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C Surgical- and Trauma-Related Infections

314 Burns

Dana M. Blyth and Clinton K. Murray[a]

SHORT VIEW SUMMARY

Definitions
- Burn size can be estimated using the rule of nines in adults and Lund-Browder chart in children.
- Mortality is estimated using the Baux score (sum of age and total body surface area [TBSA]).
- The primary insult from a burn is the wound itself.

Epidemiology
- Annually, 500,000 burn injuries receive medical treatment, and approximately 40,000 require hospitalization, of which >60% require admission to specialized burn centers.
- Of patients sustaining burn injuries, 70% are men, with 30% of patients younger than 15 years of age and 13% 60 years of age or older. The total burn size is less than 10% of TBSA in 78% of cases.
- Increasing burn TBSA is associated with increased mortality: 40% to 49.9% TBSA associated with 28% mortality, 70% to 79.9% TBSA associated with 57% mortality, and greater than 90% TBSA associated with 88% mortality.
- Of the top 10 complications in a 10-year rolling review of patients sustaining fire or flame injury, 7 were infection related, with pneumonia, cellulitis, and urinary tract infections (UTIs) the 3 most common infectious complications.
- Hospital-associated infection rates are improving but are still common in this patient population with high rates of ventilator requirements, indwelling central venous catheters, arterial lines, urinary catheters, and prolonged hospitalizations.
- The time line of bacterial infections in patients with burn injuries is relatively predictable, with skin and soft tissue infections often occurring within the first week, whereas pneumonia, bloodstream infections, and UTIs occur at a median of more than 30 days into hospitalization.

Microbiology
- Bacteria: *Streptococcus pyogenes* was the most frequently recovered pathogen historically; it has been replaced by *Staphylococcus aureus* and gram-negative pathogens such as *Pseudomonas aeruginosa* and Enterobacteriaceae, with higher resistance profiles as patients stay in the hospital longer.
- Fungi: Fungal infections typically involve the skin or lungs. Risk factors for fungal wound infection include older age, greater TBSA, hospital stays longer than 14 to 28 days, diabetes, total parenteral nutrition, prior fungal wound colonization, inhalational injury, broad-spectrum antimicrobial exposure, compressive dressings, and other immunosuppression.
- Viruses: The role of viral infections has not been clearly elucidated in patients with burns but likely includes reactivation, primary infection, or exogenous reinfection of cytomegalovirus, herpes simplex virus, or varicella-zoster virus.

Diagnosis
- Clinical and laboratory diagnosis of infection: Traditional parameters used to detect infection, including temperature, white blood cell count, respiratory status, and heart rate, are not sensitive or specific enough to be used in burn patients. There is limited evidence of the utility of other laboratory parameters such as inflammatory biochemical markers, including C-reactive protein, procalcitonin, fungal screening assays, and numerous cytokines.
- Sepsis criteria: Guidelines unique to diagnosis of burn sepsis with six criteria are used, including temperature, tachycardia, tachypnea, thrombocytopenia, hyperglycemia, and enteral feeding tolerance (see Table 314.1).
- Clinical syndrome diagnosis: Bacteremia, pneumonia, and wound infection (see Table 314.2) are critical factors.

Treatment
- Empirical therapy is based on local (hospital and unit) resistance profiles and pathogens reflective of the time from initial burn injury to recovery of pathogens by culture.
- Antimicrobial dosing reflects the hypermetabolic state associated with burn patients.
- Alternative delivery of antimicrobials in addition to systemic therapy includes limited evidence for subeschar delivery of agents, with some evidence supporting use of inhalational therapy, and a long history of topical delivery of antimicrobials (see Table 314.4).

Prevention
- Early excision and grafting plays a critical role in infection prevention.
- Infection control and prevention is challenging, especially with prolonged hospitalizations.
- Central venous catheters are often associated with infections requiring close monitoring of placement protocols.
- Perioperative and empirical antimicrobials have not been clearly shown to benefit patients but are often used.
- Other strategies to decrease infections have included selective decontamination of the digestive tract and hyperbaric oxygen therapy.

[a]The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the US Department of the Army or Air Force, the US Department of Defense, or the federal government. The authors are employees of the US government, and this work was performed as part of official duties. All material in this chapter is in the public domain, with the exception of any borrowed figures or tables.

BURN INJURY

Injuries due to severe burns rank among the most serious forms of trauma, resulting in anatomic, physiologic, endocrine, and immunologic stresses, especially when burns involve greater than 20% of the total body surface area (TBSA). In 2015 US municipal fire departments responded to an estimated 1.4 million fires, with 3280 nonfirefighter fatalities.[1] Approximately 75% of deaths occur at the scene, primarily because of inhalation of soot or absorption of carboxyhemoglobin in the blood.[2] Annually, 500,000 burn injuries receive medical treatment,

and approximately 40,000 require hospitalization, of which more than 60% require admission to specialized burn centers. Improvements in the care of patients who experience burns, especially initial burn shock resuscitation, have resulted in remarkably improved survival rates to 97% between 2005 and 2014.[1,3,4] In the 1970s a 50% survival was seen after a 30% TBSA burn compared with comparable survival with an 80% TBSA burn at the present time.[5]

The primary insult from a burn is the wound itself, which has three characteristic areas of involvement.[6] The first burn wound area is the zone of coagulation nearest the heat source and includes dead tissue forming the burn eschar. Adjacent to the necrotic tissue in the zone of coagulation is the second area, known as the zone of stasis, which is viable but at risk of ischemia because of perfusion defects. The zone of hyperemia is the third area, which consists of relatively normal skin with increased blood flow, vasodilation, and minimal cellular injury. Overall the primary concern of burn wound injuries is the burn wound eschar, with its avascular nature preventing immune cells and systemically administered antibiotics from being delivered.[7,8] The rule of nines is often used in adults to estimate the surface area of a burn. Using this formula, the head and neck and each arm are 9% of the TBSA; the anterior trunk, posterior trunk, and each leg are 18%; and the genitalia and perineum are 1%. The Lund and Browder chart, which adjusts the values of the legs and head according to age, is used for children.[9]

TYPES OF INJURIES ADMITTED TO BURN CENTERS

There are several mechanisms that result in burn injuries in addition to thermal burns that cause cellular damage based on duration and temperature of exposure. Chemical burns can involve reducing agents such as hydrochloric acid, oxidizing agents such as sodium hypochlorite, and corrosive agents such as phenol, all with varying modes of action resulting in burns. Other burn mechanisms include scalding (more common in children), contact with hot objects, electrical injuries, and radiation. Burn units also manage certain skin disorders such as Stevens-Johnson syndrome. During the years 2005–2014 hospital admissions to burn centers were largely related to fire/flame or scald injuries in 43% and 34% of cases, respectively, with the remaining from contact of a hot object in 9%, electrical in 4%, chemical in 3%, and 7% other.[10]

EPIDEMIOLOGY

Survival in Burn Injury

The American Burn Association (ABA) maintains a national burn repository that provides a 10-year rolling review of ongoing data collected from 96 hospitals in 36 states and the District of Columbia.[11] For the period 2006–2015 almost 70% of patients were men. There is a bimodal distribution of burn injuries, with 30% occurring in children 1 to 15 years of age and 54% occurring in adults 20 to 59 years of age. A further 13% of patients were 60 years of age, and 2% of patients were 80 years of age or older. Approximately three-quarters of burns involved 10% TBSA or less, with a mortality of 0.6%. Increasing burn TBSA was associated with increased mortality: 40% to 50% TBSA associated with 28% mortality, 70% to 80% TBSA associated with 57% mortality, and greater than 90% TBSA associated with 88% mortality. Overall mortality rate was 3.3%. Mortality was 5.8% for fire or flame injuries, the most common cause of burn, and was dramatically increased within this cohort by the presence of inhalation injury. The importance of age in relation to mortality of burn patients is emphasized by the Baux score (sum of age and TBSA). A Baux score of 80 to 90 is associated with a mortality of 12%, and mortality increases to almost 50% with a Baux score of 100 to 110.[11]

Overall, predictors of mortality are extremes of age, percentage of TBSA, presence of full-thickness burns, and inhalational injury, with some data supporting sex-dependent differences. For survivors, the average length of hospitalization is slightly more than 1 day per TBSA percentage burned.[11–17] Improvements in the morbidity and mortality associated with burns over the last 50 years have been attributed to early excision and grafting, external thermal regulation, early enteral feeding, use of anabolic agents, therapeutic exercise, advances in burn shock resuscitation, airway management and ventilatory strategies, and infection-control practices.[3,18–23]

Infectious Complications of Burn Injury

If patients survive the initial burn and resuscitative phase, infections are a leading cause of mortality (75% of cases).[19,24–28] Seven of the top 10 complications in the 10-year rolling review of patients experiencing fire or flame injury were infection-related, with pneumonia, cellulitis, and urinary tract infections (UTIs) being the 3 most common complications. Risk factors included older age for UTIs, scalds and burns from contact with a hot object for wound infections and cellulitis, and inhalational injury and mechanical ventilation for longer than 4 days for pneumonia.[11,29–32]

Infection preceded multiorgan dysfunction by a median of 4 days, with increasing mortality based on severity of sepsis and a mortality odds ratio of 12.5 for septic shock versus uncomplicated sepsis.[24] Primary sites of infection are the bloodstream, lungs, wounds, and urinary tract, with either lungs or wounds the most common, depending on the diagnostic definitions used.[24,33–36] Infected patients tend to be older, female, and intubated, with higher-percentage TBSA burns, longer lengths of stay, more central venous and arterial catheters, and more operations.[33] Outcomes appear worse with polymicrobial infections.[37,38] The National Healthcare Safety Network indicated that burn units have the highest rates for catheter-associated UTIs (4.8 per 1000 catheter-days) and central line–associated bloodstream infections (2.9 per 1000 central line–days) and among the highest rates for infection-related ventilator-associated complications (2.93 per 1000 ventilator-days).[39,40] Despite improvements over historical rates, these rates remain higher than predicted even when applying the standardized infection ratio, which attempts to account for various facility and patient factors that may affect health care–associated infections.[41] Endocarditis occurs in approximately 0.4% of burn unit admissions and in 9% of patients with persistent bacteremia.[42]

MICROBIOLOGY

Pathogenesis and Microbial Evolution of Burn Wound Colonization and Infection

Severe burns cause a mechanical disruption of the skin, allowing microbes to penetrate deeper tissues.[43] At the time of the burn, the normal skin structure is replaced by a moist, protein-rich, avascular eschar that is an ideal environment for microorganisms. Typically the burn surface is sterile immediately after thermal injury, but after 48 hours, the wound is colonized with skin pathogens that typically reside in sweat glands and hair follicles before the burn.[44–46] Although *Streptococcus pyogenes* was the most frequently recovered pathogen historically, this has been replaced with *S. aureus* and gram-negative pathogens, with higher resistance profiles as patients stay in the hospital longer.[47–54] A retrospective study of wound cultures obtained within 24 hours of injury revealed positive cultures in 32% and that the only independent risk factor for early gram-negative colonization was percentage TBSA. Methicillin-resistant *S. aureus* and multidrug-resistant (MDR) gram-negative pathogens were rare.[55] After 5 to 7 days, wounds become colonized with yeast or gram-positive and gram-negative bacteria from the host's normal gastrointestinal and upper respiratory tracts or from the hospital environment and health care workers' hands.[44–46,56–64]

