BURNS AND WOUND CARE MODULE

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Objectives:
1. Review the management of the patient with a severe burn
2. Discuss the utility and limitations of topical antibiotics for burn wounds
3. Discuss options for evaluating and treating a chronic wound
4. Discuss the current understanding of the mechanism behind negative pressure wound therapy

BURN RESUSCITATION

Initial care of the burn patient is the same as the ABCs of trauma. Fluid resuscitation is begun for any burn that is more than 20% total body surface area (TBSA). TBSA is estimated by the rule of 9s: 9% head, 18% anterior torso, 18% posterior torso, 9% each arm, 18% each leg, and 1% for the perineum. Lactated Ringer solution is begun using the Parkland formula: 4 mL/kg × %TBSA × body weight (kg). Half of this amount is given over the first 8 hours, and the other half is given over the next 16 hours. The Parkland formula provides a starting point; the infusion rate can be titrated to a goal urine output of 30 mL/hour. When resuscitation is delayed, this formula often underestimates the amount of fluid resuscitation needed. Following the patient’s urine output is important to properly assess adequate volume resuscitation.

BURN WOUND CLASSIFICATION

Burns are classified as first (superficial), second (partial thickness), and third (full thickness) degree. Superficial burns involve the epidermis only, are not counted in TBSA, and heal on their own. A simple topical treatment like aloe vera may be used.

Partial-thickness burns involve the dermis layer. They can be superficial or deep in the dermis. A superficial partial-thickness burn has clear blisters, is painful to touch, and blanches. A deep partial-thickness burn may have hemorrhagic blisters, and the dermis does not blanch.

Full-thickness burns involve the whole dermis and are insensate and leathery in appearance.

It can be difficult to determine the burn depth, and the depth may vary within the same wound. The burn depth may change over the first few days, which underscores the need to view the wound daily as the injury progresses.

BURN WOUNDS

Full-thickness burns that are circumferential on an extremity or the chest may require escharotomy. This would be indicated if peripheral perfusion is compromised or respiratory function is deteriorating as resuscitation continues. Incisions to release the full-thickness burn can usually be done without anesthetic. Partial thickness burns causing compression symptoms may need anesthetic to achieve tissue release.

Once a patient is hemodynamically normal, the wounds are cleaned, and a topical antibiotic is applied with an appropriate dressing. Common initial topical agents are bacitracin, silver sulfadiazine, mafenide acetate, triple antibiotic ointment, and mupirocin. Descriptions of each follow.
• **Bacitracin:** Bacitracin is active against staphylococcal and streptococcal species. It is not active against methicillin-sensitive *Staphylococcus aureus* (MRSA).

• **Silver sulfadiazine:** Silver sulfadiazine covers Gram positives, Gram negatives, and yeasts; a rare side effect is transient neutropenia. It is contraindicated in patients with a sulfa allergy.

• **Mafenide acetate:** Mafenide acetate covers Gram positives and Gram negatives (including *Pseudomonas*), and it is able to penetrate an eschar. It is a carbonic anhydrase inhibitor and therefore may cause metabolic acidosis. It should be used with caution in burns greater than 20% TBSA secondary to this complication. When used on partial-thickness burns, it may be painful on application.

• **Triple antibiotic** (polymyxin B–bacitracin–neomycin): Triple antibiotic is an ointment that covers Gram positives and Gram negatives.

• **Mupirocin:** Mupirocin covers Gram positives, including MRSA.

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**BURN WOUND TREATMENT**

Deep partial-thickness and full-thickness burns require excision of the burn followed by skin grafting. Tangential excision is used for most burns. Excision down to the fascia (fascial excision) may be necessary for some full-thickness or electrical burns. Split-thickness skin grafts (STSGs) are used to cover the defect. Typically, these grafts are meshed so that they can stretch and cover a wider area, topographically lay better, and allow drainage. STSGs are usually secured with staples, chromic sutures, or glue as they are applied. Negative pressure wound therapy (NPWT) is an increasingly common way to secure STSGs, depending on the size and location.

