Fungal Burn Wound Infection

A 10-Year Experience

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To evaluate our experience with fungal burn wound infection, we performed a 10-year review for comparison with our experience with bacterial burn wound infection. During the study period, a marked decline occurred in bacterial wound infection but not in fungal wound infection. Patients with either bacterial or fungal burn wound infection had massive injury, with burn size averaging greater than 50% of the total body surface area. Factors that appear to have markedly reduced bacterial burn wound infection, including patient isolation, topical chemotherapeutic agents, and burn wound excision, do not appear to have had a similar effect on fungal wound infection. The mechanism of spread and colonization of fungi, and the lack of effective topical chemotherapeutic antifungal agents, may explain in part our findings.

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The use of effective topical chemotherapeutic agents to reduce proliferation of microorganisms in the burn wound is one of several burn-specific treatments that have resulted in improved survival of burn patients during the past 50 years. The commonly used topical chemotherapeutic agents (mafenide acetate, silver nitrate, and silver sulfadiazine) have had a major influence in the reduced incidence of gram-negative burn wound infection, which, before the introduction of mafenide acetate in 1964, was the leading cause of death in burn patients treated at our institution. In association with the use of effective topical chemotherapeutic agents, we have noted an increased incidence of "opportunistic" infections of the burn wound caused by yeasts and fungi.

Serious fungal infections are rare in individuals with a normal immune system. They usually occur in patients who are immunosuppressed, either by a disease process or by a therapeutic intervention. Fungal infections are commonly reported in patients who have undergone transplantations and in those with the acquired immunodeficiency syndrome, malignant neoplasms, and severe injuries as well as in critically ill patients who have received antibacterial antibiotic therapy. Burn injury also results in altered immune function, which is reflected in part by the development of anergy, tolerance to skin heterografts, and the decreased responsiveness of peripheral mononuclear cells to mitogenic stimuli. The magnitude of immunosuppression is related to the extent of burn injury. The alterations of immune function in the burn patient, along with the destruction of the skin barrier, appear to increase the susceptibility of the burn patient to fungal infections. A common site of fungal infection in the burn patient is the burn wound, and the most common fungal organisms that cause burn wound infection are those that belong to the classes Plectomycetes (Aspergillus), Blastomyces (Candida), and Zygomycetes (Mucor, Rhizopus).

We performed a 10-year review of our recent experience with fungal burn wound infection. During the same period, we noted a marked reduction in the incidence of bacterial burn wound infection. Herein, we describe the differences in management of bacterial and fungal wound infections and possible explanations for the differences in the incidence of bacterial and fungal burn wound infections during the study period.

PATIENTS, MATERIALS, AND METHODS

During a 10-year period (July 1979 to June 1989), 2114 patients with thermal injury were admitted to our burn center. The medical records and autopsy protocols of the patients were reviewed and form the basis of this study. Of the 2114 patients admitted, 209 (9.9%) developed histopathologically confirmed burn wound infection. Burn wound infection was defined as the histologic identification of microorganisms in viable tissue below or adjacent to the burn wound. With the patient under local anesthesia, biopsy specimens were obtained from areas of the burn wound suspected to be harboring infection (Table 1). The typical appearance of a wound harboring an invasive fungal infection is shown in Fig 1. The diagnosis of burn wound infection was confirmed by histopathologic (frozen-section or rapid permanent-section) examination of the biopsy specimen. A representative microscopic section that shows fungal burn wound invasion is shown in Fig 2. A portion of the biopsy specimen was also sent for culture. Representative samples of surgical and autopsy specimens of the burn wound were also submitted for permanent-section examination. The current scheme used to classify the depth of burn wound...
The causative organism (species) for fungal burn wound infection could not be identified in every case due to the relatively low yield (approximately 30%) of recovery from tissue sample cultures. In those cases in which a causative organism could be identified, either by culture results or by the characteristic morphologic appearance of the organism on microscopic examination, organisms found had the following frequencies: Aspergillus species and Fusarium species, 68%; Candida species, 18%; Mucor species and Rhizopus species, 9.1%; and Mucor species and Alternaria species, less than 5% each.

During the early part of the study period, three patients required amputation of an extremity to control the spread of fungal infection or to completely encompass all infected tissue, including one patient who required a hip disarticulation to control an invasive Mucor burn wound infection. During the last 30 months of the study, 24 patients were identified as having fungal burn wound infection. These patients were treated with antimicrobial chemotherapy of the burn wound during the study period consisted of the alternating application of mafenide acetate in the morning and silver sulfadiazine in the evening. Prophylactic systemic administration of antibiotics was not used. Systemically administered antibiotics were used to treat infections diagnosed clinically or by blood culture. The type of antibiotic initially administered depended on the predominant organism encountered at our burn center at that time. Antibiotic therapy was subsequently guided by patient-specific culture, sensitivity reports, and the patient's response.