A more recent meta-analysis called into question the traditional teaching that burn wound infection microbiology is center-specific, as 60% of burn wound infections were associated with gram-negative organisms, with *P. aeruginosa* being the most common gram-negative organism, followed by *Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp., and *Proteus* spp.[65] However, international guidelines still recommend development and use of an antimicrobial stewardship program incorporating a specific local antibiogram with resistance rates within the burn population.[54,66] Rates of *Clostridioides difficile* (formerly *Clostridium difficile*) infections in the burn intensive care unit (ICU) are lower than in other ICUs, but that may be reflective of patient populations.[67] Although anaerobic bacteria are noted in numerous wound studies, they do not appear to be associated with systemic infections such as bacteremia.[68]

Fungal Colonization and Infection Following Burn Injury

Numerous fungal agents are associated with burn injuries, including *Aspergillus, Candida* (with increasing rates of non-*albicans Candida* spp.), mucormycetes, hyalohyphomycetes, and phaeohyphomycetes.[69–72] Fungal infections typically involve the skin or lungs. Risk factors for fungal wound infection include older age, greater TBSA, hospital stays longer than 14 to 28 days, diabetes, total parenteral nutrition, prior fungal wound colonization, inhalational injury, broad-spectrum antimicrobial exposure, compressive dressings, and other immunosuppression.[6,71,73,74] A single-site study revealed that mortality associated with fungal wound colonization was 27% compared with 76% for fungal wound infections. The presence of fungal wound infection increased mortality by an odds ratio of 8.2, equivalent to raising the burn TBSA by 33%.[70] Factors independently associated with mortality in fungal wound infections include older age, extensive burn TBSA, increasing number of positive cultures, and confirmation of *Aspergillus* or mucormycetes.[74]

Viral Infections Following Burn Injury

The role of viral infections has not been clearly elucidated in patients with burns but likely includes reactivation, primary infection, or exogenous reinfection of cytomegalovirus, herpes simplex virus, or varicella-zoster virus.[6] Varicella-zoster virus in children has been associated with pulmonary disease.[75] Herpes simplex virus typically occurs in healing or recently healed partial-thickness burns and occasionally around the margins of skin graft donor sites 2 to 6 weeks after thermal injury.[6,7] There is evidence that herpes simplex virus may also be associated with prolonged recovery and bacterial infections.[76] Although cytomegalovirus viremia has been associated with patients who experience severe burns, the clinical impact is unclear.[77] Whether these infections are a marker of severe immune dysfunction or directly alter immune responses is yet to be determined.[2,76]

TABLE 314.1 American Burn Association Sepsis Criteria[a]

I. Temperature: >39°C or <36.5°C
II. Progressive tachycardia
- Adults: >110 beats/min
- Children: >2 SD above age-specific norms (85% age-adjusted max heart rate)

III. Progressive tachypnea
- Adults: >25 breaths/min if not ventilated or minute ventilation >12 L/min if ventilated
- Children: >2 SD above age-specific norms (85% age-adjusted max respiratory rate)

IV. Thrombocytopenia (applicable only ≥3 days post–initial resuscitation)
- Adults: <100,000/μL
- Children: <2 SD below age-specific norms

V. Hyperglycemia (applicable only to patients without a prior history of diabetes)
- Untreated plasma glucose >200 mg/dL

or
- Insulin resistance (>7 U of insulin/h IV drip (in adults) or >25% increase in insulin requirements over 24 hours)

VI. Inability to continue enteral feedings longer than 24 hours
- Abdominal distention

or
- Residual twice the feeding rate for adults or >150 mL/h in children

or
- Uncontrolled diarrhea (>2500 mL/day for adults or >400 mL/day for children)

[a]Sepsis is of concern if 3 or more of these 6 triggers are seen.
[b]To meet the definition of burn sepsis, a documented infection (culture-positive infection, pathologic tissue source identified, or clinical response to antimicrobials) is required in combination with at least 3 of the 6 above criteria.
IV, Intravenous; *SD,* standard deviation.
Modified from Greenhalgh DG, Saffle JR, Holmes JH, et al. American Burn Association consensus conference to define sepsis and infection in burns. J Burn Care Res. *2007;28:776–790.*

DIAGNOSIS

Defining Infection in Burn Patients

The stress associated with severe burn injuries is marked by a persistent hypermetabolic response characterized by full-body catabolism, muscle and protein degradation, stunted growth, insulin resistance, increased risk for infection, and multiorgan dysfunction.[23,78,79] A review of the immunologic alterations associated with burns is beyond the scope of this chapter; however, the innate and adaptive immunologic alterations associated with burn injuries are numerous and can persist for weeks to months.[4,6,80–95]

The traditional parameters used to detect infection, including temperature, white blood cell count, respiratory status, heart rate, and Sequential (Sepsis-related) Organ Failure Assessment (SOFA) and Quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA) criteria as described in new sepsis guidelines, are not sensitive or specific enough to be used in the same fashion in burn patients because of the metabolic perturbations associated with burns. Extremes or changes in temperature; white blood cell count; percentage of neutrophils; and inflammatory biochemical markers, including C-reactive protein, fungal screening assays, and numerous cytokines, are not adequate in predicting ongoing infections.[93,94,96–100]

Sepsis and Bloodstream Infections

With these limitations in mind, the ABA released criteria for sepsis in 2007 that could be used as a trigger for the concern of ongoing infection; however, these parameters do not appear to perform ideally in the clinical setting (Table 314.1).[96,101,102] Procalcitonin continues to be the most studied biomarker to attempt to diagnose sepsis.[103–105] A meta-analysis found that using a cutoff of 1.5 ng/mL (rather than 0.5 ng/mL) led to an area under the curve of 0.8 in predicting sepsis; however, the assays used, definitions of sepsis, and included populations were highly heterogeneous, making real-world interpretation a continuing challenge.[103]

Bloodstream infections are diagnosed by using the standard analysis of pathogen, clinical syndrome, and number of positive cultures.[101] The needed quantity of blood or use of both anaerobic and aerobic bottles at the time of culturing is not clear.[68] Although patients can develop bacteremia after burn wound manipulation in the early postburn period, the clinical relevance of this bacteremia is uncertain. It is also unclear whether bacteremia is associated with mortality in burn patients.[106–108]

Pneumonia

Pneumonia is defined by a clinical syndrome consisting of two or more of the following factors: a new or persistent infiltrate, consolidation, or cavitation on chest radiograph; sepsis (as defined in Table 314.1); and a recent change in sputum or purulence in the sputum.[101,109] The diagnosis is designated confirmed, if a patient meets the clinical syndrome with microbiologic confirmation; probable, if a patient meets the clinical syndrome without microbiologic confirmation; and possible, with an abnormal chest radiograph with low or moderate clinical suspicions but microbiologic confirmation. Microbiologic criteria include tracheal aspirate having 10^5/mL organisms or more, bronchoalveolar lavage having 10^4/mL organisms or more, or protected bronchial brush having 10^3/mL organisms or more. Similar to other critically ill patients, these evaluations are not always routinely performed. Purulent tracheobronchitis, defined as fever and increased sputum without chest radiograph findings or purulent discharge coating the trachea during bronchoscopy, is encountered in burn patients. There is evidence that the presence of tracheobronchitis is associated with prolonged durations of mechanical ventilation and that antibiotic therapy may mitigate this effect.[110]

Wound Infections

Criteria for diagnosis of wound infections have been described by the ABA (Table 314.2) and others.[4,101,111] Changes of the eschar appearance including development of a dark brown, black, or violaceous discoloration or edema at the wound margin are of concern for ongoing infection. Although the definitive diagnosis of wound infection is probably histopathologic diagnosis, with invasion of bacteria into viable tissue or blood vessels, expertise and rapid turnaround are lacking in most centers. Similarly, culturing the skin through swabs or biopsies is of limited clinical usefulness due to sampling bias, poor correlation between methods, no standardized methodology, slow processing time, and lack of consistent association with ongoing bacteremia.[112–115] A systematic review determined that for culture to be useful more than one sample

TABLE 314.2 Diagnosis of Burn Wound Infection: American Burn Association Guidelines

SYNDROME	CLINICAL AND PATHOLOGIC CRITERIA: BURN SEPSIS GUIDELINES
Wound colonization	Bacteria on wound surface at low concentration (<10^5 bacteria/g tissue); no invasive infection
Wound infection	Bacteria in wound and wound eschar at high concentration (>10^5 bacteria/g tissue); no invasive infection
Invasive infection	Pathogens in burn wound at a sufficient concentration (>10^5 bacteria/g tissue [frequently]), depth, and surface area to cause suppurative separation of eschar or graft loss, invasion of adjacent unburned tissue, or sepsis syndrome (see Table 314.1)
Cellulitis	Bacteria present in wound and/or wound eschar at high concentrations (>10^5 bacteria/g tissue), with surrounding tissue revealing erythema (this alone may not require therapy), induration, warmth, or tenderness
Necrotizing infection, fasciitis	Aggressive, invasive infection with involvement below the skin resulting in tissue necrosis

Notes

1. Quantitative biopsy can assist in identifying pathogen and antimicrobial resistance profiles, but its ability to confirm a diagnosis is limited.
2. Quantitative swabs are unreliable but might assist in pathogen identification and antimicrobial resistance profiles.
3. Tissue histology can be used, but limited expertise exists.
4. Clinical parameters of wound infection include pain, erythema, color change, unexpected changes in wound appearance and depth, systemic changes, and premature separation of burn eschar.

