Herpesvirus Infections in Burn Patients*

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Herpesvirus burn wound infection was initially described by Scott and colleagues1 over four decades ago. A 2-year-old girl burned her finger on a cigarette and the area was kissed by her mother, who had a history of orolabial herpess. Although the burn appeared to heal, it became blistered 2 days after the injury, and vesicular lesions developed along the hand and arm, from which herpes simplex virus (HSV) was isolated. This case probably represented a primary herpetic whitlow developing in a thermally injured area, and indeed herpetic lesions occurred several times thereafter at the original site of the burn.

Several decades later, the problem of herpesvirus infections in burn victims was noted again, this time by health-care workers at the Brooke Army Medical Center. In a retrospective study, Nash and Foley2 found an approximate 10 percent incidence of necrotizing herpetic lesions involving the larynx or tracheobronchial tree in 97 autopsies of burn patients whose conditions had been undiagnosed antemortem. Lesions were usually focal and associated with superimposed bacterial or fungal infection. Foley et al3 described seven cases of HSV burn wound infection in patients with extensive burns (44 percent to 59 percent body surface area [BSA]), three of whom died during the third week after injury, with visceral HSV involvement manifested principally by necrotizing adrenal and hepatic lesions. The affected burns showed erosive lesions of healing wounds, often complicated by secondary bacterial infection and conversion to full-thickness loss.

Nash et al4 also described a case of primary disseminated cytomegalovirus (CMV) infection in a heavily transfused, severely burned 24-year-old man (70 percent BSA) who died 3 months postburn with multiple invasive fungal infections, acute duodenal ulceration and hemorrhage, and histologic evidence of CMV infection involving multiple organs, especially liver and lung. Subsequently, Seeman and Konigova5 found significant rises in CMV antibody titers in 20 percent of severely burned seropositive patients and also reported several fatal cases of disseminated CMV infection in burn patients.6 Such experiences have served to highlight the potential clinical importance of herpesvirus infections in burn patients. Reviewed herein is published information on the frequency, pathogenesis, clinical spectrum, and responses to antiviral therapy for herpesvirus infections in such patients.

**BURN-RELATED IMMUNOSUPPRESSION**

In addition to destroying cutaneous and mucosal integrity, multiple lines of evidence indicate that burns involving 20 percent or more BSA are associated with suppressed host inflammatory and specific immune responses.7 Although deficits in all parts of the immune system have been described, abnormalities in cell-mediated immune function appear to be of particular relevance to herpesvirus infections. One hypothesis is that immunosuppression is secondary to the formation of toxic or inhibitory substances in burn wounds, and this has provided an argument for early excision of burn tissue.

In animal models, studies using passive cell transfer methods or pharmacologic interventions (eg, cyclophosphamide, prostaglandin inhibitors, H2 receptor antihistamines) have implicated excess suppressor cell activity and host inflammatory mediators in the development of postburn immunosuppression.7 Studies of burn patients have also found various alterations in cell-mediated immunity, including the following: (1) reduced delayed-type skin test reactivity; (2) decreased T-lymphocyte counts with reduced T-helper:T-suppressor ratios and percentages of helper T cells;5,9 (3) decreased in vitro lymphocyte responsiveness to mitogenic and HSV antigenic stimuli;10 (4) decreased T-lymphocyte production of interleukin-2 (IL-2),11,12 (5) decreased natural killer (NK) cell cytotoxicity,13 and (6) diminished antibody-dependent cellular cytotoxicity to HSV-infected cells.14

In general, the magnitude and duration of these abnormalities appear to be related to the severity of the burn. In more severe burns, alterations in T-lym-
phocyte subsets, in vitro production of IL-2, and NK cell activity persist for at least 6 to 18 weeks, and decreased blastogenic responses to HSV and CMV antigens persist for at least 3 and 8 weeks, respectively.\textsuperscript{8-13} It is of note that in vitro decreases in NK cell activity are reversible in cells from some persons by IL-2 and less often by interferon gamma treatment.\textsuperscript{15} However, to our knowledge, the possible clinical value of administering such cytokines has not been studied in controlled trials.

