Title

Multidisciplinary management in Fournier's gangrene

Journal

Current Problems in Surgery, 61(7)

ISSN

0011-3840

Authors

Koch, George E
Abbasi, Behzad
Agoubi, Lauren
et al.

Publication Date

2024-07-01

DOI

10.1016/j.cpsurg.2024.101499

Current Problems in Surgery 61 (2024) 101499

Contents lists available at ScienceDirect

Current Problems in Surgery

journal homepage: www.elsevier.com/locate/cpsurg

Multidisciplinary management in Fournier's gangrene

George E. Koch, MD[a,*], Behzad Abbasi, MD[b], Lauren Agoubi, MD, MA[c], Benjamin N. Breyer, MD, MAS[d], Nina Clark, MD[c], Brian P. Dick, MD[b], Jeffrey B. Friedrich, MD, MC[e], Lindsay A. Hampson, MD, MAS[b], Alexandra Hernandez, MD, MCR[c], Rebecca Maine, MD, MPH[f], E. Charles Osterberg, MD[f], Lindsey Teal, MD, MPH[f], Capt. Tarah Woodle, MD, USAF[g], Judith C. Hagedorn, MD, MHS[a]

Introduction

- *George E. Koch. MD*

Fournier's gangrene (FG) has long been the bane of the surgeon on call. Patients present critically ill, or with the potential to become so, requiring urgent surgery. The surgery itself is no one's favorite and is followed by serial debridement, intensive care unit (ICU)-level care, wound care, and reconstruction. Academic interest in the topic has historically been robust but focused on risk factors and prognostic indicators.

Some argue that this is the old disease archetype, however. Interest in improving the standard of care in FG is on the rise, both academically and clinically, and with that interest has come recent evidence supporting multiple disease states over a more protracted course. This description of prodromal FG opens the door to prevention and early intervention while the advent of skin-sparing debridement strategies is shifting the reconstructive landscape. The potential for more functional reconstructions has inspired advancements in wound care to both optimize surgical outcomes as well as cost-effectiveness.

From the [a]Department of Urology, University of Washington, Seattle, WA; [b]Department of Urology, University of California San Francisco, San Francisco, CA; [c]Department of Surgery, University of Washington, Seattle, WA; [d]Departments of Urology and Epidemiology and Biostatistics, University of California San Francisco, University of California San Francisco, San Francisco, CA; [e]Division of Plastic Surgery, Department of Surgery, University of Washington, Seattle, WA; [f]Department of Surgery & Perioperative Care, Dell Medical School, Austin, TX; and [g]Department of Surgery, Brooke Army Medical Center, Fort Sam Houston, TX

* Address reprint requests to: George E. Koch, MD, Department of Urology, University of Washington, Ninth & Jefferson Building, 908 Jefferson St., 9th floor, Seattle, WA 98104.

E-mail address: Kochge@uw.edu (G.E. Koch).

https://doi.org/10.1016/j.cpsurg.2024.101499

This monograph is intended to give the reader an in-depth view into these advancements, almost all of which can be implemented by most urologists nationwide as they see this rare condition on call. The contributing authors bring a deep fund of knowledge and experience to their work in FG and offer cutting edge perspectives and techniques for treating these patients. It is our sincerest hope that this work will not only serve as foundational material for quality improvement initiatives, research, residency training, and clinical practice, but also as inspiration for others to take up the mantle of leadership in treating this life-altering disease.