Prophylactic systemic antibiotics are not used in patients with any depth of burn wound. All burn wounds are colonized with bacteria by the first 3 days. Rarely, the bacteria can cause infection in the dermis and deeper tissue. Burn wound sepsis is diagnosed by a skin biopsy and quantitative wound culture that grows more than 10^5 organisms. In this situation, the wound should be excised and parenteral antibiotics started.

American Burn Association and the American College of Surgeons Committee on Trauma guidelines for transfer to a designated burn center are as follows:

1. Partial-thickness and full-thickness burns of greater than 10% TBSA
2. Full-thickness burns in any age group
3. Any burn involving the face, hands, feet, eye, ear, or perineum that may result in cosmetic or functional disability
4. Electrical injury
5. Inhalation injury or associated trauma
6. Chemical burns
7. Burns in patients with significant comorbid conditions (diabetes, chronic obstructive pulmonary disease, cardiac disease)
OPEN AND CHRONIC WOUNDS

Wounds that are open or chronic may be dealt with in a variety of ways. A wound that is draining needs an absorptive dressing. A dry wound needs a dressing that maintains a moist environment. Dressings should not stick to the wound. Ideally, a dressing is changed only once per day, but changing a dressing twice a day may be necessary if the wound is dirty. It is important that the wound is cleaned at the time of the dressing change. A variety of products are available, depending on the condition of the wound. Topical antibiotics like those used in burns can also be used in chronic wounds, although they are rarely necessary.

Rarely, a squamous cell skin cancer can develop in a chronic, nonhealing wound (Marjolin ulcer). This may be more common in a burn wound that was never excised and grafted. Diagnosis is made by biopsy; if positive, treatment is wide local excision with regional lymph node dissection, if needed.

SILVER

Silver is the common ingredient in many wound dressings, including silver sulfadiazine, Acticoat®, and Aquacel Ag®, among others. Silver has antimicrobial action through the silver ion (Ag+). Ag+ disrupts the bacterial cell wall, inhibits enzymes, and binds to DNA, which interferes with cell division and replication.

Silver coatings have been used on a variety of medical devices; examples that have been studied are central venous catheters (CVC), urinary catheters, and endotracheal tubes. CVCs with chlorhexidine/silver sulfadiazine coating appeared beneficial in the day 2–10 interval in an institution where the background infection rate was high. Urinary catheters with silver alloy coating appeared cost-effective and reduced (1) asymptomatic bacteriuria for adults catheterized for less than 1 week and (2) colonization after catheterization for longer than 1 week.

Silver-coated endotracheal tubes delay the occurrence of ventilator-associated pneumonia (VAP) but do not affect other factors such as duration of intubation, intensive care unit stay, hospital stay, or mortality. Before any such device is implemented to fight these nosocomial infections, a comprehensive program must be in place to decrease the background rate of infection (i.e., judicious use of and early removal of CVC and urinary catheters, extubation protocols).

NEGATIVE PRESSURE WOUND THERAPY

NPWT is a wound care technology involving a wound dressing that has negative pressure applied to it. The intervention was developed in the 1990s. While initially many homemade devices were used, commercial devices are now available and are being used commonly in many different situations. A Cochrane report stated that between 2001 and 2007, Medicare payments for NPWT pumps and associated equipment increased from US $24 million to US $164 million. Initially, most applications were used in hospitalized patients or patients with home healthcare support. As the market developed, outpatient devices were developed and their use without direct medical supervision is commonplace.