### HSV Infections

Few longitudinal studies on the frequency of laboratory-documented HSV infections have been reported in burn patients (Table 1).\textsuperscript{10,15-17} Although some studies have relied solely on serologic monitoring, which can be confounded by assay insensitivity, inadequate humoral immune responses, incomplete follow-up, and transient antibody rises due to passive transfer from blood products support, these studies have found that one fourth or more of burn patients have evidence of HSV infection. Virus isolation from oropharyngeal secretions, a marker of active virus replication, has been found in 10 percent to 29 percent of patients in whom serial samples have been collected (Table 1). One study\textsuperscript{17} of patients without evident burn wound involvement found that the risk factors for serologically documented HSV infection were facial burn (59 percent infected in those with vs 20 percent infected in those without), inhalation injury (64 percent vs 12 percent), endotracheal intubation (58 percent vs 0 percent), full-thickness burn (50 percent vs 0 percent), hospitalization greater than 3 weeks (50 percent vs 0 percent), and age of 50 years or older (75 percent vs 30 percent). Although this study did not find differences in the frequency of infection in seropositive and seronegative patients based on initial complement fixation antibody titers, the observation that severe burns involving the face and upper respiratory tract are commonly associated with HSV infection provides some evidence that reactivation of infection is occurring in many patients.

The manifestations of HSV infection in burn patients range widely from the relatively common occurrence of asymptomatic shedding, to typical recurrent orolabial disease, to apparently infrequent instances of burn wound infection, to rare cases of visceral dissemination recognized only at autopsy. Because HSV can invade burned areas and produce erosive lesions that may be difficult to distinguish from the original wound, problems with recognition and underreporting are likely. Clinically apparent disease appeared to be uncommon in the reported series (Table 1), so that the risk of virus shedding leading to burn wound involvement could not be assessed accurately.

Since 1970, approximately two dozen cases of HSV burn wound infection have been described in sufficient detail to provide an understanding of their source and clinical characteristics (Table 2).\textsuperscript{3,18-24} Nearly 90 percent of cases have been described in male patients, probably reflecting the higher overall proportion of burns that occur in male subjects. A wide age range has been affected, but about 60 percent of cases have occurred in children younger than 10 years of age, most commonly in those younger than 5 years of age. Although some cases have developed in persons with relatively small burns, most cases have occurred in patients with more extensive burns (mean BSA, 36 percent). More than 85 percent of cases have been associated with burns involving the face and neck area. Approximately 50 percent of affected patients have been seropositive at the time of hospital admission or have had a history of previous orolabial herpes. When virus typing was performed, 90 percent of isolates were shown to be HSV type 1. In other data presented in abstract form only, Tomford and colleagues\textsuperscript{25} found that 30 pa-

### Table 1—Frequency of Laboratory-Documented HSV Infection Occurring in Burn Patients

<table>
<thead>
<tr>
<th>Study, yr</th>
<th>No. of Patients</th>
<th>% Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matthews et al,\textsuperscript{13} 1980</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>Linnemann and Pollard,\textsuperscript{13} 1983</td>
<td>401</td>
<td>8</td>
</tr>
<tr>
<td>24</td>
<td>25</td>
<td>—</td>
</tr>
<tr>
<td>Pollard,\textsuperscript{10} 1985</td>
<td>67</td>
<td>27</td>
</tr>
<tr>
<td>Kagan et al,\textsuperscript{17} 1985</td>
<td>52</td>
<td>40</td>
</tr>
</tbody>
</table>

*Percent of tested patients only. Serologic evidence of infection based on seroconversion or ≥fourfold rise in antibody titer. Minus sign indicates not reported.
†Percent of all patients in study.
‡Retrospective study.

### Table 2—Patient Characteristics in HSV Burn Wound Infections*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No./No. Reported (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male patients</td>
<td>17/19 (89)</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>14/24 (58)</td>
</tr>
<tr>
<td>10-75</td>
<td>10/24 (42)</td>
</tr>
<tr>
<td>Facial/neck burn</td>
<td>18/21 (86)</td>
</tr>
<tr>
<td>BSA</td>
<td></td>
</tr>
<tr>
<td>&lt;15%</td>
<td>4/24 (17)</td>
</tr>
<tr>
<td>15%-68%</td>
<td>20/24 (83)</td>
</tr>
<tr>
<td>Seropositive/history of orolabial HSV</td>
<td>14/18 (78)</td>
</tr>
<tr>
<td>HSV type 1</td>
<td>9/10 (90)</td>
</tr>
</tbody>
</table>

*Data taken from references 3 and 18 through 24.
tients with HSV wound infections all had face or neck burns and that type 1 virus caused all infections.