The epidemiology, pathogenesis, and risk factors for Fournier's gangrene

-Behzad Abbasi, MD and Benjamin N. Breyer, MD, MAS

FG is a necrotizing soft tissue infection of the genital tissues seen in both men and women. It is most often a result of poorly managed chronic medical conditions which lead to microvascular compromise, creating a milieu in which patients' immune systems are unable to effectively protect them against severe cellulitis, leading to a gangrenous infection. These infections are diagnosed clinically, although computed tomography (CT) is very sensitive and specific and can be useful in prognostication. The mortality rate for FG has dropped significantly from 50% historically to less than 10% in contemporary cohorts.[1]

Epidemiology

In 1883, Jean-Alfred Fournier described FG as an idiopathic necrotizing infection of soft tissues exclusive to young men.[2] FG occurs in both genders and across age groups. The available evidence on FG primarily comprises case series from tertiary centers and there is a scarcity of nationwide and worldwide studies sufficient to ascertain the epidemiology of the condition. FG constitutes 0.02% of total hospital admissions in the United States, with a male incidence rate of 1.6 per 100,000, peaking between 50 to 79 years of age.[3] Within the United States, most patients are White, followed by Black and Hispanic, and no disparity in susceptibility among different ethnicities is noted.[3,4] Presently, the epidemiology of FG in women is lacking, and substantial large studies are absent. A review of the literature by Eke and colleagues, encompassing 1726 cases, revealed a male-to-female ratio of 10:1.[5] Nonetheless, a nationwide study comprising 1680 cases documented a mere 39 women with FG, however the administrative data upon which this study is based may be biased towards reporting male cases.[3] More recently, a large institutional series by Beecroft and colleagues reported a 3:1 male predominance.[6] Given the known gaps in coding for female FG cases, institutional series may have an advantage over administrative datasets in elucidating the true incidence of FG in women.

Etiology and microbiology

FG was initially deemed idiopathic. Currently, the origin of the infection remains unidentifiable in 26% to 36% of cases.[5,7] The preliminary infection can arise from skin as well as the gastrointestinal or genitourinary tract.[5] Although evidence on predominant etiological factors varies, urethral strictures, indwelling catheters, genital trauma, and perianal abscesses are considered risk factors for FG.[8,9]

FG infections are predominantly polymicrobial and consist of aerobic and anaerobic bacteria.[10,11] Anaerobes spread consequent to tissue hypoxia and lead to gas formation and crepitus upon physical examination. A recent study showed that polymicrobial infections were associated with higher inflammatory indices as well as longer hospital stays and the need for fecal diversion.[12] Monobacterial infections are predominantly caused by group A β-hemolytic Streptococcus (GAS) or *Staphylococcus aureus*, as well as methicillin resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamase bacteria (eg, *Escherichia coli*) and are more fulminant than polymicrobial infections.[13] Lately, an increase in MRSA cases and the discovery of

multiple instances of FG caused by multi-drug resistant organisms have been observed, potentially postulating higher mortality rates.[14] Gram-negative pathogens, specifically *Vibrio* species, and fungal infections caused by *Candida* species, can also lead to FG. *Vibrio* infections are more common in Asia, in those who work closely with marine organisms, like fisherman.[15,16] *Candida* species can be cultured from infections in individuals with a history of trauma and those who are immunocompromised.[13]

Pathophysiology

In FG patients, infections initiate within the deeper skin layers, primarily the hypodermis, with superficial layers being involved in later phases.[16] This explains why the extent of damage surpasses what is initially apparent on the skin surface. The course of the infection can vary from a slow smoldering presentation to more fulminant one. Bacterial toxins cause tissue breakdown, promoting infectious spread and necrosis. The infection advances rapidly along fascial planes, reaching a velocity of 2 cm per hour, particularly in cases with streptococcal involvement.[17] Over time, arterial endarteritis and venous thrombosis develop, further contributing to tissue ischemia, necrosis, and gangrene due to ongoing breakdown. Chronic conditions like diabetes mellitus (DM) that impact microvasculature exacerbate arterial damage, promoting anaerobic bacterial proliferation and fascial necrosis.[18] Hypoxia triggers pain that gradually resolves, as damage to the neurovascular structures of the skin and soft tissues progresses.[16] In later stages, causative organisms, directly or via toxins, induce systemic toxicity and organ hypoperfusion from distributive shock, precipitating multiple organ failure and eventually death.[19]

Risk factors

Disease development

Conditions that cause impaired microcirculation and immunosuppression are shown to predispose to FG, namely, DM, chronic alcohol use, smoking, obesity, human immunodeficiency virus (HIV), renal/liver failure, and malignancy, of which DM and obesity are the most common.[13] Approximately 36% to 56% of individuals with FG exhibit DM and 51.5% of them are characterized as overweight.[4,7] Several studies have suggested that low socioeconomic status may predict FG.[5,20] Nevertheless, it remains uncertain whether socioeconomic status serves as an independent predictor or if its influence is mediated by factors such as alcoholism and obesity.