The benefits of NPWT include convenience and possible enhanced wound healing. Convenience exists in that most systems are closed and wound drainage is removed from the wound, avoiding multiple dressing changes and dealing with wound odor. Wound dressing changes are usually reduced, which also decreases pain for the patient. These systems allow quantitation of wound drainage, which may be helpful in making clinical decisions about wound management.
The claims of enhanced wound management are more difficult to quantify. NPWT is suggested to work by 4 mechanisms of action: (1) contraction of the wound, (2) creation of a stable wound environment, (3) removal of extracellular fluid, and (4) microdeformation of the wound promoting healing. There are many published papers on NPWT, but few are prospective randomized studies. Although the anecdotal evidence and personal experience in using NPWT is compelling, when subjected to rigorous assessment such as a Cochrane review, the evidence of effectiveness is weak at this time. There are also potential risks or downsides to the therapy. Tissue maceration and retained foreign bodies are possible, and bleeding may be induced either from wound irritation or by the negative pressure effect on open vessels, especially veins, when used on open traumatic wounds.

A number of reviews of NPWT have been conducted by the Cochrane group. The use of NPWT on open surgical incisions to promote wound healing was compared in 2 small studies. No clear advantage was identified in wound healing. Another review focused on NPWT applied to closed incisions as well as skin grafts. No differences were found in surgical site infection, wound dehiscence, or reoperation for closed wounds. Skin grafts had a lower reoperation rate when treated with NPWT compared with standard wound dressings. One trial in closed orthopedic wounds documented a 60% incidence of wound blisters with the NPWT device. Diabetic foot wounds have some positive data indicating that NPWT promotes healing faster than standard alginate dressings. NPWT had a complete closure rate for diabetic ulcers of 42% compared with 28% for alginate dressings.

The other use of NPWT is for the management of open abdomens after abdominal surgery. This usually occurs when massive bleeding or infection occurs and the abdomen cannot be primarily closed. This dressing facilitates the management of wound drainage. It is usually used as a temporary dressing with a return to the operating room for fascial closure in 1–3 days.

**References: Burns and Wound Care**

Antibiotics
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Objectives:
1. Review characteristics of commonly used antibiotics
2. List options for MRSA treatments
3. Review classes of fungal agents

Antibiotic therapies are of tremendous importance. Inappropriate empiric therapy and delayed initiation of therapy contribute to increased mortality, development of resistance, increased healthcare costs, and lack of compliance with national standards. Lack of compliance with national standards results in financial penalties on reimbursement.

Antimicrobial drug development has been declining for years, and the future does not look promising. Therefore, appropriate use of currently available antibiotics—referred to as antimicrobial stewardship—is imperative. Stewardship is summarized as appropriate drug selection based on patient-specific risk factors, such as appropriate dose, route, and frequency; deescalation based on culture and sensitivity reports; and duration of therapy compliant with evidence-based treatment guidelines. The assumption is that these principles will yield optimal outcomes when treating various types of infections while minimizing unnecessary resistance and healthcare costs. To aid prescribers, the Infectious Disease Society of America has published treatment guidelines for major disease states (available at www.idsociety.org).

BETA-LACTAM ANTIBIOTICS

Beta-lactam (BL) antibiotic is a general term describing antibiotics that contain a BL ring in their molecular structure. BL antibiotics include penicillins, cephalosporins, carbapenems, and BL/BLase inhibitors. Each of these antibiotic classes manifests its activity on the bacterial cell wall, resulting in time-dependant killing. Extended infusions may increase efficacy and reduce treatment costs. BL antibiotics are well tolerated. Potential adverse effects include hypersensitivity reactions, interstitial nephritis, drug fever, thrombocytopenia, and possibly hemorrhagic complications as a result of disturbing synthesis of Vitamin-K dependent clotting factors and biliary sludging for those that concentrate in the bile. Patients with allergies to a specific BL antibiotic should be considered at risk for allergic reactions to other BL antibiotics.