Modified from Greenhalgh DG, Saffle JR, Holmes JH, et al. American Burn Association consensus conference to define sepsis and infection in burns. J Burn Care Res. *2007;28:776–790.*

is required, biopsies generally outperform swabs in predicting sepsis, higher bacterial loads may predict worse clinical outcomes (but need to be combined with depth of invasion to be relevant), and interpretation must be done in the setting of clinical findings.[7,116,117]

Pseudomonas aeruginosa can colonize the wound, resulting in yellow-green exudates, but invasive infection should be considered only when there are purple-black and punched-out areas of the wound.[118] *Candida* infections can appear as small pustules, whereas *Aspergillus* appears as gray-brown plaques. Histology for fungal diagnosis must be augmented with culture because of inaccuracies of histology, presence of mixed cultures, and the need to provide definitive identification of fungi to assist in antifungal selection.[71]

TREATMENT

Empirical Therapy of Infections

Therapy of infections in patients with burns is focused on the site of infection and offending pathogen. Empirical therapy should rely on the specific antibiogram of a burn unit because resistance profiles in burn units may not reflect other units or wards in the same hospital.[54,66,67] Some burn units rely on individual patients' quantitative wound cultures on admission and use routine periodic screening of the skin to predict infecting pathogens. The usefulness of this method is unclear with sampling and technique bias.[45,116,119–122] Empirical therapeutic choices should focus on pathogens with notable mortality such as *K. pneumoniae* instead of pathogens with increased antimicrobial resistance but less virulence such as *Acinetobacter baumannii*. The benefit of empirical therapy is unclear in patients who experience a burn without evidence of ongoing infection.[48,50,123]

Dosing of Antimicrobials in Burns

Physiologic response to severe burns can be divided into two stages, with the first being the ebb or resuscitative stage (within the first 12 hours and lasting 48–72 hours). This first, transient stage during which few infections are diagnosed is characterized by hypovolemia and decreased cardiac output, so clinicians can expect prolonged drug distribution, decreased maximal serum concentrations, delayed onset of action, and slower drug elimination. Much more frequently the clinician is facing the complications of drug dosing during the second, or hypermetabolic, phase of burn injury, which is characterized by hyperdynamic circulation, increased tissue perfusion, and hypoalbuminemia. This leads to faster drug delivery, time to peak serum concentration, and a shorter half-life. There are also complex changes in protein binding, volume of distribution over time, and high levels of interpatient and intrapatient variability, with limited data available. This may make reaching pharmacokinetic and pharmacodynamic targets challenging with conventional dosing, with providers facing the potential for toxicity with dose or frequency increases. Further study of real-time optimization of drug dosing and consideration of therapeutic drug monitoring as available may ultimately improve outcomes.[124–130] However, a recent small, single-center study evaluating therapeutic drug monitoring of four antimicrobials (vancomycin, imipenem, meropenem, and piperacillin-tazobactam) failed to show improvement in clinical outcomes, including mortality.[131]

Alternative routes of drug delivery have been considered to improve outcomes. Although newer guidelines recommend inhaled antimicrobials for treatment of pneumonia to be considered as an adjunct for patients with ventilator-associated pneumonia who are not responding to intravenous antimicrobials alone, no clear benefit or harm has been shown in burn patients.[132–134] Historically, subeschar clysis was used in deep burns when early excision was not the standard of care, and it is still used in areas where early surgical interventions and adequate support are not available. Methods include introduction of antibiotic agents or other antimicrobials such as povidone-iodine plus Neosporin (polymyxin B/neomycin/bacitracin).[135,136]

Antifungal Therapy

Therapy of fungal infections depends on identification of the genus and species as well as the site of infection. In a multicenter review, 13% of fungal cultures yielded *Aspergillus* spp.; however, another study in a large burn unit reported that almost half of *Aspergillus* isolates were *Aspergillus terreus,* limiting the use of amphotericin B as empirical monotherapy for fungi.[69,71] The role of empirical therapy or preemptive therapy, when a fungus is recovered from the skin but is not yet invasive, is intriguing, especially in patients with 30% to 60% TBSA burns, because they may benefit the most from early therapy to prevent invasive infection and subsequent excess morbidity and mortality.[70]

Surgical Management and Topical Therapy

Although surgical management is regarded as care of the wound, it is also vital in treating and preventing infections.[43] Early excision and grafting (considered standard of care in resource-rich countries) is not universally defined but is typically within the first few days of injury and certainly within the first week to 10 days.[66] Early excision and grafting appears to be associated with a shorter length of hospitalization, improved graft take, and improved infection and mortality rates in patients without inhalation injury, but its impact on sepsis is unclear.[8,137–139] Coverage of the burn area is fundamental to burn care and ideally involves immediate coverage with autologous skin grafts for permanent closure. However, this is not an option in patients with grossly infected, questionably viable wounds or when donor skin for autografting is not available (in the setting of extensive burns or in a patient who is not stable enough for additional harvest).[140] In these cases, temporary coverage with allograft or other skin substitutes provides a wound barrier, prevents evaporative losses, and prepares the wound bed for autograft.[8] Temporary coverage options include allografts (living-donor or cadaveric skin, either fresh or frozen), xenografts (typically porcine skin), and synthetic coverage (acellular or cellular matrices) (Table 314.3).[8,140–146] A survey of 111 burn specialists from 36 countries revealed that providers still do not feel that an ideal skin substitute is available. Most providers use skin substitutes in daily practice, and 81% rated them as "essential" in patients with >60% TBSA burns, with allografts most commonly used (51%), followed by xenografts (28%).[147]

Topical therapies are used to prevent and treat infections and include mafenide acetate, honey, silver sulfadiazine, silver nitrate, and silver

TABLE 314.3 Common Select Burn Wound Coverage Options

PRODUCT	DESCRIPTION	USE AND ADVANTAGES	APPROXIMATE COST AND LIMITATIONS
Permanent Coverage			
Autograft	• Patient serves as own donor of split-thickness skin graft from uninjured donor site	• Gold standard, permanent coverage • Excellent ingrowth • Can be stretched for expansions between 1:1 and 9:1	• Coverage requires donor site availability (can be limited in extensive burns) • Widely stretched autografts (ratios higher than 3:1) are more fragile, prone to infection and desiccation, and so frequently covered with allograft to improve take • Risk of wound complications at both graft and donor site
Temporary Coverage: Biologics			
Fresh allograft	• Living donor or cadaveric skin graft	• Fresh living allograft is gold standard for temporary coverage • Excellent ingrowth • Excellent test for autografting • Longest survival in those with largest burn wounds • Can serve as scaffolding for future ingrowth	• $2461/sq ft • Short 14-day shelf life refrigerated (with change of medium every 2–3 days) • Unpredictable availability • Risk of infection and disease transmission
Frozen allograft	• Cryopreserved cadaveric skin graft	• Widely available (most commonly used temporary coverage) • Good test for future autografting • Less expensive than fresh allograft • Indefinite shelf life when frozen	• $1997/sq ft • About 54%–73% viability of fresh tissue • Risk of infection and disease transmission (though longer time for adequate donor screening than fresh allograft)
Xenograft	• Dermis ± epidermis (most frequently porcine)	• Low cost, available option for short-term coverage or testing a wound for autografting • Prolonged shelf-life (18–24 months depending on formulation and storage)	• $133/sq ft • Inferior to allograft for excised burn wounds • Good adherence, but no ingrowth • Theoretical concern for disease transmission (prion disease and porcine retroviruses) • Cultural and religious restrictions on use
Temporary Coverage: Select More Commonly Used Dermal Substitutes ***Natural Biologic Materials***			
Alloderm (LifeCell, Branchburg, NJ)	• Acellular dermal cadaveric allograft • Fresh human cadaveric skin chemically treated to remove all cellular material in the dermis	• Applied to a wound bed, serves as a template for dermal regeneration, allowing for subsequent thinner autograft • Acellular and immunologically inert	• $14,000–$28,000/sq ft • High cost compared with allograft • Risk of disease transmission • Now rarely used because of concerns that it may act as a barrier to diffusion of nutrients to the autograft
Constructed or Artificial Biologic Materials			
Integra (Integra Lifesciences, Plainsboro, NJ)	• Acellular bilayered substitute • Dermal matrix of type 1 bovine collagen/shark-derived chondroitin-6-sulfate covered by silicone	• Most widely accepted artificial skin substitute • Vascularizes in 3–4 weeks, after which time silicone epithelium can be peeled away, and an ultrathin autograft can be placed	• $14,000–$28,000/sq ft • Higher risk for infection • Poor take of cultured epithelial autografts • Despite wide adoption, still a paucity of scientific evidence for its use
Matriderm (Dr Suwelack Skin and Health Care AG, Billerbeck, Germany)	• Radiated bovine collagen matrix with α-elastin hydrolysate	• Typically used in single-stage procedure with immediate skin grafting • Improved cosmesis and elasticity in small trials	• $4500/sq ft • Limited scientific evidence

Data from Rowan MP, Cancio LC, Elster EA, et al. Burn wound healing and treatment: review and advancements. Crit Care. *2015;19:243; Saffle JR. Closure of the excised burn wound: temporary skin substitutes.* Clin Plast Surg. *2009;36:627–641; Shahrokhi S, Anna A, Jeschke MG. The use of dermal substitutes in burn surgery: acute phase.* Wound Repair Regen. *2014;22:14–22; Greenhalgh DG. The use of dermal substitutes in burn surgery: acute phase.* Wound Repair Regen. *2014;22:1–2; and Debels H, Hamdi M, Abberton K, et al. Dermal matrices and bioengineered skin substitutes: a critical review of current options.* Plast Reconstr Surg Glob Open. *2015;3:e284.*

dressings (Table 314.4).[148,149] These agents have various adverse event profiles, clinical application characteristics, and antimicrobial activity.[150,151] A delicate balance must be achieved between antimicrobial activity and cytotoxicity to keratinocytes and fibroblasts, which would delay wound healing if used on more superficial burns that might heal without intervention.[150] It is unclear whether the limited fungal coverage of these agents results in increased fungal infections.[70]

PREVENTION

Infection Prevention and Health Care–Associated Infections

Infection prevention and control is fundamental to decreasing infectious complications associated with burns. Its importance cannot be overemphasized, and this lesson is highlighted repeatedly with the literature replete with descriptions of outbreaks.[152–155] Bacterial propagation involves hospital equipment such as mattresses, patient care with hydrotherapy, and movement of patients and equipment between the general ICU and burn unit.[52,58,61,154,156] Other studies have shown aerosolization of bacteria during wound dressing changes.[157] Burn units should be designed to minimize transmission through dedicated burn space, no common treatment rooms, centralized dedicated operating rooms and facilities, and individual patient rooms with anterooms or individual doors. In addition, aggressive standard infection-control procedures for resistant pathogens are recommended.[4,45,62,158] Pulsed-xenon ultraviolet light disinfection has been associated with decreased environmental bioburden. A more recent study reported a trend toward decreased MDR organisms among all bacteria, decreased rate of MDR gram-negative rods per 1000 occupied bed days, and increased median time to hospital-associated *C. difficile* from 66 days to none during the intervention and postintervention period of 290 days.[159]

TABLE 314.4 Application of Topical Agents for Deep Burns

AGENT	PENETRATION	SPECTRUM	SIDE EFFECTS	COMMENTS
Mafenide acetate (Sulfamylon)	Penetrates eschar	Gram-positive and gram-negative bacteria	Painful on application; metabolic acidosis	Twice daily or alternate with silver sulfadiazine; lack of antifungal activity
Silver sulfadiazine (Silvadene, Thermazene, Flamazine)	Poor eschar penetration	Gram-positive and gram-negative bacteria; *Candida* spp.	Leukopenia; pseudoeschar formation on wound surface obscures visualization of wound surface; cutaneous hypersensitivity rarely reported; contraindicated in sulfonamide-allergic patients	Can treat through leukopenia; delays healing of superficial burns compared with alternative dressings/topical antimicrobials
Silver nitrate	Poor eschar penetration	Gram-positive and gram-negative bacteria; *Candida* spp.	Discolors wound bed; electrolyte changes including hyponatremia, hypocalcemia, hypokalemia, hypomagnesemia; bacterial conversion of nitrate to nitrite may rarely lead to methemoglobinemia	Apply in thick layers with mesh gauze frequently to keep moist (labor intensive); stains environment black; change dressing twice daily
Silver dressing (Acticoat, Silverlon)	Limited eschar penetration	Gram-positive and gram-negative bacteria; *Candida* spp.[a]	Discolors wound	
Hypochlorous solutions (Dakin solution)	Unknown	Gram-positive, gram-negative (including MDROs), fungi, and viruses	Cytotoxicity	Buffered 0.5% NaOCl, concentrations as low as 0.00025% have been found to be effective; action of NaOCl is short-lived (initially continually dripped into wound dressings), now typically applied 2–3 times daily as gauze-soaked dressings

