Infections in Burn Patients

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Systemic sepsis resulting from invasive infection remains the leading cause of death among patients hospitalized with major thermal injury. Prevention of infection and death in burn patients requires a thorough knowledge of the multiple predisposing factors involved and expert application of appropriate diagnostic, supportive, and therapeutic modalities. The improved survival in this population is a result of all of these factors, not any one. It is this principle and the adherence to a treatment program that encompasses all the modalities which are so essential in the care of burn patients if continuing progress is to be made in this field. This article describes the current management of infection and infection control in burn patients. The burn wound and pulmonary system remain the major foci for infection in this population. Less common types of infection include suppurative thrombophlebitis, suppurative chondritis, bacterial endocarditis, urinary tract sepsis, sinusitis, intra-abdominal sepsis, and infections of the eyes. Prophylaxis protocols involve proper control of the environment and an anticipation of bacterial colonization. A number of specific monitoring and treatment guidelines have evolved that have proved effective over the years in minimizing morbidity and mortality.

Infection with systemic sepsis is a major problem in the treatment of burn patients. During the past three decades, the pathophysiology of this process has been more clearly defined and many new therapeutic modalities have been developed. A steady improvement in survival figures has resulted. The size of a burn injury producing 50 percent survival (LA_{50}) has traditionally been used to compare outcomes from different centers and time periods. **Table I** depicts the progression of such survival data from 1949 to 1980. Many centers now report that even patients with extensive burns have a chance of survival [4–6].

The leading cause of death in the burn population remains infection. In Cincinnati, 75 percent of the deaths from burn injuries occurring after five days resulted directly or indirectly from infections [7], whereas 63 percent of the deaths from burn injuries in Birmingham were due to sepsis [8]. **Table II** depicts the causes of 75 deaths in 937 consecutive admissions to the New York Hospital Burn Center over a four-year period. Fifty-four percent were attributed to infection.

Burn patients have profoundly altered host defenses. Many complex alterations in both the cellular and humoral components of the immune systems of burn patients have been described. **Table III** lists some of these various defects, which encompass virtually all phases of the immune system's response. Research in both animals and humans contin-

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TABLE I Survival following Burn Injury (LA_{50}*)

Reference	Year	Age (years)			
		0–14	15–44	45–64	≥65
[1]	1949	51	43	23	9
[2]	1963	48	56	29	—
[3]	1979	62	63	38	23

*LA_{50} is the size of a burn injury producing 50 percent survival.

TABLE II Principal Causes of Death in Burn Patients

Cause	Percent
Irreversible burn shock	15
Smoke inhalation	13
Septic complications	54
Cardiovascular complications	11
Miscellaneous	8

From [3].

TABLE III Immunologic Changes in the Burn Population

Decreased neutrophil phagocytosis [9]
Decreased neutrophil killing ability [9]
Decreased neutrophil chemotaxis [10]
Increased circulating immunosuppressors [11]
Decreased macrophage activity
Decreased lymphocyte response to mitogen stimulation [12]
Decreased T suppressor cells [13,14]
Decreased lymphocyte stimulator interleukin-2 [15,16]
Decreased fibronectin [17]
Decreased gamma globulin [17]

TABLE IV Mainstays of Treatment for Burn Patients

- Early resuscitation and support
- Effective monitoring
- Nutritional support
- Wound care with timely burn wound closure
- Selective antibiotic administration

ues to further define the changes that occur, with the hope of modifying the responses to increase the host's resistance to infection.

At the same time, a growing body of knowledge is developing that describes how various treatment modalities impact on the immune system, namely nutrition, burn wound debridement and excision, topical and systemic antibiotics, and improved resuscitation and monitoring. Although burn wounds produce alterations in immune function, these in turn can be modified by certain supportive measures. Survival of burn patients is improving as a result of all of these modalities, and, thus, the actual impact of any single treatment entity is more difficult to determine. No single therapeutic entity correlates well with reversal of established infection or prevention of septic complications and, therefore, optimum results are only achieved with a full treatment program involving a number of major areas (**Table IV**). It is the complexity of this program and the need for multi-specialty support and personnel that has made the development of burn centers a necessity.