Length of stay

A large study showed that the median length of stay is 9 days (interquartile range 5-17 days).[4] However, a recent review of FG literature exhibited a mean length of stay of 18.5 days.[21] Factors such as older age, teaching hospital affiliation, greater comorbidity count, suprapubic tube insertion, fecal diversion, complicated wound closure, delay in transfer to a high volume center, and complications (eg, skin defects and orchiectomy) have been linked to longer hospital stays.[4,22,23]

Mortality

Nationwide studies have reported contemporary FG mortality rates ranging from 4.7% to 7.5%.[3,4] Research suggests that medical centers with greater patient caseloads exhibit better mortality outcomes among patients with severe infection.[23] Predominant patient factors linked

Table 1
Summary of mortality predictors for Fournier's gangrene (adopted from Bowen et al., 2022[21]).

	Year	N	N, Female	Predictors
Creta *et al.* [207]	2020	161	Unknown	Higher FG Severity Index
Tenório *et al.*[208]	2018	124	25	extension to abdomen, raised potassium and creatinine, SFGSI>2,
Furr *et al.*[4]	2017	9,249	0	Age, hospital volume >10 cases/year, Medicaid insurance, renal failure, coagulopathy
Lauerman *et al.* [61]	2017	168	Unknown	Increased serum WBC and lactate
Kim *et al.*[209]	2015	636	Unknown	Age, BMI
Sugihara *et al.*[210]	2012	379	77	Age, CCI score, Sepsis/DIC at admission, debridement area ≥ 3,000 cm 2
Yilmazlar *et al.*[31]	2010	80	23	UFGSI ≥ 9
Sorensen *et al.*[3]	2009	1680	39	Age, CCI score, admission via transfer, heart failure, renal failure, and coagulopathy

BMI, body mass index; CCI, Charlson comorbidity index; DIC, disseminated intravascular coagulation; FG, Fournier's gangrene; SFGSI, simplified Fournier's gangrene severity index; UFGSI, Uludag Fournier's gangrene severity index; WBC, white blood cells.

to mortality in FG patients include advanced age, impaired coagulation, renal failure, and congestive heart failure (Table 1).[7,21,24-26] Other studies highlight that deviations in homeostasis are predictive of death among FG patients, including increase in leukocyte count, serum levels of creatinine and lactate, and reduced hematocrit and serum albumin measure.[21] Moreover, the requirement for mechanical ventilation or dialysis, along with delayed patient transfer, time to initial surgical debridement, extent of surgical debridement, and treatment approach, have been shown to predict mortality in patients with FG.[21] These findings collectively suggest that poorer health status, the extent of the disease, lack of access to care, and lack of experience with the management of FG contribute to adverse outcomes and mortality in FG.

Severity indexes

Laor and colleagues introduced the Fournier's Gangrene Severity Index (FGSI), a numerical scoring system based on 9 physiological variables at admission, to assess patient outcomes and mortality risk.[27] These parameters include body temperature, heart rate, respiratory rate, serum levels of sodium, potassium, creatinine, bicarbonate, hematocrit, and leukocyte count, each graded 0-4, with summed scores producing the FGSI score.[27] A score >9 indicated a 75% probability of death, while scores ≤9 suggested a 78% probability of survival.[27] Although the accuracy of the FGSI in outcome prediction is debated, multiple studies have associated higher scores with increased mortality risk.[28-30] To enhance predictive capacity, the Uludag FGSI (UFGSI) was introduced, incorporating age and disease extent into FGSI parameters.[31] UFGSI predicted death in 94% of cases with scores >9 and 84% survival for scores ≤9, providing more sensitivity but less specificity compared with FGSI.[32] A simplified version of the FGSI (simplified FGSI [SFGSI]), has been introduced and validated with only 3 physiological variables including hematocrit and blood potassium and creatinine levels.[33] SFGSI has been demonstrated to be non-inferior to FGSI in predicting mortality.[32] However, the choice of tool depends on physician preference and the clinical context as these scoring systems may not be useful in the emergency setting.[21,33,34] FG's diverse presentation requires clinical judgment for timely intervention, as it remains an unpredictable disease entity.