[a]Data are limited.
MDRO, Multidrug-resistant organism; *NaOCl,* sodium hypochlorite.
Modified from Murray CK. Burns. In: Bennett JE, Dolin R, Blaser MJ, eds. Principles and Practice of Infectious Diseases. *8th ed. Philadelphia: Saunders; 2015; Cartotto R. Topical antimicrobial agents for pediatric burns.* Burns Trauma. *2017;5:33; and Norman G, Christie J, Liu Z, et al. Antiseptics for burns.* Cochrane Database Syst Rev. *2017;7:CD011821.*

A retrospective study from a single site revealed that a hospital-associated infection (HAI) was diagnosed in 7% of patients over a total follow-up time of more than 81,000 days.[64] Among patients with one HAI, almost 20% had a subsequent HAI, 10% had 3 HAIs, and 6% had ≥4 HAIs during their hospitalizations. The most common HAIs were bloodstream infections (25%) and skin and soft tissue infections (19%), followed by catheter-associated UTIs (14%) and ventilator-associated pneumonias (13%). The probability of diagnosis of an HAI increased with duration of hospitalization, such that 50% of patients with hospitalizations greater than 80 days had at least one HAI. Whereas skin and soft tissue infections occur early (median of 3 days into hospitalization), the remaining HAIs including bloodstream infections, respiratory infections, and UTIs as well as *C. difficile* typically occur following the first month of hospitalization.[54,64] However, this same unit noted a decrease in central line–associated bloodstream infections (from 14 to 2 per 1000 central line–days) between 1999 and 2012, which was attributed to increased use of bundles and a multifaceted proactive infection prevention approach.[160] Central catheter–related sepsis is similar to other critical care units, with catheter-related sepsis associated with the number of lines placed and total number of central line–days, and appears to be higher in patients with femoral or internal jugular central lines compared with subclavian central venous catheters.[161,162] Distancing the insertion site from the burned area can decrease infections, but it is unclear whether guidewire exchange is comparable to insertion at a new site.[163,164] In one study, changing lines every 3 days was associated with fewer infections than changes every 4 days.[165] A self-reported survey of all ABA-certified adult burn units showed that 61% of units performed prophylactic line changes every 3 to 7 days, and 40% reported using more femoral lines due to lack of optimal sites.[166]

Antimicrobial Stewardship in the Burn Unit

Antimicrobials have been studied for use as broad prophylaxis early in burn hospitalizations, perioperatively, and as gut decontamination. The most recent analysis in 2013 concluded that the available evidence was limited but did not show decreased risk of burn wound infection, invasive infection, or mortality, which was in contrast to a 2010 Cochrane analysis that included the same studies but a slightly different primary endpoint (death from any cause).[66,167,168] Notably, prophylactic antibiotics in children have been associated with a higher secondary infection rate.[169]

The use of perioperative antibiotics at the time of débridement or dressing changes has been shown to modify rates of bacteremia but not clinical outcome and is of questionable usefulness, especially in patients with a burn TBSA less than 40% to 60%.[114,170] However, perioperative antimicrobials may be useful for severely burned patients with aggressive débridements or patients undergoing skin grafting.[171] Perioperative antimicrobials remain common practice despite little evidence supporting their use and risks, including resistance; diarrhea; *C. difficile* infection; allergies; and hepatic, renal, and bone marrow toxicities.[66]

A systematic review of selective gut decontamination using enteral or systemic antimicrobials showed that similar to nonburned critically ill patients, this intervention was associated with decreased mortality as well as bacteremia and pneumonia caused by Enterobacteriaceae, although one included trial showed an increase in methicillin-resistant *S. aureus* bacteremia. Limitations included high rates of diarrhea in patients receiving enteral antimicrobials, failure to examine *C. difficile* rates, and a high risk of bias in most of the included studies.[172,173] Additionally the current ABA guidelines for ventilatory-associated pneumonia discourage routine prophylactic use of antimicrobials in hospital settings where there are high levels of antimicrobial resistance because of concerns for associated selection pressure.[109]

Other Strategies to Modify Infection Risk

Adjunctive strategies have also been integral to improved mortality. Early enteral feeding may blunt the hypermetabolic response and decrease intestinal permeability, thus preserving the intestinal barrier and potentially affecting enterogenic infections.[174–178] Each unit of blood transfused in patients with burn injuries is associated with increased mortality and infectious complications, even after controlling for severity of disease.[179] TRIBE, a multicenter prospective trial enrolling 345 patients, randomly assigned patients with burns ≥20% TBSA to restrictive (hemoglobin 7–8 g/dL) or liberal (hemoglobin 10–11 g/dL) transfusion strategies throughout their hospitalization and showed that although the restrictive group had fewer transfusions, there were no significant differences in the primary outcome of bacteremia or secondary outcomes of mortality, UTI, pneumonia, wound infections, hospital or ICU length of stay, organ dysfunction, or wound healing.[173] Hyperbaric oxygen therapy has been evaluated, with mixed results.[180–182]

CONCLUSIONS

Patients who experience burn injuries are subjected to the most physiologic stress. Because infections are the most common cause of mortality after surviving the early postburn period, efforts are required to mitigate excessive death rates through adequate preventive measures and enhanced vigilance for infections and appropriate therapy. Burn units are ideal for outbreaks of MDR pathogens, which can affect other patients and the entire health care facility if adequate infection-control measures are not in place. The management of burn patients requires a multidisciplinary approach, including infectious disease physicians.

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The complete reference list is available online at Expert Consult.

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315 Bites

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SHORT VIEW SUMMARY

Definition
- Bite wounds are common injuries caused by a wide variety of domestic and wild animals, as well as humans.

Epidemiology
- Bites occur in 4.7 million Americans yearly and account for 800,000 medical visits, including approximately 1% of all emergency department visits.

Microbiology
- The bacteria associated with bite infections may come from the environment, the victim's skin flora, or most frequently, the oral flora of the biter, which can also be influenced by the microbiota of the biter's ingested prey and other food.

Diagnosis
- The diagnosis is made by the patient's reported history of events. Microbiologic assessment of infected wounds is performed through aerobic and anaerobic cultures.
- Radiographic evaluation can be considered if there is a high likelihood of bony injury.

Therapy
- Irrigate wounds with copious amounts of water.
- Débride devitalized or necrotic tissue.
- Primary wound closure is usually not advocated unless wounds are extensive and closure is necessary for cosmetic or functional reasons. When possible, delayed primary closure or allowing the wound to close by secondary intention is recommended.
- Loose approximation of wound edges with adhesive strips or sutures may be necessary for selected, fresh, uninfected larger wounds. Closure of facial wounds may be considered when coupled with preemptive antimicrobial therapy.
- In most cases of terrestrial animal bites, antimicrobial therapy when indicated should include coverage for *Pasteurella* (*Eikenella* in human bites), *Streptococcus, Staphylococcus,* and anaerobes, including *Fusobacterium, Porphyromonas, Prevotella,* and *Bacteroides* species.
- Oral antimicrobial choices in adults can include the following (see Table 315.3):
  - Amoxicillin-clavulanic acid 875/125 mg, 1 tablet by mouth twice daily
  - Metronidazole 500 mg, 1 tablet by mouth three times daily *plus* trimethoprim-sulfamethoxazole 1 double-strength tablet by mouth twice daily
  - Moxifloxacin 400 mg, 1 tablet by mouth daily
  - Doxycycline 100 mg, 1 tablet by mouth twice daily
- Intravenous antimicrobial choices in adults can include the following:
  - Ampicillin-sulbactam 1.5 to 3 g IV every 6 hours
  - Cefoxitin 1 to 2 g IV every 6 to 8 hours
  - Moxifloxacin 400 mg IV daily
  - Ertapenem 1 g IV daily
  - Ceftriaxone 1 to 2 g IV daily *plus* metronidazole 500 mg IV three times daily
- Empirical regimens for marine- and freshwater-acquired infections should cover *Vibrio* and *Aeromonas* species, respectively, with agents such as third-generation cephalosporins (e.g., cefotaxime) and fluoroquinolones.

Prevention
- As a routine, antimicrobials are not advocated for every uninfected animal bite injury.
- In general, 3 to 5 days of preemptive antimicrobial therapy can be considered for acute moderate-to-severe uninfected animal bite injuries, especially those to the hands or face, in the presence of preexisting edema, and in immunocompromised hosts. Longer courses may be considered for injuries that are severe or those penetrating joints or bony structures.
- Provide tetanus and rabies immunization, as indicated.

Bite wounds are common injuries caused by a wide variety of domestic and wild animals, as well as humans. Most data on the incidence of infection, bacteriology, and the value of various medical and surgical interventions in the treatment of such injuries come from small studies or anecdotal case reports. Such studies often lack randomization, concentrate on unusual organisms or complications, and are inherently biased by the types of patients with moderate or severe injuries who elect to seek medical attention. Bite wounds can consist of lacerations, avulsions, punctures, scratches, and crush injuries. Although the majority of patients never seek and often do not need extensive medical care, awareness of the magnitude of the infectious complications from bites is necessary.

ANIMAL BITES

Bite wounds are common injuries caused by a wide variety of domestic and wild animals, as well as humans.[1] The American Pet Products Association 2017–2018 survey reported the US pet dog and cat ownership number at approximately 184 million.[2] Bites occur in 4.7 million Americans each year[3] and account for 800,000 medical visits, including approximately 1% of all emergency department visits.[4] There were 1610 animal-related fatalities in the United States during the period of 2008 to 2015. The majority of human fatalities were from farm animals (e.g., cattle and horses), insects (hornets, wasps, and bees), and dogs.[5] Most dog bites (85%) are provoked attacks by either the victim's own pet or a dog known to the victim and occur during the warm weather months.[6] Bite wounds are often to the extremities, especially the dominant hand. Facial bites are more frequent in children younger than 10 years of age and lead to 5 to 10 deaths per year, often because of exsanguination.[7] Larger dogs can exert more than 450 lb/in^3 of pressure with their jaws, which can lead to extensive crush injuries.