This article reviews infection in burn patients. However, in the course of the discussion, it is assumed that all supportive mechanisms are in place, that the impact on the immune system of the burn patient has not been aggravated by inadequate nutrition or poor wound management, and that the patient is being treated in a properly equipped and staffed burn center. With this in mind, patterns of infection become evident, which are described in detail. Burn patients are also susceptible to some specific infections whose pathophysiology is less well defined. Currently, early recognition of these appears to be the only way to allay morbid consequences.

BURN WOUNDS

Thermal injury destroys the barrier function of skin that prevents the passage of bacteria, fungi, or viruses. The heat of initial injury destroys surface microorganisms. Except for gram-positive organisms located in the depths of the sweat glands or hair follicles, the burn wound is initially free of major bacterial contamination. If topical antimicrobial agents are not used prophylactically to reduce the rate of bacterial proliferation, the wound may become colonized with millions of gram-positive bacteria per gram of tissue within 48 hours. Topical chemotherapeutic agents prevent the rapid development of gram-positive bacterial overgrowth. Gram-negative bacteria typically appear in the wound from three to 21 days after injury. Topical agents appear to slow their proliferation such that although wound sterilization is rarely achieved, the bacterial concentration can be maintained at low levels. If bacterial growth reaches a level of 10^5 organisms per gram of tissue, invasion of viable subcutaneous tissue with bloodstream dissemination is likely [18]. This syndrome is termed "burn wound sepsis." The local manifestations of burn wound sepsis may be minimal or may be accompanied by cellulitis or localized hemorrhagic necrosis. The diagnosis can only be confirmed by histologic examination of a full-thickness biopsy of the wound showing invasion of underlying viable subcutaneous fat and blood vessels by microorganisms.

The mainstay of non-operative treatment in patients in whom surgical management is not indicated remains topical antibacterial agents. Historically, the use of a single topical agent to protect against burn-wound sepsis has uniformly resulted in an initial rise in the LA_{50} in all age groups. With continued prolonged use, the emergence of

resistant microorganisms has resulted in an eventual decline in the LA_{50} in all age groups. The emergence of resistant microorganisms eliminated the improvement in survival initially noted with topical use of Sulfamylon and Silvadene [19,20]. Massive amounts of topical agents continue to be used in treating burn injuries. In 1979, at the New York Hospital Burn Center, 4.4 tons of topical agent were used in treating 340 patients [21]. The emergence of highly resistant strains is a seemingly inevitable conclusion if single agent topical or prolonged inappropriate use is practiced.

Routine prophylactic administration of antibiotics in the immediate post-burn period was originally used to prevent the occurrence of group A beta-hemolytic streptococcal cellulitis. This particular infection is now uncommon in burned patients and easily treated when it occurs. Recent studies have demonstrated that prophylactic penicillin administration is of no benefit and may be dangerous. In a study performed at the University of Washington Burn Center, Durtschi et al [22] found that routine administration of penicillin failed to lower the incidence of early gram-positive cellulitis. Alexander [23] reported an increase in Candida in cultures from the wounds and urine and more serious infections in patients given penicillin prophylaxis. Wickman [24] found that administration of prophylactic penicillin for five to seven days was associated with more rapid emergence of resistant gram-negative organisms. Therefore, systemic prophylaxis with antibiotics early in burn patient management is a practice that although once common has now been abandoned. In centers in which penicillin prophylaxis has been discontinued, there has *not* been an associated increase in the incidence of streptococcal cellulitis [22,23,25].

The majority of burn wound infections are now caused by single strains of gram-negative bacteria. Although Pseudomonas aeruginosa infections were common in the early 1960s, the incidence has now decreased. A large number of other opportunistic gram-negative organisms have replaced P. aeruginosa in importance. Almost all specialized burn facilities occasionally recognize local epidemics of burn wound infection with resistant organisms. These mini-epidemics arise secondary to persistent antibiotic pressure within a burn facility as a result of stereotyped prophylactic therapy [26,27]. The most troublesome organisms have included Enterobacter cloacae [19], Providencia stuartii [28], Serratia marcescens, and Klebsiella.