Imaging

Radiography, ultrasonography (US), CT, and magnetic resonance imaging (MRI) are valuable adjuncts to the clinical evaluation for FG cases. Cross-sectional imaging can indicate whether perineal disease has tracked to the retroperitoneum. Plain film radiography offers cost-effective and accessible visualization, detecting gas formation prior to crepitus but has a limited role in

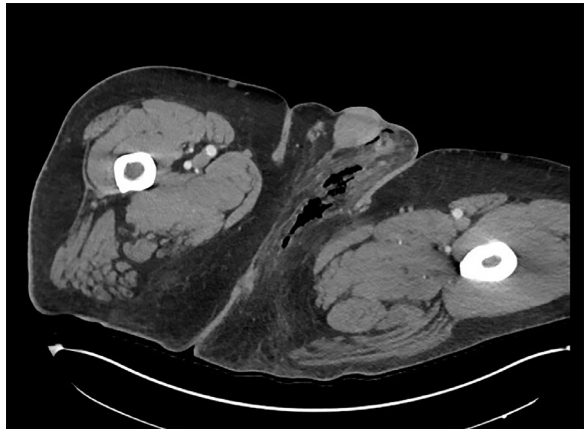

Fig. 1. Axial computed tomography (CT) image of induration in left scrotal contents (narrow arrow) and gas formation (thick arrow) due to Fournier's gangrene that extends to the left inguinal canal.

FG imaging.[35] US is optimal for scrotal content assessment, indicating testicular FG involvement and potential intra-abdominal or retroperitoneal source. CT surpasses plain films and US in confirming FG and for surgical planning.[35,36] CT exhibits the highest diagnostic specificity for FG (Fig. 1).[37] Radiologists have devised and validated a CT scoring system that assigns numeric values to findings, including fascial air, muscle/fascial edema, tracking fluid, lymphadenopathy, and subcutaneous edema.[38,39] A cumulative score of $\geq$6 on this system indicates the presence of necrotizing fasciitis.[39] Nonetheless, MRI surpasses US and CT due to its heightened soft tissue contrast and comprehensive assessment of disease extent and initial infection site.[40-42] It may even be necessary if results from other imaging methods are inconclusive, particularly in cases of FG coupled with perianal fistulae and abscesses.[41,43] However, deferring operative intervention for an MRI examination is discouraged when CT is readily accessible, cheap, and faster.[35,43] These modalities support FG diagnosis but must not replace clinical assessment. Imaging should not delay surgery if clinical suspicion is high. Examination of genitalia, perineum, anorectal areas, and overall patient health remains pivotal.

Medical management in Fournier's gangrene

-Nina Clark, MD, Alexandra Hernandez, MD, MCR, Lauren Agoubi, MD, MA, and Rebecca Maine MD, MPH

The mainstay of initial care of the patient with FG is timely surgical debridement; however, these patients also require excellent perioperative medical care for good outcomes. A multidisciplinary team approach is often needed for these patients, especially when they present with systemic illness. For many, this care team should include the expertise of an intensivist familiar with managing critically ill surgical patients. The medical care of the FG patient should focus on several key aspects: 1) controlling and treating infection, 2) managing fluids and electrolytes, 3) addressing the systemic inflammation associated with sepsis, 4) managing medical conditions associated with the both preexisting comorbidities and acute in-hospital complications, and 5) controlling pain and managing complex wound care needs.