Cephalosporins

The cephalosporin drug class has a reported allergic cross-reactivity of 5–10% to penicillin. Drugs in this class should be avoided in patients with serious or immediate reactions (anaphylaxis, bronchospasm) but may be tried in patients with mild or delayed reactions, although drug desensitization would be a safer approach. Moving from first- to third-generation
cephalosporins, the Gram-negative activity is enhanced at the expense of some Gram-positive activity, although all generations (including fourth) lack activity against enterococci. Cephalosporins have good tissue penetration and distribute well to organs.

First-generation cephalosporins, such as cefazolin, are commonly used for perioperative prophylaxis because of their activity against skin flora such as methicillin-sensitive Staphylococcus aureus (MSSA) and Staphylococcus epidermidis. Cefazolin may also be used therapeutically for routine Gram-positive pathogens. Cefazolin has some activity against anaerobes associated with mouth flora. The term cephamycin is used to describe a subset of cephalosporins that have enhanced activity against anaerobes, including mouth and colon flora. Two of these are cefoxitin and cefotetan. Although second-generation cephalosporins have less Gram-positive activity than do first generations, they are good options for a mixed infection or perioperative prophylaxis for bowel surgery.

Third generations, such as ceftriaxone, can be used in combination with the antianaerobic metronidazole to broaden the spectrum of activity. This combination is efficacious for uncomplicated and complicated intra-abdominal infections when multidrug resistant pathogens are not suspected. Fourth-generation cefepime has the broadest spectrum of Gram-negative activity and maintains activity against Pseudomonas aeruginosa, as does the third-generation ceftazidime, making it a viable option for nosocomial infections, including pneumonia. The recently developed fifth-generation ceftobiprole and ceftaroline retained activity against MRSA, including exotoxin-producing strains. Of the 2, only ceftobiprole maintains activity against P. aeruginosa. Both agents have marginal activity against enterococci.

**Beta-Lactam/Beta-Lactamase Inhibitors**

Piperacillin/tazobactam and ticarcillin/clavulanate offer an enhanced spectrum of activity compared with cefepime, particularly against anaerobes and Gram-negative pathogens such as P. aeruginosa. Ampicillin/sulbactam has a narrower spectrum as a result of the less-potent beta-lactamase inhibitor sulbactam, which results in less Gram-negative activity. All these agents maintain activity against resistant organisms that are cephalosporinase and beta-lactamase producing, which would otherwise render cephalosporins ineffective. Only patients previously exposed to antibiotics and those at risk for resistant pathogens should receive these drugs empirically. These agents must be avoided in patients with penicillin and beta-lactamase allergies. Amoxicillin/clavulanate is an oral option that allows for step-down therapy.

**Carbapenems**

Carbapenems maintain activity against a wide spectrum of bacteria, including those harboring resistance to other drug classes, such as cephalosporinas and extended-spectrum beta-lactamases (ESBL). As a result, this drug class should not be used routinely as a first-line treatment but should be reserved for complicated and resistant infections. Cross-reactivity with penicillin allergy is less defined compared with cephalosporins, but it is estimated to be 10% or more. Meropenem, imipenem-cilastatin, and doripenem have similar spectrums of activity and are generally interchangeable. They maintain activity against most clinically significant Gram-positive and Gram-negative pathogens (including MSSA, enterococci, and P. aeruginosa) and anaerobes. Ertapenem has a narrower spectrum that lacks activity against enterococci and P. aeruginosa. Its use may select out for these pathogens in clinical practice.
Carbapenems may reduce seizure threshold and should be avoided in high-risk patients. Meropenem may have the lowest risk of seizure in the drug class and is often used for infections related to the central nervous system.