Both fungal and viral burn wound infections may occur, but fortunately both are extremely rare [29]. The clinical syndrome associated with fungal overgrowth of a burn wound is usually characterized by a rapid, progressive toxemia. The wound often shows a change in color with the center of the wound appearing infarcted. This is surrounded by an area of inflammation characterized by violaceous discoloration. The diagnosis is confirmed by biopsy in which invasion of subcutaneous tissue by broad-based hyphae can be demonstrated. The organisms most commonly implicated in significant invasive infection with subsequent dissemination are Aspergillus, Mucor, Candida, and Geotrichum species.

Fungal infections in burn wounds spread rapidly along fascial planes [26,30]. After the fungus gains access to the bloodstream, distant metastases to the lung, brain, and kidneys are frequently observed. Systemic or topical antifungal agents do not by themselves eradicate the infection in these patients. Survival is dependent on wide excision of lesions on the trunk or head and proximal amputation of extremities that exhibit lesions extending to fascia. Reinspection of excision sites at 48-hour intervals for recurrence is often lifesaving, since recurrence at the margins necessitating further excision may occur.

Viral infections in burn patients are usually caused by herpes simplex, although rare infections with cytomegalovirus may also occur. Infection usually manifests itself by the appearance of small vesicles in reepithelializing second-degree burns followed by loss of superficial epithelium. Secondary bacterial infection often follows in two to three days. Occasionally viremia may occur [31], although most viral infections are self-limiting and usually disappear in seven to 10 days.

To diagnose viral infections in burns, cutaneous lesions are scraped, and the samples are examined under light microscopy for intranuclear inclusion bodies. Systemic dissemination is difficult to confirm, although it should be suspected in patients with characteristic surface lesions, fever, disorientation, and pulmonary changes. Tracheobronchial involvement can be confirmed by cytologic examination of mucus obtained via bronchoscopy. Viral lesions are often found in the peritonsillar areas and under the surface of the tongue. When viral infection leads to death, ulcerated lesions are often demonstrated in the tracheobronchial tree, esophagus, lung, liver, and adrenal glands.

Yeast infections, primarily caused by Candida albicans, may also occur. Clinically, they may produce a cheesy exudate beneath the burn eschar. Candida is rarely invasive through the burn wound. Access to the blood stream usually occurs through the lungs or gastrointestinal tract, or along an intravenous catheter. Wound infections can be easily controlled by adding nystatin to the topical agent in use. Systemic infection is managed as in any other patient with systemic candidiasis.

THE LUNGS

Serious pulmonary compromise is often observed in patients with major burns secondary to the inhalation of incomplete products of combustion. This results in severe tracheobronchitis, leading to destruction of the lower respiratory epithelium with loss of ciliary action, severe bronchospasm, and the development of mucus and cellular

plugs within tertiary bronchi. This favors the proliferation of bacteria in an already immunocompromised host. These bacteria may originate from the burn wound either by hematogenous spread or, more commonly, by aerosolization of bacteria emanating from the wound during physical manipulation of the patient. Before the utilization of topical chemotherapeutic agents and improved wound management techniques, about two thirds of the pulmonary infections in burn patients represented hematogenous dissemination from the wound to the lungs [32]. Hematogenous pneumonia is now relatively infrequent, and most pulmonary infections are bronchopneumonias secondary to the inhalation of organisms into a lung damaged by inhalation injury in an immunocompromised host.

Corticosteroids have been shown to be ineffective in preventing the changes in the lung caused by smoke inhalation and in fact increase morbidity and mortality by increasing the risk of subsequent infection [33,34]. Similarly, aerosolized antibiotics or prophylactically administered systemic antibiotics have no value in patients with inhalation injury and may result in the emergence of resistant organisms [35,36].