These observations suggest that most patients experience reactivation of oropharyngeal viral shedding followed by infection of their burn wound. However, no direct genetic analysis of isolates from burn wound and oropharyngeal secretions has proved this presumed route of infection. In addition, in at least four instances, 3,18,20,21 seronegative individuals have experienced apparent primary infections. Exposure to family members with active orolabial herpes has been documented in at least two cases, 18,21 and in one instance, DNA restriction endonuclease studies indicated that two HSV strains were identical, suggesting that nosocomial cross-infection had occurred.25

More than 90 percent of studied cases have been associated with fever, and lesions have usually been detected between 1 and 3 weeks following the initial burn (Table 3). Although the onset of lesions averaged 15 days following the burn, some cases occurred within the first week and approximately one quarter occurred after 3 weeks. Concurrent active orolabial herpes has been described in a minority of patients but is probably both underrecognized and underreported. Areas of active epidermal regeneration are most commonly affected. Healing partial-thickness burns have been involved in more than 80 percent of reported cases, whereas areas of full-thickness epidermal loss appear to be spared. Infection can lead to rapid desquamation of areas of previous epithelialization, with erosive changes and hemorrhage of burn wounds. A Kaposi’s varicelliform-like eruption with vesicles developing around the circumference of the burn wound and subsequent development of erosive lesions has also been described.21,22 Lesions on nonburn skin have been reported in about 20 percent of cases, and uncommonly, donor graft sites or the grafts themselves have been predominantly involved. In one case, 20 extensive herpetic vesiculation developed 5 days postoperatively in chest and abdominal

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Table 3—Clinical Characteristics of HSV Burn Wound Infections*

<table>
<thead>
<tr>
<th>No./No. Reported (%) of Patients</th>
<th>Onset, d</th>
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<tbody>
<tr>
<td></td>
<td>&lt;7</td>
</tr>
<tr>
<td></td>
<td>7-21</td>
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<tr>
<td></td>
<td>22-36</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td>Active orolabial HSV</td>
<td>3/24 (13)</td>
</tr>
<tr>
<td>Partial-thickness burn</td>
<td>20/24 (83)</td>
</tr>
<tr>
<td>Nonburn skin</td>
<td>5/24 (21)</td>
</tr>
<tr>
<td>Donor site</td>
<td>3/24 (13)</td>
</tr>
<tr>
<td>Graft</td>
<td>1/24 (4)</td>
</tr>
</tbody>
</table>

*Data taken from references 3 and 18 through 24.

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autografts, even though the donor sites, oropharynx, and perineal areas were free of lesions. Herpes simplex virus type 2 virus was recovered, and no source of infection was documented. Clinical examples of various manifestations of HSV-related burn wound infections are shown in Figures 1 to 4. When results have been reported, Tzanck smears have been uniformly positive.

The outcome of infection has varied considerably with the series. Initial reports 3 of death due to visceral HSV involvement of the liver, adrenals, and other organs, or due to secondary bacterial infection, have not been confirmed in more recent experience. Overall, more than 80 percent of described patients have healed lesions in a period ranging from 4 to 28 days. 18-24

Intravenous acyclovir therapy has been used in about one third of patients and topical therapy has been used in several others, but the lack of controlled trials makes it difficult to assess whether treatment has influenced the healing of lesions. However, the dramatic clinical improvement in some patients following the institution of systemic acyclovir18 and the
extensive experience in mucocutaneous infections of other immunocompromised patients suggest that this intervention speeds healing. Furthermore, Tomford and colleagues 25 used intravenous acyclovir in 10 of 30 cases of herpetic burn wound infection and reported prompt responses. In contrast, 4 (22 percent) of 18 patients treated with topical acyclovir failed to respond clinically and had to be switched to intravenous therapy. All patients eventually recovered.

Such experiences indicate that documented HSV burn wound or graft site infection should be treated with systemic acyclovir. Similarly, in patients with clinically apparent recurrent orolabial herpes, systemic acyclovir therapy is indicated if the patient has evidence of contiguous spread to upper respiratory tract, esophagus, or head and neck, and may be prudent if there are significant risk factors for herpetic wound infection. However, the risk of developing burn wound invasion among individuals who have localized orolabial lesions or asymptomatic salivary shedding is not defined. Similarly, a possible role for acyclovir prophylaxis in those who are HSV seropositive and at high risk because of extensive burns, with involvement of the face or neck and/or inhalation injury, would require appropriate clinical trials. No data are available to determine whether acyclovir pharmacokinetics are affected, and dose adjustments are required in extensively burned patients.

In summary, relatively few cases of herpetic burn wound infection have been described in the literature, but the usual clinical picture is one of self-limited wound infections occurring several weeks after thermal injury. Areas of active epidermal regenera-
tion, particularly healing partial-thickness burn sites, are typically involved. Intravenous acyclovir treatment has been associated with prompt clinical improvement.