The bacteria associated with bite infections may come from the environment, the victim's skin flora, or most frequently, the oral flora of the biter, which can also be influenced by the microbiome of the biter's ingested prey and other food (Table 315.1). Patients who present early after an incident often do not have an established infection and are usually concerned about crush injuries, care of disfiguring wounds, or the need for rabies or tetanus immunization.[6] These uninfected wounds are frequently contaminated with multiple strains of aerobic and anaerobic bacteria, similar to the spectrum found in documented bite infections. Between 2% and 30% of wounds will become infected and, rarely, may require hospitalization.[8–10,11,12] Patients presenting late, often longer than 8 hours after injury, usually have established infection.[6,8,10,11,13] Infection

TABLE 315.1 Common Bacterial Isolates From Dog and Cat Bite Wounds

Acinetobacter spp.
Aggregatibacter (Actinobacillus) actinomycetemcomitans
Aggregatibacter (Haemophilus) aphrophilus
Bacteroides tectus
Bergeyella (Weeksella) zoohelcum
Capnocytophaga canimorsus
Capnocytophaga cynodegmi
Corynebacterium minutissimum
Eikenella corrodens
Enterococcus spp.
Finegoldia magna
Fusobacterium nucleatum
Fusobacterium russii
Leifsonia (Corynebacterium) aquatica
Leptotrichia buccalis
Micrococcus luteus
Moraxella spp.
Neisseria canis
Neisseria weaveri
Pasteurella canis
Pasteurella dagmatis
Pasteurella multocida subsp. *multocida*
Pasteurella multocida subsp. *septica*
Pasteurella stomatis
Peptostreptococci
Porphyromonas asaccharolytica
Porphyromonas canoris
Porphyromonas gulae (gingivalis)
Prevotella bivia
Prevotella heparinolytica
Prevotella intermedia
Prevotella melaninogenica
Prevotella zoogleoformans
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus intermedius
Streptococci, α-hemolytic, β-hemolytic
Veillonella parvula

is manifested as localized cellulitis or abscess with gray and malodorous purulent discharge.[14] Fever, regional adenopathy, and lymphangitis occur in the minority of patients. Bites involving bones and joints may result in tenosynovitis, septic arthritis, and osteomyelitis. Chronic pain in a joint with limited range of motion may be suggestive of infection within a joint or bony structure.

Rarely, overwhelming sepsis, endocarditis, meningitis, or brain abscesses may develop after a bite injury. Fatal infections caused by *Capnocytophaga canimorsus* in association with asplenia or liver disease have been noted.[15–17] This organism may be difficult to isolate and identify and may require up to 14 days of incubation to grow on blood cultures. In addition, it has the potential capacity to escape the host immune system by both passive and active mechanisms.[18] It is generally susceptible to penicillin, cephalosporins, and fluoroquinolones but variably resistant to aztreonam and aminoglycosides (Table 315.2).[19]

Individuals with immunocompromising conditions, including chronic corticosteroid use, and those with preexisting edema of an extremity are more prone to severe infections and complications.

Dog and cat bite wound infections are considered to be predominantly related to the microbiology of their oral flora.[6,9,13,14,20–22] Although most attention has focused on *Pasteurella multocida,* the spectrum of organisms associated with dog and cat bite wound infections is much greater. Holst and colleagues[23] noted the following distribution of 159 *Pasteurella* strains isolated over a period of 3 years from human infections, mostly from bite wounds: *Pasteurella multocida* subsp. *multocida* (60%), which was the isolate in all bacteremia cases; *Pasteurella multocida* subsp. *septica* (13%), which has a greater prevalence in cats than in dogs and may have a preferential affinity for the central nervous system; *Pasteurella canis* biotype 1 (18%), which was isolated exclusively from dog bite wound infections; *Pasteurella stomatis* (6%); and *Pasteurella dagmatis* (3%), which may cause systemic infections. A study of 107 infected dog and cat bite wound infections showed that 75% of cat bites grew *Pasteurella* species on culturing *(P. multocida* subsp. *multocida,* 54%), as

TABLE 315.2 Antimicrobial Susceptibilities of Bacteria Frequently Isolated From Animal and Human Bite Wounds

	PERCENTAGES OF ISOLATES SUSCEPTIBLE					
	***Staphylococcus aureus* (MSSA)**	***Eikenella corrodens***	**Anaerobes**	***Pasteurella multocida***	***Capnocytophaga canimorsus***	***Staphylococcus intermedius*[b]**
Penicillin	10	99	50/95[c]	95	95	30
Dicloxacillin	99	5	50[d,e]	30	NS	70
Amoxicillin-clavulanic acid	100	100	100[d,e]	100	95	70
Cephalexin	100	20	40[d,e]	30	NS	95
Cefuroxime	100	70	40[d,e]	90	NS	NS
Cefoxitin	100	95	100[d,e]	95	95	NS
Ceftriaxone	99	100	70	100	NS	100
Ceftaroline	100	NS	70	100	NS	100
Erythromycin	100	20	40[d,e]	20	95	95
Tetracycline	95	85	60[d,e]	90	95	NS
Doxycycline	100	100	95	100	NS	100
TMP-SMX	100	95	0	95	V	100
Ciprofloxacin	100	100	40[d,e]	95	100	100
Levofloxacin	100	100	60[d,e]	100	100	100
Moxifloxacin	100	100	85[d,e]	100	100	100
Azithromycin	100	80	70[d,e]	100	100	NS
Clarithromycin	100	60	70[d,e]	70	100	NS
Clindamycin	93	0	75[d,e]	0	95	95

[a]Data are compiled from various studies.
[b]*Staphylococcus intermedius* may be mistakenly identified as methicillin-resistant *Staphylococcus aureus.*[26]
[c]Percentage of human bite isolates/percentage of animal bite isolates.
[d]*Fusobacterium canifelinum* is intrinsically resistant, whereas human *Fusobacterium nucleatum* is susceptible.
[e]Some peptostreptococci are resistant.
MSSA, Methicillin-susceptible *Staphylococcus aureus*; *NS,* not studied; *TMP-SMX,* trimethoprim-sulfamethoxazole; *V,* variable.

did 50% of dog bites (*P. canis,* 26%; *P. multocida* subsp. *multocida,* 12%).[14] In this study, other common aerobic organisms isolated from infected dog and cat bite wounds included *Streptococcus, Staphylococcus* species (including *Staphylococcus aureus*), and *Neisseria* species. Anaerobic organisms, when present, were almost always in mixed infections with aerobic organisms and commonly included *Fusobacterium, Porphyromonas,* and *Prevotella* species in dog bites and *Fusobacterium, Porphyromonas,* and *Bacteroides* species in cat bites.[14]

Table 315.1 lists common pathogens found in dog and cat bite wound infections. *Staphylococcus intermedius* is coagulase positive, can be mistaken for *S. aureus,* and is fourfold more common in canine flora[24,25] but possesses β-galactosidase activity, which differentiates it from *S. aureus.* It may masquerade as methicillin-resistant *S. aureus* (MRSA) owing to false-positive rapid penicillin-binding protein 2a latex tests,[26] although an increasing number (approximately 30%) of isolates may be resistant to oxacillin. MRSA has been cultured from a variety of companion animals, including cats, and has been documented to be transmitted from a healthy pet cat to humans, and the human strains and feline strains are indistinguishable.[27,28] MRSA may be a potential causative secondary invader, especially in patients who are not responding to initially administered antibiotics that often do not exhibit activity against MRSA and in those known to be colonized with MRSA.

Capnocytophaga canimorsus[17] is difficult to grow on most routine solid media but can grow on chocolate agar and heart infusion agar with 5% rabbit blood when incubated in CO_2 and a variety of liquid media, including BACTEC aerobic medium (Becton, Dickinson and Company, Franklin Lakes, NJ).[16] This species can be differentiated from other *Capnocytophaga* species by the presence of positive oxidase and catalase reactions.[17] Centers for Disease Control and Prevention (CDC) group DF-2–like strains have been classified as *Capnocytophaga cynodegmi.* CDC group M-5 has been classified as *Neisseria weaveri* and has been associated with dog bites.[29] CDC group EF-4a is now called *Neisseria animaloris,* and EF-4b is *Neisseria zoodegmatis. Haemophilus felis,* initially identified as *Aggregatibacter (Haemophilus) paraphrophilus,* requires factor V and CO_2 for growth and is common in cat nasopharyngeal flora.[30]

Bergeyella (previously designated as *Weeksella*) *zoohelcum* has been associated with bite cellulitis, sepsis, and meningitis.[31] Other new aerobic species include *Neisseria canis* from a cat bite,[32] *Flavobacterium* group IIb–like isolates from a pig bite,[33] *Actinobacillus lignieresii* and *Actinobacillus equi*–like bacterium from horse bites,[34] and CDC group NO1, a nonoxidative gram-negative rod[35] different from *Acinetobacter* species associated with dog and cat bites. Orf virus infection has been transmitted by a sheep bite.[36] When appropriate culturing techniques are used, anaerobes are isolated in up to 70% of animal bite wounds, almost always in mixed culture.[6,11,13] Approximately 50% to 60% of cat and dog bite wounds contain *Bacteroides tectus, Prevotella heparinolytica, Prevotella zoogleoformans, Prevotella bivia, Porphyromonas gingivalis, Porphyromonas canoris, Fusobacterium nucleatum,* and *Peptostreptococcus anaerobius.*[37–40] *Fusobacterium canifelinum* is an intrinsically fluoroquinolone-resistant species isolated from dog and cat bites.[41]

Little difference has been noted in the types of bacteria isolated from noninfected wounds seen early and infected wounds seen later.[6] All moderate-to-severe bite wounds, except those not clinically infected and more than a few days old, should be considered contaminated with potential pathogens.

Wounds inflicted by cats are frequently scratches or tiny but somewhat deep punctures located on the extremities and are at higher risk of becoming infected.[42] Deep puncture wounds over or near a joint, especially on the hands, may result in osteomyelitis and septic arthritis. *Pasteurella multocida* has been isolated from 50% to 70% of healthy cats and is a frequent pathogen in cat-associated wounds.[14,23,42] *Erysipelothrix rhusiopathiae* has also been isolated from cat bite wounds.[14] Cougar, tiger, and other feline bites also yield *P. multocida.*[34] Tularemia has likewise been transmitted by cat bites.[43] People are also bitten by a variety of other animals, including unusual domestic pets, farm animals, wild animals, aquatic animals, and laboratory animals.[4,44–47] Monkey bites cause more swelling and infection than do many other animal bites.[48] Old World monkeys may transmit a potentially lethal subtype B virus (herpesvirus simiae; see Chapter 141).[49] Case series or reports of various animal bites—including terrestrial mammals (e.g., monkeys, bears, pigs, ferrets, horses, sheep, Tasmanian devils); reptiles (e.g., snakes, Komodo dragons, lizards, iguanas, alligators, crocodiles); rodents (e.g., rats, guinea pigs, hamsters, prairie dogs); swans; and sharks with unusual isolates—have been reported.[50–53]

MANAGEMENT OF ANIMAL BITES

Table 315.3 notes the elements for the treatment of animal bite wounds. The most problematic elements of the management of wounds that are seen early include the following:

1. The use of preemptive antibiotics in wounds that are seen early but are not infected. As a routine, antimicrobial therapy is not advocated in every uninfected animal bite injury. However, because 85% of such wounds harbor potential pathogens and one cannot reliably predict which wounds will become infected, selected wounds are best treated with oral antimicrobial therapy with agents active against common bite pathogens (see Table 315.2) for 3 to 5 days. Recommendations about patient selection vary and are based on limited evidence.[54] In general, 3 to 5 days of preemptive antimicrobial therapy is advocated for acute moderate-to-severe injuries, especially those to the hand or face, in the presence of preexisting edema, and in immunocompromised hosts.[55] Longer courses may be considered for injuries that are severe or those penetrating joints or bony structures.
2. The decision to suture the wound. The role of primary wound closure in animal bites remains controversial. The literature on this topic has a number of limitations such as the time from injury to presentation, the extent and location of injuries, wound closure methods, and administration of antibiotics. For cosmetic and functional reasons, facial and neck wounds and extensive large wounds, especially those overlying the joints, are difficult to leave open and are usually sutured after irrigation coupled with antimicrobial prophylaxis. Limited studies are available to determine whether the risk of infection is increased with primary wound closure in animal bites.[56–58,59] In one study of 345 dog bite wounds, puncture wounds and wounds that were closed were more likely to become infected.[58] In a randomized controlled trial of primary closure versus nonclosure of dog bite wounds, the infection rate between the two groups was similar but primary suturing improved cosmetic appearance.[59] It is our experience and recommendation that, if cosmetically or functionally reasonable, small bite wounds can be left open and allowed to close by secondary intention. Larger wounds, especially those overlying the face, neck, and joints, may be sutured or loosely approximated and closed by delayed primary closure.