LESS COMMON SITES OF INFECTIONS IN BURN PATIENTS

Suppurative Thrombophlebitis. Suppurative thrombophlebitis was, until recently, the third most common infection observed in hospitalized burn patients. It occurred in approximately 5 percent of hospitalized patients with burns exceeding 20 percent of the total body surface area [37]. This problem is associated with the peripheral insertion of synthetic catheters for venous infusions. Many centers have now minimized this complication by changing infusion catheters as well as the site of intravenous insertion every 72 hours.

The diagnosis of septic thrombophlebitis should be considered whenever systemic signs of sepsis are apparent or blood cultures show growth in the absence of an obvious source of infection. This disease is particularly insidious, as the syndrome is rarely accompanied by any local or systemic signs prior to the proliferation of bacteria. Local tenderness of an involved vein, distal edema, or a positive Homans' sign are unusual, and suppuration within a thrombosed peripheral vein may occur weeks after removal of an indwelling venous catheter.

If this problem is suspected, all peripheral veins used for prolonged intravenous infusions must be explored under local anesthesia. A small venotomy is made and the vein is milked in a retrograde fashion. In addition, a small biopsy specimen of the wall should also be taken and examined histologically. The presence of intraluminal pus or bacteria within the intima of the vein confirms the diagnosis. Immediate operative excision of the entire vein is mandatory to prevent a progressive septic course, since "skip" areas, i.e., normal-appearing vessel between two infected portions of vein, may occur.

Suppurative Chondritis. Cartilage has a poor blood supply and when it underlies a full-thickness burn wound, it is prone to infection. The cartilaginous support of the ear is at greatest risk in burn patients, although the costal chondral cartilages and the cartilaginous coverings of the interphalangeal joints of the hands are also frequently affected.

The diagnosis of suppurative chondritis of the ears is made clinically. The patient will exhibit marked tenderness on movement of the pinna of the ear, and asymmetry of the ears is evident due to an increased angle between the ear and the posterior scalp on the involved side. If not treated, suppurative chondritis may progress with invasion of the infecting organisms into the mastoid bone and later development of intracranial abscesses.

The infected cartilage must be excised either by local excision in early cases or by a full bivalving of the ear by an incision along the edge of the helix in more advanced cases. Late reconstruction of the ear is often required following this more extensive procedure.

Bacterial Endocarditis. The incidence of bacterial endocarditis at autopsy in the burn population has been reported to be as high as 0.6 percent [38]. Burn patients are particularly prone to have frequent brief episodes of transient bacteremia that are often associated with debridement or manipulation of the burn wound. Persistent growth of either streptococcal or staphylococcal organisms in blood cultures without an obvious source of infection, or a changing cardiac murmur, should suggest the diagnosis. Echocardiography may confirm the presence of valvular vegetations.

Urinary Tract. Patients with major burns often require indwelling Foley catheters for prolonged periods. Periurethral and prostatic abscesses occasionally occur and are diagnosed and managed as in any other critically ill patient by immediate incision and drainage to prevent systemic spread.

Intra-Abdominal Infection. Intra-abdominal infections rarely occur in burn patients. However, when they do occur, the diagnosis is often delayed because local peritoneal signs are masked by stress levels of circulating corticosteroids, by the presence of burns on the abdominal wall that make physical examination difficult, and by the use of morphine in high doses for analgesia. Although minor stress ulcerations develop in most burn patients during the first 24 hours after burn injury, progression to hemorrhage or perforation is now rare because of the prophylactic use of antacids, better burn wound sepsis control, and improved nutritional support. The sudden onset of distention or paralytic ileus should alert physicians to this potential complication, and appropriate radiographic studies to rule out the presence of free intraperitoneal air should be performed.

Other infrequent causes of intra-abdominal sepsis include acalculous cholecystitis, appendicitis, and pancreatitis. Acalculous cholecystitis, often associated with pro-

longed periods of dehydration and nasogastric suction, is suggested by fullness in the right upper quadrant or the presence of a palpable mass, and is confirmed by abdominal sonography.

