawacki B. Fungemia and colonization with nystatin-resistant *Candida rugosa* in a burn unit. Clin Infect Dis 1994;18:77–82.
27. Becker WK, Cioffi WG Jr, McManus AT, et al. Fungal burn wound infection. A 10-year experience. Arch Surg 1991;126: 44–8.
28. Bruck HM, Nash G, Stein JM, Lindberg RB. Studies on the occurrence and significance of yeasts and fungi in the burn wound. Ann Surg 1972;176:108–10.
29. Munoz P, Burillo A, Bouza E. Criteria used when initiating antifungal therapy against *Candida* spp. in the intensive care unit. Int J Antimicrob Agents 2000;15:83–90.
30. Holzheimer RG, Dralle H. Management of mycoses in surgical patients—review of the literature. Eur J Med Res 2002; 7:200–26.
31. Ho KM, Rochford SA, John G. The use of topical nonabsorbable gastrointestinal antifungal prophylaxis to prevent fungal infections in critically ill immunocompetent patients: a meta-analysis. Crit Care Med 2005;33:2383–92.
32. Wenzel RP. Nosocomial candidemia: risk factors and attributable mortality. Clin Infect Dis 1995;20:1531–4.
33. Still J, Belcher K, Law E. Management of candida septicaemia in a regional burn unit. Burns 1995;21:594–6.
34. Sheridan RL, Weber JM, Budkevich LG, Tompkins RG. Candidemia in the pediatric patient with burns. J Burn Care Rehabil 1995;16:440–3.
35. Xiao-Wu W, Herndon DN, Spies M, Sanford AP, Wolf SE. Effects of delayed wound excision and grafting in severely burned children. Arch Surg 2002;137:1049–54.
36. Spebar MJ, Lindberg RB. Fungal infection of the burn wound. Am J Surg 1979;138:879–82.
37. Hart DW, Wolf SE, Chinkes DL, et al. Determinants of skeletal muscle catabolism after severe burn. Ann Surg 2000;232: 455–65.
38. Peck MD, Weber J, McManus A, Sheridan R, Heimbach D. Surveillance of burn wound infections: a proposal for definitions. J Burn Care Rehabil 1998;19:386–9.
39. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2003, issued August 2003. Am J Infect Control 2003;31: 481–98.
40. Tufano R. Focus on risk factors for fungal infections in ICU patients. Minerva Anestesiol 2002;68:269–72.
41. Gore DC, Chinkes D, Heggers J, Herndon DN, Wolf SE, Desai M. Association of hyperglycemia with increased mortality after severe burn injury. J Trauma 2001;51: 540–4.
42. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128–40.
43. Gastmeier P, Weigt O, Sohr D, Ruden H. Comparison of hospital-acquired infection rates in paediatric burn patients. J Hosp Infect 2002;52:161–5.
44. Mayhall CG. The epidemiology of burn wound infections: then and now. Clin Infect Dis 2003;37:543–50.