**FLUOROQUINOLONES**

Fluoroquinolones (FQ) most often used in practice are moxifloxacin, levofloxacin, and ciprofloxacin. They have good tissue penetration and serve as empiric therapy for most infections when multidrug resistance is not suspected. Moxifloxacin has strong Gram-positive activity, good Gram-negative activity, and strong anaerobic activity, but it lacks urine penetration and should not be used for urinary tract infections. It lacks activity against *Clostridium difficile* and is associated with *C. difficile* infection (CDI) outbreaks as a result of killing competitive flora in the bowel. Levofloxacin maintains good activity against most bacteria, whereas ciprofloxacin has strong Gram-negative activity at the expense of only moderate Gram-positive and anaerobic activity. FQs often maintain in vitro activity against MSSA and MRSA but yield a high incidence of treatment failure and resistance; FQ use should be avoided for the treatment of these bacteria. Ciprofloxacin can treat Enterococcus in the urine where it achieves concentrations, but it should be avoided in other sites of infection. FQs should be avoided in patients at risk for seizures as they may reduce the seizure threshold. FQs have multiple drug interactions, most notably in the surgical intensive care unit are warfarin, theophylline, and specifically ciprofloxacin with tizanidine; concurrent use should be avoided. They also prolong QTc interval and should be used cautiously with drugs with similar effects such as fluconazole and amiodarone.

**AMINOGLYCOSIDES**

Aminoglycosides (AG) are among the most potent Gram-negative antimicrobials available and have been used effectively for decades. Resistance rates decrease from gentamicin to tobramycin to amikacin having the most robust activity profile. They remain the gold standard for Gram-negative bacteremia, because of the potency and concentration in the serum. However, their empiric use has diminished, because of the availability of less toxic therapeutic alternatives. AGs remain a reliable drug class for many multidrug-resistant pathogens. They may be used synergistically with BL antibiotics for resistant strains of *S. aureus* and Enterococcus; the BL antibiotic disrupts the bacterial cell wall, allowing the AG to penetrate the bacteria and manifest its activity. Dosing has evolved to extended interval, usually 5–7 mg/kg/day (15–21 mg/kg/day for amikacin), to optimize the concentration-dependent killing. A peak to minimal inhibitory concentration (MIC) ratio of 10:1 has yielded increased survival. Nephrotoxicity is common, with a reported incidence as high as 20%; renal function should be closely monitored.

Ototoxicity may also occur. Nephrotoxicity and ototoxicity may not be reversible. Pharmacist consultation has demonstrated increased efficacy with decreased toxicity and should routinely be considered.

**MRSA TREATMENT OPTIONS**

Infections caused by MRSA are associated with increased morbidity, mortality, and healthcare costs. Vancomycin, a glycopeptide with a broad Gram-positive spectrum, has been the cornerstone of MRSA treatment for decades. Over time, the MIC has risen, but true resistance is relatively rare. Vancomycin also has activity against enterococci, but its use has induced the development of vancomycin resistant enterococci (VRE), which is on the rise. For both
staphylococci and enterococci, BL antibiotics should always be used, if possible, based on susceptibility results, because their efficacy is greater than that of vancomycin for these bacteria. Nephrotoxicity associated with vancomycin is concerning; dosing should be patient specific to minimize potential risk. Most institutions have pharmacokinetic consulting services that can optimize dosing to achieve evidence-based troughs (ranging from 10–20 µg/mL, depending on indication) while minimizing adverse effects.

Linezolid is well established for the treatment of nosocomial pneumonia and complicated skin and skin structure infection (SSTI). It also maintains activity against VRE, although similar to vancomycin, resistance is on the rise. Limited data suggest superiority of linezolid over vancomycin for the treatment of pneumonia, but this finding remains controversial. The oral formulation is well absorbed and offers a useful option for patients able to tolerate oral medications. The drug’s weak monoamine oxidase inhibition increases the risk of serotonin syndrome—a rare but fatal complication—when used concurrently with other serotonergic agents. This combination should be avoided, if possible. Adverse effects include optic neuropathy, peripheral neuropathy, and pancytopenia, commonly manifested as thrombocytopenia. Limiting the duration of treatment to less than 14 days reduces the likelihood of these complications. A major advantage of linezolid is that it has equivalent serum levels, whether given orally or intravenously.