Sinusitis and Middle Ear Infections. Burn patients often require prolonged nasotracheal intubation and/or the use of nasogastric tubes for gastric decompression or enteral feeding. Sinusitis or ear infections due to edema and inflammation of the mucosa or the nasopharynx may lead to impaired drainage from sinuses or the middle ear. Persistent unexplained sepsis should prompt an examination of these areas. Treatment is as in patients without burns.

The Eyes. Patients with corneal burns usually secondary to chemical injury are at risk for secondary infection if corneal ulceration or perforation occurs. In the presence of insignificant corneal damage, particular attention should be paid to the prevention of surface drying by instillation of methylcellulose, utilization of topical antibiotic ointments, or performance of tarsorrhaphy. When severe ulceration occurs or perforation of the cornea is incipient, immediate coverage of the defect is mandatory using a conjunctival flap, a corneal transplant, or a protective soft lens.

ROLE OF THE ENVIRONMENT IN BURN WOUND SEPSIS

Seventy to ninety percent of burn wounds are autocontaminated from the patient's own gastrointestinal or respiratory tract. The remainder become colonized due to cross-contamination. However, 65 percent of those wounds that are colonized by cross-contamination develop significant infection, as compared with only 39 percent of those that are autocontaminated [39].

A number of studies have examined the use of bacterially controlled nursing units or laminar airflow systems [39–42]. The efficacy of these systems in the prevention of fatal burn wound sepsis has never been proved by a prospective randomized clinical trial. Installation of such systems is extraordinarily expensive. Furthermore, utilization of such devices may impose a physical barrier to medical surveillance and increase the psychologic distress of patients as a result of isolation. Similar survival and cross-contamination rates are reported from units utilizing careful isolation protocols that require the use of gloves, gowns, hats, and masks when attending patients and that minimize opportunities for wounds to be cross-contaminated in central treatment facilities such as hydrotherapy or physical therapy areas.

SPECIFIC MONITORING AND TREATMENT GUIDELINES

Quantitative biopsy cultures of the burn wound obtained at 48-hour intervals allow constant monitoring of the wound with regard to bacterial proliferation. This has proved to be the only reliable means of predicting burn wound sepsis, since clinical symptoms usually occur too late to effect reversal of progressive sepsis. The technique of burn wound biopsy used by most centers may be summarized as follows [43,44]:

The burn wound surface is sterilized with 70 percent alcohol, since surface bacteria in the burn wound are usually heterogenous and reflect exposure to bacterial fallout from the immediate environment. Full-thickness biopsies measuring 5 × 10 mm are then taken from representative areas of full-thickness injury. The tissue is weighed, homogenized, and then serially diluted before incubation on blood agar plates. At 24 hours, colony counts are performed and the concentrations of organisms are calculated by multiplying the colony count by the number of serial dilutions and dividing the result by the weight of the tissue. Bacterial concentrations of 10^5 organisms or greater per gram of tissue during the first three weeks following the burn injury, or a 100-fold increase in the number of organisms in a 48-hour period, is indicative of incipient burn wound sepsis.

Topical Antibacterial Agents. A wide selection of topical agents is available to inhibit bacterial growth in burn wounds. The four most commonly used agents are listed in **Table V**. In general, each of these agents has advantages and disadvantages, but none to date has fulfilled all of the requirements for an ideal topical agent. With prolonged use of any single agent, resistant organisms inevitably emerge. Use of topical antimicrobial agents has decreased mortality among patients with burns over less than 40 percent of their body surface. However, they have had little effect on mortality among those with larger burns, particularly among those with more than 70 percent of the body surface affected [45]. In most centers today, topical agents are used in association with surgical excision for deeper injuries.

Burn Wound Excision and Closure. Current surgical approaches to early wound closure vary from immediate complete wound excision to the fascia and closure with a combination of autografts and skin substitutes within the first post-burn week [46] to sequential excision and grafting beginning from two to four days after injury and continuing every four to five days until wound closure [47,48]. Early debridement and wound closure increases survival among children with full-thickness burns that involve more than 60 percent of the body surface [46], and some evidence now exists that this type of approach also improves survival in adults [47–49]. Removal of the necrotic eschar appears to reverse many immunologic defects that occur [50,51], and with improved anesthesia support and critical care monitoring, early excision has become increasingly more popular in the past two decades. Burn wounds are at risk for infection as long as they remain open wounds. Timely closure eliminates this risk.