When gram-negative burn wound infection was diagnosed, mafenide acetate applied twice daily was used as the sole topical agent.
commonly cause burn wound infection. A rapid histologic environment, serious fungal infections are quite unusual in
the high mortality rate noted in each group: 74.5% in patients of spread from the hospital environment. While the change to
bacterial infection group. The severity of injury is reflected in positive bacteria appear to have an additional, airborne route
burn size of 62.5% of the total BSA in the group with fungal the burn wound appears to be primarily from endogenous
species, Rhizopus species, and Fusarium species combined, decreased the incidence of bacterial burn wound infection in
thrombophlebitis. The incidence of fungal burn wound infection, in contrast,
Aspergillus
organisms caused disseminated fungal infection with the following frequencies: Aspergillus species, 71%; Candida species, 19%; and
Mucor species, Rhizopus species, and Fusarium species combined, 10%. Six of the patients were noted to have fungal
infection developed in only two of these patients, and none re-
quired an amputation to control the fungal infection.
In the 21 patients who died of disseminated fungal disease, the following visceral organs were involved: lungs (15 cases),
heart (12 cases), kidneys (10 cases), brain (four cases), thyroid
gland (one case), and liver (one case). Organisms caused disseminated fungal infection with the following frequencies:
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species, Rhizopus species, and Fusarium species combined,
10%. Six of the patients were noted to have fungal
thrombophlebitis.

**COMMENT**

The patients who developed burn wound infection of either fungal or bacterial origin had massive injury, with an average
burn size of 62.5% of the total BSA in the group with fungal infection and 54.4% of the total BSA in the group with bacteri-
al infection. We also noted a high incidence of inhalation injury: 47% in the fungal infection group and 51% in the
bacterial infection group. The severity of injury is reflected in the high mortality rate noted in each group: 74.5% in patients
with fungal infection and 70.6% in patients with bacterial infection.

Burn wound infection was suspected when there was a characteristic change in the appearance of the burn (Table 1) or when blood cultures were positive for organisms that commonly cause burn wound infection. A rapid histologic technique was used to examine biopsy specimens of the burn
wound to confirm the diagnosis of burn wound infection. Cultures of the burn wound biopsy specimen were performed to assist in the identification of the causative organism but were not used to diagnose burn wound infection.

Burn wound infection, both fungal and bacterial, diagnosed by biopsy specimen and histopathologic examination, was treated with a combination of techniques that have been demonstrated to reduce mortality caused by both types of infection. For bacterial burn wound infection, this included systemically administered antibiotics, subeschar clysis of a semisynthetic penicillin, and the use of an absolute topical chemotherapeutic agent, mafenide acetate. Surgical excision of the involved tissue was performed if the patient's condition permitted. The excised wound was initially covered with a biologic dressing, and placement of autografts was delayed until there was no evidence of residual infection. This was done in an attempt to minimize loss of autograft due to prolif-
eration of microorganisms in the wound bed. Control of the burn wound infection was documented by histopathologic examination of biopsy specimens obtained before surgery or of the tissue excised during surgical débridement of the wound.

Fungal wound infections were treated primarily by wide surgical excision of all infected tissue. Delays in the placement of autografts and use of biologic dressings were similar to that described for bacterial burn wound infection. Previous re-
ports have described the frequent necessity to amputate to completely excise all the infected tissue to control aggressive fungal infections of the extremities. Early identification of fungal infection from biopsy specimens followed by appropri-
ate surgical therapy has decreased the need for amputation to control progressive infection, as only three amputations were required during the study period.

During the study period, there was a marked decrease in bacterial burn wound infection but very little change in the incidence of fungal burn wound infection. The decrease in bacterial burn wound infection occurred in 1983. In 1982-
1983, the protocol at our burn center was changed from an open-ward to an isolation (one bed per room) intensive care unit (ICU). During the opening of the new ICU, an admission and staffing plan was designed to prevent contact between patients admitted to the newly opened ICU and those who had been cared for on the open-ward ICU. The opening of the new facility was associated with the elimination of an endemic strain of Pseudomonas and an overall reduction in gram-

dative isolation techniques, combined with effective topical chemotherapy and early excision and grafting of the burn wound, appear to have markedly decreased the incidence of bacterial burn wound infection in
our unit.