Infection control

The primary focus of infection control for FG is early and complete debridement of infected tissue. Studies and guidelines recommend initial debridement within 6 to 12 hours of presentation.[44,45] Even hospitals without the capacity to provide definitive long-term critical care, reconstruction, and rehabilitation for FG should strongly consider performing an initial debridement

of infected tissue prior to transfer.[46] This is especially true if transferring to another facility could lead to delays in operative intervention. General surgeons and/or urologists with limited experience with FG can still effectively perform an initial debridement to decrease the burden of infected tissue, therefore helping to reduce the systemic effects of the infection. At our institution, we often arrange for immediate transfer to a higher level of care after initial debridement, sometimes directly from the OR at the presenting institution. Ideally, the initial debridement will 1) remove all infected tissue, 2) minimize operative time, 3) be performed with some consideration of the eventual reconstruction, and 4) avoid diversion procedures like suprapubic catheter placement or fecal diversion, especially in an unstable patient. Although all infected and necrotic tissue should be resected, several authors have demonstrated the safety of skin-sparing procedures during initial debridement when the skin itself is not frankly necrotic.[47-50] For more details on reconstruction, please see the section below on post-debridement reconstruction following Fournier's gangrene. Another critical component of the initial debridement is the collection of wound cultures, which includes both swabs of wound/pus and bacterial tissue. These cultures are critical to guide antibiotic de-escalation during the patient's care.

Antibiotics

Along with timely and complete debridement, early initiation of appropriate antibiotics is essential for the treatment of patients with FG.[51] Antibiotic selection is based on the typical organisms responsible for FG infections. An understanding of the different etiologies of FG is essential to choosing the right antimicrobials. There are 3 primary routes of infection in the genital region that can result in FG, including urogenital, anorectal, and dermatologic. Injury to any of these areas can result in infections that lead to FG. Several other conditions, along with interventions involving the urogenital or anorectal tracts can cause FG, including strictures or perforations, as can gynecologic procedures including episiotomies for vaginal deliveries. Infections in the groin such as Bartholin's abscess, perirectal abscess, and furuncles can progress to FG. Finally, radiation, cancer, immunosuppression, and implanted devices have also been associated with the development of FG. Although dermatologic sources of FG are more likely to have a single causative organism like *Streptococcus* spp. or *Staphylococcus* spp., polymicrobial or type I necrotizing infections are most common in the groin.[52,53] Understanding that urogenital and anorectal etiologies are common in this disease explains this pattern.

As early initiation of antibiotics is a cornerstone of the management of sepsis and severe infections, parenteral antibiotic therapy should not be delayed until culture data are available.[54] Broad spectrum antibiotics should be initiated as quickly as possible when FG is suspected. Initial antibiotic selection should target the 4 primary causes of necrotizing infections including MRSA, GAS, gram negative organisms, and anaerobic organisms, especially *Clostridium* spp. Historically, our institution used a combination of 3 antibiotics to adequately cover each group of organisms. Vancomycin, dosed by weight and managed by monitoring serum levels, covers MRSA. Clindamycin provides coverage both for GAS and for *Clostridium* spp. as well as other anaerobic infections. Piperacillin-tazobactam, a third-generation cephalosporin, treats GAS as well as the gram negatives organisms common in FG infections. These recommendations are summarized in Figure 2 and Table 2. Institutional guidelines for empiric antibiotics for FG can help ensure more patients receive appropriate antibiotics early in their disease course. It should be noted, however, that even in high volume institutions with published recommended antibiotics regimens, up to 25% of patients do not receive the appropriate recommended empiric antibiotics.[51] Thus, it is imperative that the team managing the patient in the perioperative period is vigilant about initial antibiotic selection.