Use of Systemic Antibiotics. The ideal antibiotic is one that rapidly penetrates to the site of the infecting organisms when administered, and is bactericidal, nontoxic, and quickly cleared when no longer required. Unfortu-

TABLE V Topical Chemotherapeutic Agents for Burn Wounds

Agent	Antibacterial Spectrum	Disadvantages
Silver nitrate (0.5 percent)	Most gram-positives organisms, some Pseudomonas strains	Hyponatremia Hypochloremia Failure to penetrate eschar
Silver sulfadiazine (Silvadene)	Most gram-positive and gram-negative organisms	Skin allergy Thrombocytopenia Resistant organisms
Sodium mafenide (Sulfamylon)	Most gram-positive and gram-negative organisms and anaerobes	Painful skin allergy Carbonic anhydrase inhibition Resistant organisms
Povidone-iodine (Betadine)	Gram-positive and gram-negative organisms and fungi	Painful, excessive drying Hyperiodemia syndrome

nately, no such agent is available. Burn patients present a specific problem for treatment of infection in that full-thickness burns are relatively avascular in nature. When avascular tissue becomes infected, the ingress of host defense factors and systemically administered antibiotics may be prevented. Burn injuries and their subsequent treatment create a dynamic pathophysiologic condition that may alter the pharmacokinetic characteristics and subsequent effectiveness of systemic antibiotics [52]. Since the development of assays for serum antibiotic concentrations, it has become apparent that drugs may bind, be inactivated, or be excreted somewhat more efficiently in burned patients than in non-burned patients, resulting in serum levels that are low and often subtherapeutic [53–57]. It is also evident that dosage requirements may vary between similar patients. Whenever a systemic agent is used in burn patients, it is imperative that serum levels be frequently assessed and the dosage schedule adjusted accordingly.

The choice of a systemic antibiotic agent in burn patients is based on a number of considerations including:

- Infecting organism
- Pattern of sensitivity
- Status of the patient
- Impact on the endogenous flora of the unit
- Availability of assay for serum level determination

The various classes of antibiotics have their own characteristic therapeutic properties, side effects, and toxicity. In general, bacterial organisms acquire resistance to antibiotics by chromosomal mutation or by acquisition of extrachromosomal resistance factors or plasmids. Both mechanisms have been demonstrated in burn patients. The tremendous number of organisms present in an infected burn wound may result in a mutant strain acquiring resistance to any single agent. More commonly, the greater risk to burn patients is the acquisition of an organism with a plasmid coded for resistance to multiple antibiotics. Such plasmids may transfer antibiotic resistance from one species to another. Pseudomonas and Enterobacteriaceae are the most likely organisms capable of donating and accepting plasmids. To date, there is no effective way to destroy plasmids and, therefore, clinicians must constantly monitor the environment for the presence of organisms with resistance to multiple antibiotics and must take appropriate measures to discourage cross-contamination of such organisms.

A number of generalizations can be made concerning the choice of an antibiotic agent in burn patients:

- Despite all efforts, burn patients will be exposed to microorganisms.
- No single agent or combination of agents can destroy all the organisms to which burn patients are exposed.
- Treatment involves first identifying the organism responsible for clinical sepsis and then choosing an appropriate agent(s).
- Combinations of antibiotics are not always synergistic or even additive in effect.
- Multi-agent therapy may have the untoward effect of predisposing to superinfection by yeast, fungi, or resistant bacteria.
- Antibiotics should be used long enough to produce an effect but not long enough to allow for superinfection by opportunistic or resistant organisms.
- Dosages must be adjusted on the basis of serum concentrations when serum assays are available.
- In general, since the penetration of systemic antibiotics into burn eschar remains an area not fully studied, they cannot be the only therapeutic modality used to treat burn wound infection.
- Above all, active surveillance of burn patients and of the environment in which they are being treated is mandatory for effective treatment.

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