Tigecycline is a broad-spectrum glycylcycline approved for complicated infection and immunity and SSTI. Tigecycline maintains activity against MRSA, VRE, and ESBL-producing pathogens. However, tigecycline lacks activity against \textit{P. aeruginosa}, which greatly limits its role as monotherapy. Owing to its similarities to tetracycline, it has been slow to gain acceptance for the treatment of serious, life-threatening infections. An unexplained increase in all-cause mortality was observed in patients receiving tigecycline in both phase 3 and 4 studies. Further, tigecycline monotherapy should be avoided in patients with perforated bowel due to poorer outcomes reported in phase 3 trials. Its use is often limited to treating patients with beta-lactam allergies, patients intolerant to conventional therapy, or patients with polymicrobial infections. Side effects are minimal compared with other agents, most commonly manifested as nausea and vomiting.

Daptomycin has good activity against MRSA but has little role in the surgical intensive care unit except for treatment of endocarditis or for complicated SSTI where other therapies have failed or are contraindicated. Daptomycin is inactivated by pulmonary surfactant and should not be used to treat bacterial pneumonia. The most common serious adverse effects are myopathy and rhabdomyolysis, for which baseline and weekly creatine phosphokinase measurement is recommended. It is associated with the development of eosinophilic pneumonia. If any of these are observed, daptomycin should be immediately discontinued.

In addition to the previously discussed agents, several other oral options are available with activity against community-associated MRSA, including trimethoprim/sulfamethoxazole, doxycycline, and clindamycin. These agents are not used for severe nosocomial MRSA infection, but they are often used for community-acquired MRSA infections involving SSTI.

\section*{C. \textit{DIFFICILE} TREATMENT OPTIONS}

CDI is an increasingly common complication in healthcare, including in the intensive care unit. Treatment is determined by both episode (initial versus recurrent) and severity of infection. Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI and has the
lowest acquisition cost of all treatment. Intravenous and oral metronidazole are both effective treatment options.

Oral vancomycin is generally reserved for more severe infections due to demonstrated superiority compared with metronidazole. Intravenous vancomycin is not effective for CDI. Rectal therapy may be considered when oral therapy is not an option. Combination therapy with metronidazole and vancomycin may be considered in severe or complicated CDIs.

Fidaxomicin is a macrocyclic antibiotic recently approved for CDIs. It is as effective as vancomycin but was associated with a lower recurrence rate compared with vancomycin treatment.

FUNGAL TREATMENT OPTIONS

Fluconazole, an azole antifungal, remains the standard of care for most uncomplicated Candida infections in the intensive care unit, but local susceptibility patterns must also be considered. It maintains good activity against Candida albicans, the most prevalent species in the intensive care unit, although its activity has decreased against Candida glabrata over the years, the second most prevalent species.

New guidelines for fungal therapy were released in 2016 from the IDSA. These guidelines suggest that first-line treatment for candidemia should be with an echinocandin, such as caspofungin, rather than fluconazole. This recommendation is made because echinocandins are cidal agents for Candida rather than inhibitory, which is how azoles work. Further, more Candida glabrata that is typically resistant to the azoles is being seen. The guidelines also encourage sensitivity testing of Candida spp. If the fungus is sensitive to azoles, then the appropriate treatment should be step down therapy to fluconazole.

Voriconazole, another azole, has slightly enhanced activity against Candida species, but it is usually reserved to treat Aspergillus infections. Both agents are associated with elevations in liver enzymes and QTc prolongation but are generally well tolerated. For moderately severe to severe illness or patients with recent azole exposure, empiric therapy should consist of an echinocandin rather than an azole. Echinocandins have more potent activity against Candida than azoles and maintain activity against some Aspergillus species. Caspofungin, micafungin, and anidulafungin are generally considered interchangeable in terms of activity spectrum and side-effect profile. They are generally well tolerated, although they can be associated with elevation in liver enzymes.

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References: Antibiotics