The incidence of fungal burn wound infection, in contrast, remained remarkably stable during the same period. The true fungi are ubiquitous in the environment and can be cultured from heating and ventilation ducts, wound dressing supplies, laundry items, and plants and soil. Candida colonization of the burn wound appears to be primarily from endogenous sources. The spread of endemic strains of gram-negative bacteria occurs primarily via patient-to-patient contact or dissemination by the hospital staff. Fungi, yeast, and gram-
positive bacteria appear to have an additional, airborne route of spread from the hospital environment. While the change to single-bed ICU rooms appears to have been effective in the cessation of miniepidemics of gram-negative burn wound in-
fecction, it has not been as effective in decreasing the spread of fungi, yeast, and gram-positive organisms.

Despite the ubiquitous distribution of fungi in the hospital environment, serious fungal infections are quite unusual in the immunocompetent host. The massive burn injury of the

**Table 3.** Annual Incidence of Burn Wound Infection

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Admissions</th>
<th>Bacterial Burn Wound Infection</th>
<th>Fungal Burn Wound Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979 (0.5 year)</td>
<td>140</td>
<td>9 (6.4)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>1980</td>
<td>225</td>
<td>20 (8.9)</td>
<td>23 (10.2)</td>
</tr>
<tr>
<td>1981</td>
<td>229</td>
<td>12 (5.3)</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>1982</td>
<td>209</td>
<td>12 (5.7)</td>
<td>19 (9.1)</td>
</tr>
<tr>
<td>1983</td>
<td>186</td>
<td>3 (1.6)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>1984</td>
<td>185</td>
<td>2 (1.1)</td>
<td>19 (10.2)</td>
</tr>
<tr>
<td>1985</td>
<td>197</td>
<td>2 (1)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td>1986</td>
<td>206</td>
<td>1 (0.5)</td>
<td>13 (6.3)</td>
</tr>
<tr>
<td>1987</td>
<td>221</td>
<td>3 (1.4)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>1988</td>
<td>223</td>
<td>3 (1.3)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>1989 (0.5 year)</td>
<td>90</td>
<td>1 (1.1)</td>
<td>9 (10)</td>
</tr>
</tbody>
</table>

*Values are number (percent of total admissions).

**Table 4.** Annual Incidence of Disseminated Fungal Disease, 1979-1989

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
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</tr>
<tr>
<td>1980</td>
<td>2</td>
</tr>
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<td>1981</td>
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<td>1988</td>
<td>0</td>
</tr>
<tr>
<td>1989</td>
<td>1</td>
</tr>
</tbody>
</table>

Fungal Burn Wound Infection—Becker et al
patients who developed fungal burn wound infection (62.5% of the total BSA) is associated with alterations in host defense mechanisms, including neutrophil function, lymphocyte subpopulation distribution, and immunoglobulin production. While none of the changes in immune function can be pinpointed as the cause of the increased susceptibility to infection that is observed in burn patients, it is probable that an association exists between these changes and the occurrence of fungal infections in the burn patient. At present, no technique reliably alters the immune system in the burn patient, other than the prevention of complications and the achievement of early wound closure. The use of systemically administered antibacterial antibiotics, which suppress normal flora and appear to increase the risk of fungal infections, should be reserved for documented infections and used only for the period necessary to control the infection.

Topical chemotherapy consisting of mafenide acetate, silver nitrate, or silver sulfadiazine is effective, in both experimental and clinical settings, in decreasing the proliferation of bacteria in the burn wound. No similar topical agent with proved effectiveness in experimental burn models is available to decrease the proliferation of yeast and fungi in the burn wound. Several topical antifungal chemotherapeutic agents may prove to be useful in burn patients. Clotrimazole, applied as a 1% cream, is an effective agent against Candida in patients without burns and is also useful in the treatment of dermal infections caused by dermatophytes; it is not useful in the treatment of systemic fungal infections. Clotrimazole is poorly absorbed through normal skin, and its ability to penetrate the burn eschar is unknown. This agent was used to treat a number of the patients in this study, usually after a biopsy-proved diagnosis of fungal wound colonization (stage 1c) or fungal wound infection (stage 2) was made; it was not applied to the burn wound prophylactically. Nystatin is a polyene macrolide antibiotic similar to amphotericin B. It is available only for topical or oral use because of toxic effects associated with parenteral administration. It is effective against Candida species and most of the true fungi. In one study, nystatin (100 000 U/mL) mixed 1:1 with silver sulfadiazine was believed to effectively decrease the incidence of Candida burn wound infection and septicemia. In that study, the diagnosis of Candida burn wound infection was based in part on culture and not on histopathologic examination of the wound wound. Also, the criteria used to define sepsis were non-specific and did not require proof of infection. The purpose of this study is to test the hypothesis that study alone cannot be used to document the effectiveness of nystatin in the treatment of candidal burn wound infection. Moreover, the clinical effectiveness of nystatin against other fungi in burn patients remains unproved. The possibility that topical antifungal agents, such as nystatin, may interact with and alter or decrease the effectiveness of other topical agents when they are combined must be considered when such drug combinations are used.