The most common causes of therapeutic failure are the following:

1. Failure to elevate the affected edematous extremity.
2. Inadequate antimicrobial therapy (see Table 315.2). Most fastidious animal pathogens are susceptible to penicillin or amoxicillin. Because of resistance of certain bacteria, including *P. multocida,* first-generation cephalosporins, dicloxacillin, erythromycin, clindamycin, and metronidazole should be avoided as a sole antimicrobial agent; however, they can be used in combination with antibiotics that have activity against *Pasteurella* species. In vitro data suggest that some fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin), trimethoprim-sulfamethoxazole, ertapenem, and second-generation oral cephalosporins (e.g., cefuroxime) are active against many bite isolates.[60,61–68] Ceftaroline, an anti-MRSA cephalosporin, has activity against *Pasteurella* species and other aerobic gram-positive isolates recovered from animal bite wounds.[69,70,71] Empirical regimens for marine- and freshwater-acquired infection should cover *Vibrio* and *Aeromonas* species, respectively, with agents such as third-generation cephalosporins (e.g., cefotaxime) and fluoroquinolones.

TABLE 315.3 Management of Bite Wounds

History
Animal Bite

Ascertain the type of animal, whether the bite was provoked or unprovoked, and the situation/environment in which the bite occurred. Follow rabies guidelines (see Chapter 163) for details on management of bites that carry a risk of rabies.

Patient

Obtain information on antimicrobial allergies, current medications, splenectomy, liver disease, or other immunosuppressive conditions.

Physical Examination

Assess nerve and tendon function along with signs and symptoms of infection.

Culture

Obtain aerobic and anaerobic cultures from infected wounds.

Irrigation and Débridement

Irrigate with water and débride devitalized or necrotic tissue.

Radiographs

Plain radiographs should be obtained if bony penetration is highly possible; radiographs can also provide a baseline for future evaluation of osteomyelitis.

Wound Closure

Primary wound closure is usually not advocated unless wounds are extensive and closure is necessary for cosmetic or functional reasons, especially large facial or neck wounds or those overlying the joints. When possible, delayed primary closure or allowing the wound to close by secondary intention is recommended.

Antimicrobial Therapy
Early Presenting (Uninfected) Wounds

Provide antimicrobial therapy for (1) moderate-to-severe injuries, especially if preexisting edema or significant crush injury is present; (2) bone or joint space penetration; (3) deep hand wounds; (4) immunocompromised patients (including those with advanced liver disease, asplenia, or chronic steroid therapy); (5) wounds adjacent to a prosthetic joint; and (6) wounds in close proximity to the genital area. In most cases, coverage should include *Pasteurella* (*Eikenella* in human bites), *Staphylococcus, Streptococcus,* and anaerobes, including *Fusobacterium, Porphyromonas, Prevotella,* and *Bacteroides* species (see Table 315.2).

Infected Wounds

Cover *Pasteurella* (*Eikenella* in human bites), *Staphylococcus*, *Streptococcus,* and anaerobes, including *Fusobacterium, Porphyromonas, Prevotella,* and *Bacteroides* spp. (see Table 315.2). The following oral antimicrobials can be considered in adults for most terrestrial animal and human bites:

- First choice: Amoxicillin-clavulanic acid 875/125 mg, 1 tablet by mouth twice daily
- Penicillin allergy:
  - Metronidazole 500 mg, 1 tablet by mouth three times daily *plus* trimethoprim-sulfamethoxazole, 1 double-strength tablet by mouth twice daily
  - Moxifloxacin 400 mg, 1 tablet by mouth daily
  - Doxycycline 100 mg, 1 tablet by mouth twice daily
- In adults in whom intravenous antibiotics are deemed necessary, single antimicrobial choices can include ampicillin-sulbactam, cefoxitin, ertapenem, or moxifloxacin.
- Empirical regimens for marine- and freshwater-acquired infection should also cover *Vibrio* and *Aeromonas* species, respectively, with agents such as third-generation cephalosporins (e.g., cefotaxime) and fluoroquinolones.

Hospitalization

Indications can include signs and symptoms of systemic toxicity.

Immunizations

Provide tetanus and rabies immunization, if indicated.

Elevation

Elevation may be required if preexisting edema is present.

Immobilization

For significant injures, consider immobilizing the extremity, especially the hands, with a splint.

Follow-Up

Patients should be reminded to follow up within 48 hours or sooner for worsening or unresolved symptoms.

Reporting

Reporting the incident to a local health department may be required in selected cases.

3. Failure to recognize osteomyelitis and septic arthritis. Long-standing pain or continuous diminished range of motion of a joint near a bite wound may be an indication of complications such as osteomyelitis or septic arthritis. Pain out of proportion to the severity of the wound may be an indicator of potential periosteal or joint penetration.

VENOMOUS SNAKEBITES

Venomous snakes, usually vipers (rattlesnakes, copperheads, cottonmouths, or water moccasins), bite approximately 8000 people in the United States yearly, and 5 or 6 of these die, usually children or the elderly, who receive either no or delayed antivenom therapy.[72] The majority of bites occur in young men in the southwestern United States between April and September.[72] Envenomation can cause extensive tissue destruction and devitalization that predisposes to infection from the snake's normal oral flora. Sparse data exist on the incidence and bacteriology of snakebite infections. In rattlesnakes, the oral flora appears to be fecal in nature because the live prey usually defecates in the snake's mouth coincident with ingestion. Common oral isolates include *Pseudomonas aeruginosa,* coagulase-negative staphylococci, and *Proteus* and *Clostridium* species.[73,74] Other potential pathogens isolated from rattlesnakes' mouths have included *Bacteroides fragilis* and *Salmonella*

enterica subsp. *arizonae* and *S. enterica* subsp. *diarizonae* (*Salmonella* groups IIIa and IIIb, respectively). *Crotalus* rattlesnake venom has innate, broad activity against aerobic gram-positive and gram-negative bacteria but not against anaerobes.[75,76] The role of empirical antimicrobial therapy for noninfected wounds is not well defined.

LIP WOUNDS AND PARONYCHIA

Wounds of the lips and paronychia and infections of the structure surrounding the nails account for most self-inflicted bite wounds. Paronychia is more frequent in children who suck their fingers and results from direct inoculation of the oral flora into the fingers. Brook[77] took cultures from 33 children with paronychia. Aerobes and anaerobes were each found in pure culture in 27% of cases, and mixed infection was found in 46% of cases. The most frequent aerobic organisms isolated were viridans streptococci, group A streptococci, *S. aureus, Haemophilus parainfluenzae, Klebsiella pneumoniae,* and *Eikenella corrodens.* The most frequently isolated anaerobic bacteria were *Bacteroides* species, *Fusobacterium* species, and gram-positive cocci. Therapy should include drainage, antibiotics for moderate-to-severe infections, and avoidance of further bacterial contamination.

HUMAN BITES

Human bites generally have higher complication and infection rates than do animal bites. In addition, transmission of human immunodeficiency virus, hepatitis B virus, or hepatitis C virus must be considered. Occlusional human bites may affect any part of the body but most often involve the distal phalanx of the long or index fingers of the dominant hand. About 10% to 20% of wounds are "love nips" to the breasts and genital areas.[20,78,79] Bites to the hand are often deep and more frequently become infected than do bites to other areas.[80] Bites may also be caused by, or be harbingers of, child abuse.[81]

Important prognostic factors for the development of infection include the extent of tissue damage, the depth of the wound and which compartments are entered, and the pathogenicity of the inoculated oral bacteria.[82–85] The typical patient is a young male who is assaulted by another young male. The first infectious symptoms occur approximately within the first 24 hours after injury, but patients often do not seek medical care until approximately a day or two after the incident.[85] Viridans streptococci, especially *Streptococcus anginosus,* are the most common wound isolates. *Staphylococcus aureus* infection occurs in 30% to 40% of wounds and is usually present in patients who present 3 to 4 days after the injury and have attempted self-débridement of the wound. There have been few reports of MRSA isolated from clenched-fist injuries.[86,87] Other reported isolates have included *Haemophilus influenzae, H. parainfluenzae, Aggregatibacter (Haemophilus) aphrophilus, Aggregatibacter (Haemophilus) paraphrophilus, Klebsiella* species, *Enterobacter cloacae, Prevotella* and *Peptostreptococcus* species, and *F. nucleatum.*[82,85] Up to 45% of the anaerobic gram-negative bacilli isolated from human bite wounds may be penicillin resistant and β-lactamase positive.[62,88] *Candida* species were found in 8% of patients in one study, although their pathogenicity was not determined.[85]

MANAGEMENT OF HUMAN BITES

Aerobic and anaerobic cultures should be obtained for infected wounds. Wounds should be irrigated with water and, if necessary, surgically débrided.[89] As much as possible, immobilization of the affected area, including splinting if necessary, and elevation should be instituted.

Initial antimicrobial therapy should provide coverage for *Staphylococcus, Streptococcus, Eikenella,* and anaerobic organisms such as *Prevotella, Fusobacterium,* and *Veillonella* species. Patients who present early with uninfected wounds may also be considered candidates for shorter duration of antimicrobial therapy. Amoxicillin-clavulanic acid as monotherapy or combination therapy with metronidazole plus trimethoprim-sulfamethoxazole can be used for the treatment of human bites. First-generation cephalosporins, dicloxacillin, erythromycin, clindamycin, and metronidazole are not effective as monotherapy because of inactivity of these agents against *E. corrodens.* In addition, first-generation cephalosporins, dicloxacillin, and erythromycin do not provide adequate activity against culprit anaerobic organisms.

Many patients (32% in one study[85]), especially those with extensive deep hand injuries, require hospitalization. Plain radiographs can be considered for wounds in close proximity to joints and bones. Similar to animal bite wounds, we do not recommend primary closure of small wounds, even for uninfected human bite wounds, especially those on the hands. If possible, approximation of the wound margins with adhesive tape or delayed primary closure (3–5 days) can be alternatives to primary closure in certain circumstances. Facial wounds may present a special situation because of the possibility of scarring and disfigurement and may require primary closure.

CLENCHED-FIST INJURIES

"Clenched-fist" injuries are traumatic lacerations that occur when one person strikes another in the mouth with a clenched fist. These injuries are most common over the third and fourth metacarpophalangeal joints of the dominant hand, but they may also occur over the proximal interphalangeal joints. Complications of this type of injury often include septic arthritis or osteomyelitis. These lacerations are commonly only 12 to 14 mm long but, despite their innocuous appearance, frequently lead to serious complications because of the proximity of the skin over the knuckles to the joint capsule and the potential spread of infection into subcutaneous tissues and web spaces.