CMV Infections

Longitudinal surveys have also found high frequencies of laboratory evidence of CMV infection in burn patients (Table 4).10,15-17,26,27 Serologic evidence for CMV infection has been found in approximately 20 percent to 40 percent of patients in most series. Although less commonly documented, virus recovery from oropharyngeal secretions or urine has been detected in about 30 percent of patients in several studies (Table 4).10,16 The likelihood of detecting infection depends on multiple factors, including surveillance methods, duration of follow-up, and extent of burn. Up to 85 percent of CMV-seropositive patients with large burns will shed virus if followed up on a sustained basis.10

Cytomegalovirus infection subsequent to burns may be primary, ie, due to exogenous infection of previously uninfected (seronegative) patients, or secondary, ie, due to reactivation of endogenous virus or possible exogenous reinfection in infected (seropositive) patients. Although secondary infections are more common, primary infections have been found in approximately one half of severely burned patients and in about one in five seronegative patients overall (Table 5). The risk factors for CMV infection include transfusion of CMV-seropositive blood products, use of skin allografts from CMV-seropositive donors, immunosuppression related to burns and cyclosporine use, extensive (>30 percent BSA) and full-thickness burns, and prolonged hospitalization (>3 weeks).10,17

Several studies have found that patients who develop laboratory evidence of late-onset CMV infection at 2 to 4 months postburn have received more blood products that those who do not.16,27 Bale et al28 described one case of symptomatic CMV infection that occurred in a seropositive 45-year-old man (55 percent BSA burn) receiving multiple transfusions and cadaveric skin grafts from four CMV-seropositive donors, as well as cyclosporine immunosuppression. The patient had fever and pneumonia without other pathogens during the eighth hospital week, and skin biopsy specimens showed cytomegalic changes. Recovery followed after withdrawal of cyclosporine therapy. Restriction enzyme analysis of the patient’s isolates revealed two distinct infecting strains.

The spectrum of CMV-related illness is broad in burn patients. Most infections appear to be clinically inapparent,27,29-30 but several CMV-related deaths have been reported.1,6 Prolonged unexplained fever and lymphocytosis related to CMV infection may begin at least 1 month postburn and last 1 to 4 weeks.16,31 In addition to infrequent cases of hepatitis, pneumonitis, and gastrointestinal ulceration, direct infection of burn wounds may indicate disseminated infection.31,32 The risk of developing disease is not well characterized but appears to be greater in those developing primary infections. In one series described by Economidou et al,30 three of six CMV-seronegative patients who received only seronegative blood products developed early seroconversions (median, 23 days) and positive urine cultures after receiving cadaveric skin allografts from seropositive donors. Two of these primarily infected patients had apparent CMV disease, one with pneumonia and hepatitis, and the second with fever and gastrointestinal symptoms. Two others developed late seroconversion.

In another case, Ng and Chan35 described a
44-year-old man with 40 percent BSA burn who developed severe bleeding from rectal ulcers at the time of primary CMV infection. Although cultures from multiple sites, including rectum, were negative, the biopsy specimen showed numerous CMV intranuclear inclusions. In addition, a possible association between CMV infection and bacterial infections in burn patients has been suggested in clinical studies.5,30 To our knowledge, the possible efficacy and tolerability of anti-CMV chemotherapy with ganciclovir or foscarnet have not been described in burn patients.

**Varicella-Zoster Virus (VZV) Infections**

Development of varicella in children during treatment for cutaneous burns has been associated with prominent lesions in areas of healing partial-thickness burns and donor sites, perhaps related to unique susceptibility of regenerating epidermal cells.3 In one burn unit outbreak, one index case and all six susceptible contacts aged 1 to 7 years (2 percent to 22 percent BSA) experienced varicella.35 More numerous and deeper lesions, described as punched out, hemorrhagic, and associated with higher rates of secondary infection and scarring, developed in partial-thickness burns and healing donor sites. Losses of some skin autografts but no visceral complications occurred. Weintraub et al35 recommended that susceptible patients should not be admitted to a unit with active varicella cases, that grafting procedures be delayed, if feasible, in patients with active disease until the eruption subsides, and that varicella zoster immune globulin could be considered for prophylaxis in more severely burned susceptible contacts.

More recently, systemic acyclovir therapy, in higher doses than those used for HSV infection, has been found to speed the healing of lesions in varicella of immunocompromised36 and, if initiated within 24 h of rash onset, previously healthy children.37 Oral (20 mg/kg four times daily up to 800 mg per dose) or, in more seriously ill burn patients, intravenous (10 mg/kg/8 h) acyclovir should be administered as soon as possible after lesion onset. Although herpes zoster has been reported in an elderly burn patient,15 no association has been recognized between burn-related immunosuppression and development of VZV reactivation.

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