Systemically administered amphotericin B should be used to treat patients who are suspected, on clinical grounds, to have disseminated fungal infection, who exhibit evidence of spread of fungal infection beyond the confines of the burn wound, or who have microvascular involvement detected on wound biopsy specimen (stage 2c). The use of amphotericin B may be associated with serious toxic effects, including fever, nephrotoxic effects, electrolyte disturbances, and hypotension. Because of these toxic effects, amphotericin B should not be used to treat patients with localized fungal burn wound infection who do not exhibit evidence of either microvascular invasion or systemic disease. Prompt surgical debridement of the infected tissue should be performed in this setting. Several r' derivative forms of amphotericin B have been developed, including liposomal amphotericin B and amphotericin B methyl ester. These agents may be less toxic than the standard form of amphotericin B and may also offer increased antifungal specificity. Promising results with these derivatives have been obtained in clinical trials. Further evaluation will be necessary to enable widespread clinical use.

Other systemic antifungal agents include fluconazole, micafungin, itraconazole, ketoconazole, and fluconazole and are most often used in combination with amphotericin B in the treatment of systemic fungal infections caused by the Blastomyces. Ketoconazole will penetrate the brain and cerebrospinal fluid and may be useful for fungal meningitis or a brain abscess. Flucytosine is not absorbed from the gastrointestinal tract and may be useful for fungal meningitis or a brain abscess. Fluconazole has proved useful as single-agent therapy in the treatment of disseminated candidal and cryptococcal infections. The effectiveness of these agents either alone or in combination with amphotericin B for disseminated fungal infection caused by the filamentous fungi remains unproved. Our findings emphasize the need to perform histopathologic examination of the burn wound to diagnose the presence of burn wound infection. The yield of fungi from cultures of burn wounds is not high, even when fungi are visible on microscopic sections. Those organisms that are recovered by culture may take days or even weeks to grow, which severely limits the clinical utility of such a culture. Biopsy and frozen-section and rapid permanent-section analysis of the burn wound provide clinically relevant information on the microbial status of the wound and permit prompt institution of appropriate treatment.

Fungal burn wound infection, which currently occurs in approximately 7.5% of our admissions each year, is now the most common infectious complication involving the burn wound at our burn center. Factors that led to a decline in bacterial burn wound infection appear to have had little effect on the incidence of this complication. Early biopsy diagnosis of this complication, followed by the institution of appropriate therapy, primarily surgical debridement of the involved area, appear to have limited some of the adverse consequences of this complication, such as the need for amputation to control the infection and the development of disseminated fungal disease. This is documented by the low incidence of disseminated fungal infection and lack of need for amputation to control fungal infection during the final 30 months of the study period, during which a consistent treatment regimen was utilized. Fungal burn wound infection occurs most often in patients with extensive burn wound injury, who have a high mortality rate related to the extent of injury per se. The development and testing in experimental animal models of effective topical antifungal chemotherapeutic agents, followed by clinical trials of such agents, may enable the burn surgeon to identify means by which the proliferation of fungi in the burn wound can be controlled and the incidence of fungal burn wound infection reduced.

References
section technique to evaluate early burn wound biopsy: a comparison with the rapid section technique. J Trauma. 1985;24:1394-1397.
18. Grogan JB. Altered neutrophil phagocytic function in burn patients.

Discussion

JOHN F. BURKE, MD, Boston, Mass: The Brooke experience is different from that usually reported in that the fungal infections reported in the literature are almost all Candida rather than other forms and were restricted to bloodstream infections with very few burn wound infections. Why does this difference exist? Were the people at Brook making the diagnosis more accurately or was there another reason? Because Aspergillus is a prominent player in the Brooke report, one wonders about the air handling systems, as Aspergillosis is a notorious creator of problems there.

DR AHRENHOLZ: Have the authors identified risk factors in the development of fungal infection? What is the role of serial prospective wound biopsies?

DR LINEAWEAVER: What is your current topical therapy, and what concentration of Dakin's solution was used?

DR WALTER: There are three sources of fungi: leaky plumbing, rugs, and, the major one, air handling. The problems created by fiberglass in ducts and its interaction with high and low humidity are factors to be considered.

DR PECK: What fungal prophylaxis do you employ, and what topical anti-microbial treatment do you use?