Typically, patients who sustain a clenched-fist injury do not take good care of their wound, ignore it until a day or more after the injury, and then awaken with a painful, throbbing, and swollen hand. The swelling usually spreads proximally but not distally and results in decreased range of motion. A purulent discharge is often present. Lymphangitis, adenopathy, fever, or other signs of systemic infection are infrequent.

The bacteriology of clenched-fist injuries is similar to that of human bites and usually consists of the normal human oral flora.[10,82,90] Viridans streptococci, especially *S. anginosus,* are the most frequent isolates, but *S. aureus* may be present in 20% to 40% of cases. Anaerobic bacteria can be recovered in more than 55% of clenched-fist injuries, including *Prevotella* species, *F. nucleatum,* and *Peptostreptococcus* (including *Finegoldia magna*). *Eikenella corrodens* is an often overlooked but especially important pathogen in clenched-fist injury infections.[90–93] It has a prevalence rate of 59% in human gingival plaque[79] and may be isolated in 25% of clenched-fist injuries.[91] It can act synergistically with viridans streptococci and is a common cause of osteomyelitis. Although *E. corrodens* is susceptible to penicillin, it is resistant to penicillinase-resistant penicillins, clindamycin, and metronidazole and is variably resistant to cephalosporins.[62–66]

Initial physical examination is often limited because the majority of patients are in severe pain and unable to fully comply with the examination. Management should include irrigation and débridement when necessary. Elevation of the injured extremity is helpful in reducing associated swelling. Plain radiographs can be obtained to rule out fracture and to serve as a baseline for assessing osteomyelitis. Tetanus immunization should be administered when indicated. Secondary débridement to remove necrotic tissue or to drain abscesses may be required.

Empirical antimicrobial therapy should include coverage for *Staphylococcus, Streptococcus, Eikenella,* and anaerobes, including *Prevotella, Fusobacterium,* and *Veillonella* species. Failure of first-generation cephalosporins and penicillinase-resistant penicillins, when used alone, has been reported and is often due to their inactivity against *E. corrodens.*[91–96] If resistant gram-negative rods are isolated, therapy should be altered according to the results of culture. What role β-lactamase–positive *Prevotella* and *Porphyromonas* species will have in the selection of antimicrobial therapy has not been specifically determined.

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The complete reference list is available online at Expert Consult.

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316 Immunization

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The two most effective means of preventing disease, disability, and death from infectious diseases have been sanitation and immunization.[1] Both approaches antedated understanding of the germ theory of disease. Artificial induction of immunity began centuries ago with variolation, the practice of inoculating fluid from smallpox lesions into skin of susceptible persons. Although this technique usually produced mild illness without complications, spread of disease did occur, with occasional complications. In 1796, Jenner demonstrated that milkmaids who had contracted cowpox (vaccinia) were immune to smallpox. He inoculated the vesicular fluid from cowpox lesions into the skin of susceptible people and induced protection against smallpox, thus beginning the era of immunization.

Immunization, the act of artificially inducing immunity or providing protection from disease, can be active or passive. Active immunization consists of inducing the body to develop defenses against disease. This usually is accomplished by means of administration of vaccines or toxoids that stimulate the body's immune system to produce antibodies or cell-mediated immunity, or both, which protects against the infectious agent.[2] Passive immunization consists of providing temporary protection through administration of exogenously produced antibody. Two situations in which passive immunization commonly occurs are through transplacental transfer of antibodies to the fetus, which may provide protection against certain diseases for the first 3 to 6 months of life, and injection of immunoglobulins for specific preventive purposes. A more detailed description of the immune mechanisms involved follows.

Immunizing agents include vaccines, toxoids, and antibody-containing preparations from human or animal donors. Several important definitions are provided here.

1. *Vaccine:* a suspension of attenuated, live, or killed microorganisms (bacteria, viruses, or rickettsiae), or fractions thereof, that is administered to induce immunity and thereby prevent infectious disease.
2. *Toxoid:* a modified bacterial toxin that has been rendered nontoxic but retains the ability to stimulate formation of antitoxin.
3. Immunoglobulin products include standard immune globulin (IG) for intramuscular (IM) use, hyperimmune globulins that are available for IM and/or intravenous (IV) use, standard immune globulin intravenous (IGIV), immune globulin subcutaneous (IGSC), antibodies of animal origin, and monoclonal antibodies. IG is a sterile, concentrated protein solution containing antibodies from human blood that reflect the infectious and immunization experience of the population from whose plasma the IG was prepared. IG contains 15% to 18% protein, consisting primarily of the immunoglobulin G (IgG) fraction (90%) with trace amounts of immunoglobulin A (IgA) and immunoglobulin M (IgM). IG primarily is indicated for routine protection of certain immunodeficient persons and for passive immunization against measles and hepatitis A. IGIV is indicated primarily for replacement therapy in immunoglobulin G (IgG) deficiency and pediatric human immunodeficiency virus (HIV) infection, treatment of Kawasaki disease, and idiopathic thrombocytopenic purpura. IGSC is indicated primarily for treatment of antibody deficiency.
4. Specific immunoglobulin: special preparations are obtained from donor pools preselected for high antibody content against a specific disease—for example, hepatitis B immune globulin (HBIG), varicella-zoster immune globulin (VariZIG), rabies immune globulin (RIG), tetanus immune globulin (TIG), and botulism IGIV used to treat infant botulism.

The constituents of immunizing agents include the following:

1. *Suspending fluid:* This frequently is as simple as sterile water or saline, but it may be a complex fluid containing small amounts of proteins or other constituents derived from the medium or biologic system in which the immunizing agent is produced (serum proteins, egg antigens, cell culture–derived antigens).
2. *Preservatives, stabilizers, antibiotics:* These components of vaccines are used (1) to inhibit or prevent bacterial growth in viral culture or the final product (preservatives and antimicrobial agents) or (2) to stabilize the antigen against changes in temperature and/or pH (stabilizers). They include materials such as mercurials (thimerosal), gelatin, and specific antimicrobial agents. Allergic reactions may occur if the recipient is sensitive to any of these additives. Preservatives are required for multidose vaccine formulations or vials to prevent bacterial or fungal growth, should they be introduced on repeated entry into the vial. Thimerosal, an ethylmercury-containing preservative, has been the major preservative used in vaccines around the world. A review of the mercury content of vaccines in the United States in 1999 indicated that some children had received quantities of ethylmercury from thimerosal in excess of some federal guidelines for methyl mercury. As a precautionary measure, thimerosal as a preservative was removed from most vaccines in the immunization schedule to the extent feasible.[3] However, some of these vaccines may contain trace amounts (www.fda.gov/cber/vaccine/thimerosal.htm). Subsequent studies of potential adverse consequences of thimerosal have not demonstrated significant harm from its use in vaccines. It is likely had these data been available in 1999, the United States would not have made the decision to remove thimerosal from vaccines for children.[4,5] Some vaccines for children contain other preservatives (e.g., 2-phenoxyethanol) or do not need a preservative because they are packaged in single-dose vials. Influenza vaccines in multidose vials used in adults and combined adult-type tetanus and diphtheria toxoids (Td) contain thimerosal as a preservative.[6]
3. *Adjuvants:* An aluminum salt is used in some vaccines to enhance the immune response to vaccines containing inactivated microorganisms or their products (e.g., toxoids and hepatitis B vaccine). Bivalent human papillomavirus vaccine contains an aluminum salt combined with monophosphoryl lipid A. An oil-in-water adjuvant is used in one influenza vaccine licensed in the United States and in other vaccines licensed outside the United States. Recombinant zoster vaccine (RZV) contains monophosphoryl lipid A combined with saponin. Vaccines with such adjuvants should be injected deeply into muscle masses

because subcutaneous or intracutaneous administration can cause local irritation, inflammation, granuloma formation, or necrosis.[7]

IMMUNOLOGIC BASIS OF VACCINATION

Two major approaches to active immunization have been used: use of live (attenuated) infectious agents, and use of inactivated, or detoxified, agents or their extracts. For many diseases (including influenza, poliomyelitis, typhoid, and measles), both approaches have been used. Live-attenuated vaccines are believed to induce an immunologic response more similar to that resulting from natural infection than do killed vaccines. Inactivated or killed vaccines can consist of inactivated whole organisms (e.g., hepatitis A vaccine), detoxified exotoxin (e.g., diphtheria and tetanus toxoids), soluble capsular material either alone (e.g., pneumococcal polysaccharide), or covalently linked to carrier protein (e.g., *Haemophilus influenzae* type b [Hib] conjugate vaccines), chemically purified components of the organism (e.g., acellular pertussis, inactivated influenza vaccines [IIVs]), or recombinant proteins (e.g., hepatitis B virus [HBV], serogroup B meningococcal vaccine [MenB-FHbp/MenB-4C], virus-like particles [VLPs; e.g., human papillomavirus (HPV)], or RZV).

Determinants of Immunogenicity

The immune system is complex, and antigen composition and presentation are critical for stimulation of the desired immune response. Immunogenicity is determined not only by the chemical and physical states of the antigen but also by the genetic characteristics of the responding individual, the physiologic condition of the individual (e.g., age, nutrition, sex, pregnancy status, stress, infections, immune status), and the manner in which the antigen is presented (route of administration, dose or doses and timing of doses, and presence of adjuvants).[8,9]

Live Versus Killed or Subunit Vaccines

Because the organisms in live vaccines multiply in the recipient, antigen production increases logarithmically until controlled by the immune response induced by the antigen. The live-attenuated viruses (e.g., measles, rubella) generally are believed to confer lifelong protection in those who respond. By contrast, killed vaccines (e.g., diphtheria, tetanus, rabies, typhoid) generally do not induce permanent immunity with one dose, requiring repeated vaccination and subsequent boosters for development and maintenance of high levels of antibody. Exceptions to this general rule may include hepatitis B vaccine, for which long-term immunologic memory has been demonstrated for approximately 30 years after vaccination[10], and inactivated polio vaccine (IPV), for which the duration of immunity is unknown. Although the amount of antigen initially introduced is greater with inactivated vaccines, multiplication of organisms in the host results in a cumulatively greater antigenic input with live vaccines.

Most vaccines include protein antigens, which generate a T-lymphocyte–dependent immune response. This response induces immunologic memory, booster effects with repeat administration, and good immunogenicity in all age groups. However, purified bacterial capsular polysaccharide vaccines induce a T-lymphocyte–independent immune response, which does not lead to immune memory and cannot be boosted with repeated injections.[11] Polysaccharide vaccines have poor immunogenicity in infants and young children. Covalent linkage of the polysaccharide to a carrier protein converts it from a T-lymphocyte–independent to a T-lymphocyte–dependent antigen (e.g., conjugated Hib, pneumococcal, and meningococcal vaccines), which produces a good immune response in infants and children.

Dose

The amount of antigen determines the immune response. Presentation of an insufficient amount of antigen may result in no immune responsiveness. There is usually a dose-response curve relationship between antigen dose and peak response obtained beyond a threshold; however, responsiveness may reach a plateau, failing to increase beyond a certain level despite increasing doses of vaccine.

Adjuvants

The immune response to some inactivated vaccines or toxoids can be enhanced by addition of adjuvants, such as aluminum salts (either alone or in combination with monophosphoryl lipid A).[11a] Adjuvants are particularly useful with inactivated products, such as diphtheria and tetanus toxoids, acellular pertussis vaccines (DTaP), and hepatitis B vaccine. The mechanism of enhancement of antigenicity by adjuvants is not well defined; however, it is increasingly clear that adjuvants activate the innate immune system through pathogen-associated molecular patterns (PAMPs). Licensed adjuvants for use in humans in the United States include aluminum salts alone or with monophosphoryl lipid A, squalene-based oil-in-water emulsion, and synthetic oligodeoxynucleotides.[12]

Route of Administration

The route of administration can determine the nature of the immune response to a vaccine or toxoid. IM or subcutaneous delivery results in a predominantly IgG response. Oral (e.g., rotavirus vaccine and typhoid vaccine Ty21a) or nasal (e.g., live-attenuated influenza vaccine [LAIV]) vaccination is more likely to result in production of local IgA compared with IM injection, although systemic IgG also is induced. The immunogenicity of some vaccines is reduced when not given by the recommended route. For example, administration of hepatitis B vaccine subcutaneously into the fatty tissue of the buttock was associated with substantially lower seroconversion rates than injection intramuscularly into the deltoid muscle.[13]

Most vaccines are administered either intramuscularly or subcutaneously.

Age

The immune response to a vaccine varies with age. Although children and young adults usually respond well to all vaccines, differences in response capability exist during early infancy and older age. The presence of high levels of passively acquired maternal antibody in the first few months of life impairs the initial immune response to some killed vaccines (e.g., hepatitis A vaccine,[14] diphtheria toxoid) and many live vaccines (e.g., measles). Prematurely born infants of low birth weight should be immunized at the usual chronologic age in most cases. Infants with birth weights less than 2000 g may require modification of the timing of hepatitis B immunoprophylaxis, depending on maternal hepatitis B surface antigen (HBsAg) status.[15] Some studies have suggested a reduced immune response in very-low-birth-weight infants (<1500 g) immunized according to the usual schedule; however, antibody concentrations achieved usually are protective. In older adults, the response to antigenic stimulation may be diminished (e.g., influenza, hepatitis B vaccines). This has led to the development of higher-potency influenza vaccines for use in the elderly.

COMPONENTS OF THE IMMUNE RESPONSE

The immune response traditionally is divided into two components: the innate immune response, which is rapid, nonspecific, and serves as an immediate first line of defense against an infection, and the adaptive immune response, which develops over a matter of days, is specific for the foreign antigen, and results in long-term immune memory. The latter protects the host against subsequent challenge with the same or immunologically similar pathogens and is the underlying principle of vaccination. The innate immune response is mediated by natural killer (NK) cells, which recognize and kill virally infected cells; by complement, which is activated by components of bacterial cell walls; and by phagocytes, including macrophages and dendritic cells (DCs), which ingest microorganisms and foreign particulates.[16] The adaptive immune response relies on antigen-presenting cells (APCs), such as DCs, for activation and is mediated by T and B lymphocytes. T lymphocytes can be divided into CD4 (helper) and CD8 (cytotoxic) lymphocytes and are responsible for cell-mediated immune responses. CD4 helper T lymphocytes can be further subdivided into Th1 lymphocytes, which predominantly lead to cell-mediated responses, and Th2 lymphocytes, which predominantly lead to humoral responses. B lymphocytes produce antibody specific for the immunizing agent and require CD4–T-lymphocyte help. Interactions between APCs, helper T-lymphocytes, and B-lymphocytes involve class II major histocompatibility complex (MHC) antigens, whereas interactions between cytotoxic T lymphocytes and their target involve MHC class I antigens.[17] Soluble mediators or cytokines are secreted by

all cell types and serve as activation and differentiation factors for different cell lineages. These include interleukins, interferons, and others.[18] A further class of CD4 T lymphocytes (Treg) plays an essential role in the regulation of the adaptive immune response.[19]

The innate immune response is able to respond differently to different types of pathogens, and these differential responses help determine the nature of the subsequent adaptive response.[20] Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and others, encoded in the germline recognize PAMPs and contribute to immune activation by inducing proinflammatory cytokines, which in turn modulate the adaptive immune response. As alluded to earlier, this has significant implications for adjuvant development.[21,22]

MOBILIZATION OF THE ADAPTIVE IMMUNE RESPONSE

On exposure to an infectious organism or a vaccine, the innate immune system is mobilized through APC recognition of PAMPs that are present either in the organism or in the adjuvant. Activated APCs (macrophages and DCs) secrete proinflammatory cytokines and chemokines, which recruit other leukocytes to the site of infection. When activated, DCs migrate to the draining lymph nodes, where they interact with T lymphocytes through the MHC-peptide complex.[23] Once the organism or antigen is internalized, it is killed and broken down into peptides. These peptides are transported to the cell surface through membrane trafficking and bind to MHC class I or class II molecules. MHC class I molecules are able to bind peptides that are 8 to 10 amino acids in length, whereas MHC class II molecules are more permissive, binding peptides of 13 amino acids and greater.[24]

The first step in the induction of a T-lymphocyte–dependent antibody response is the activation of naïve CD4 helper T lymphocytes by presentation of an antigen by phagocytes or DCs. The T-lymphocyte receptor recognizes the MHC-peptide complex, and this recognition triggers secretion of cytokines, which stimulate maturation of naïve helper T lymphocytes. In the presence of interleukin-12 (IL-12), Th1 lymphocytes will differentiate, and these in turn will secrete IL-2 and interferon-γ. In the presence of IL-4, Th2 lymphocytes will differentiate and secrete IL-4 and IL-5. These two cytokines are essential for the differentiation and maturation of B lymphocytes into antibody-secreting plasma cells.

Naïve B lymphocytes recognize a specific antigenic epitope on native antigen through the immunoglobulin receptor on their surface but are unable to differentiate into antibody-secreting lymphocytes without T-lymphocyte help. A given B lymphocyte can be activated only by a T lymphocyte responding to the same antigen, though not necessarily to the same epitope. A helper T lymphocyte will recognize the MHC class II complex on the surface of the B lymphocyte and deliver a signal for B-lymphocyte differentiation. This leads to B-lymphocyte proliferation and maturation in a clonal manner. Class switching (from IgM to IgG and IgA) and affinity maturation occur, and antigen-specific plasma cells develop. However, not all B lymphocytes become plasma cells. Some mature into memory B cells, which are long-lived and form the basis of the rapid secondary response on the next encounter with the pathogen.[25] Although the mechanism of maintenance of these cells is not clear, the ability to mount a strong secondary response after many years argues for a homeostatic mechanism that regulates these cells. The antibodies formed after vaccination express a variety of antigen-binding specificities (i.e., recognize different structures on a complex multideterminant antigen), reflecting the sum of the large number of individual clonal B-lymphocyte responses that make up an antibody response.

Antibodies mediate protection through a variety of mechanisms. They may inactivate soluble toxic protein products of bacteria (antitoxins), facilitate intracellular digestion of bacteria by phagocytes (opsonization), interact with components of serum complement to damage the bacterial membrane with resultant bacteriolysis (lysins), prevent infectious virus from infecting cells (neutralizing antibodies), or interact with components of the bacterial surface to prevent adhesion to mucosal surfaces (anti-adhesins). Antibodies cannot readily reach intracellular sites of infection, the sites of viral and some bacterial replication. However, antibodies are effective against many viral diseases through interaction with viruses before initial intracellular penetration occurs and through prevention of locally replicating viruses from disseminating from the site of entry to an important target organ, as in the spread of poliovirus from the intestine to the central nervous system or rabies from a puncture wound to peripheral neural tissue.

Virally infected cells can be killed by cytotoxic CD8 T lymphocytes. As the virus replicates in a cell, viral proteins are processed and presented on the cell surface as an MHC class I–peptide complex, which is then recognized by cytotoxic T lymphocytes. Cells infected with intracellular bacteria, such as *Mycobacterium leprae,* are recognized and killed in the same way.

UNANTICIPATED RESPONSES

Independent of antibody production, stimulation of the immune system by vaccination may, on occasion, elicit a hypersensitivity response. Killed measles vaccine, used in the United States between 1963 and 1967, induced incomplete humoral immunity and cell-mediated hypersensitivity, resulting in development of a syndrome of atypical measles in some children on subsequent exposure to measles.[26] In addition, some antibodies produced may not be protective but block the reaction of protective antibodies with antigens, inhibiting the body's defenses. Some vaccines may induce immunologic tolerance that results in blunting of the immune response on subsequent exposure to the antigen (e.g., meningococcal polysaccharide vaccine [MPSV]).[27] Concerns have been raised that immunizations might induce autoimmune disorders. However, careful reviews of both the possible biologic mechanisms and epidemiologic evidence generally have failed to confirm vaccines as causes of these disorders.[28] The evidence was insufficient to accept or reject a causal relationship between vaccines and allergic disorders, particularly asthma.[29] A subsequent epidemiologic study failed to show an association between vaccines and asthma.[30] Concerns also have been raised that the number of antigens in the current vaccine schedule might overwhelm an infant's immune system, leading to chronic diseases and predisposing to other serious infections.[31] As a result of removal of whole-cell pertussis vaccine and smallpox vaccine from the current immunization schedule, the number of immunogenic proteins and polysaccharides a child is exposed to today is actually smaller than in the past. Estimates suggest that an infant is capable of responding to 10,000 vaccine antigens simultaneously.[32] The Institute of Medicine (IOM) concluded that available evidence favored rejection of a causal relationship between vaccines and increased risk for infections. IOM also concluded that available evidence favored rejection of a causal relationship between vaccines and type 1 diabetes mellitus.[29]

TEMPORAL COURSE OF THE IMMUNE RESPONSE

On first exposure to a vaccine, a primary response is induced, and a protective immune response will develop in about 2 weeks. Circulating antibodies do not usually appear for 7 to 10 days, and the immunoglobulin class of the response changes over this period of time. Early-appearing antibodies are usually of the IgM class and of low affinity; late-appearing antibodies are usually of the IgG class and display a high affinity. IgM antibodies may fix complement, making lysis and phagocytosis possible. As the titer of IgG rises during the second week (or later) after immunogenic stimulation, the IgM titer falls. IgG antibodies are produced in large amounts and function in the neutralization, precipitation, and fixation of complement. The antibody titer frequently reaches a peak in about 2 to 6 weeks and then falls gradually. The switch from IgM synthesis to predominantly IgG synthesis in B lymphocytes is mediated by T-lymphocyte help. Uncommonly, people may not respond to a vaccine, experiencing a primary vaccine failure. This may be due to a genetic inability to respond to vaccine, but other factors are involved. For example, almost all children who do not respond immunologically to the first dose of measles-mumps-rubella (MMR) vaccine will acquire measles immunity after a second dose.[32]

After a second exposure to the same antigen, a heightened humoral or cell-mediated response, an anamnestic response, is observed. These secondary responses occur sooner than the primary response, usually within 4 to 5 days, and depend on a marked proliferation of antibody-producing cells or effector T lymphocytes. Effector T lymphocytes, also