Clindamycin, which acts by inhibiting ribosome function, provides an additional advantage in the early treatment of severe infections with toxin-producing organisms like *Clostridium* spp., *Staphylococcus* spp. and GAS by inhibiting protein synthesis and therefore toxin production. Both *Staphylococcus* and *Streptococcus* produce superantigens, while *Clostridium spp.* produce alpha and theta-toxins which contribute to the physiologic shock state in patients infected with these

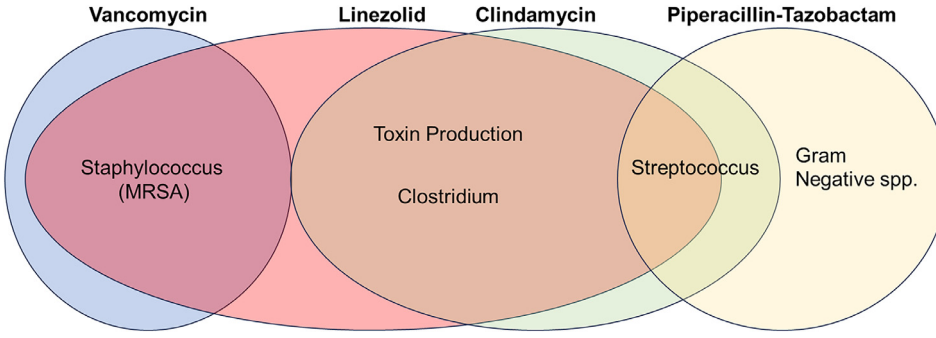

Fig. 2. Antibiotic coverage in necrotizing soft tissue infection.

Table 2
Antibiotic regimen for necrotizing soft tissue infections based on culture results.

Polymicrobial	Piperacillin/tazobactam and vancomycin or linezolid*
Methicillin resistant *S. aureus*	Vancomycin or linezolid*
Streptococcus pyogenes	Penicillin and clindamycin or linezolid*
Clostridia spp	Penicillin or linezolid*, clindamycin
Vibrio vulnificus	Doxycycline and ceftazidime
Aeromonas hydrophilia	Doxycycline and ciprofloxacin

* Consider sife-effect profile and antibiotic duration.

organisms. Thus, inhibition of these toxins can improve the course of the patient with FG. Although higher-dose clindamycin was a central part of the treatment regimen at our institution, recent studies have demonstrated increased resistance of GAS to clindamycin in different regions.[55,56] There are also increasing rates of clindamycin resistance in *Clostridium spp*.[57,58] Oxazolidinones (linezolid and tedizolid) demonstrated positive results in the treatment of severe GAS infections in mice and have similar abilities to inhibit the protein synthesis needed for toxin production.[59] Linezolid is also active against MRSA, and may be an alternative to vancomycin, which has been associated with increased risk of acute kidney injury (AKI) in critically ill patients when used alongside piperacillin-tazobactam.[60]

With rising resistance rates in our local population, as well as the concern for AKI in patients treated with both vancomycin and piperacillin-tazobactam, we recently updated our antibiotic regimen for FG to linezolid and piperacillin-tazobactam. This regimen provides both excellent coverage of the major causative organisms and protein synthesis inhibition to decrease bacterial toxin productions associated with shock syndromes. Linezolid, however, can have severe side effects, including bone marrow suppression, and should be narrowed to another antibiotic as soon as possible, as described below.

De-escalation and discontinuation of antibiotics

While early initiation of broad-spectrum antibiotic coverage is essential, it is equally important to de-escalate antibiotic therapy as soon as possible. This both avoids adverse effects associated with antibiotics and minimizes the development of antibiotic resistance. This is especially important if the empiric regimen includes antibiotics with higher risk profiles, such as linezolid or the combination of vancomycin and piperacillin-tazobactam. Limited data are available to help guide the de-escalation process for antibiotics in FG and other necrotizing soft tissue infections (NSTI). Even in high volume centers with established NSTI or FG management protocols, there is significant variability in antibiotic duration.[51] Authors analyzed a group of 360

patients with NSTI (150 with FG) treated during a 3-year period whose only antibiotic therapy during admission was for the treatment of their soft tissue infection. Half of the patients completed 9.8 days of total antibiotics, with a median of 7 days of antibiotic therapy after final debridement.[51] This is despite guidelines that suggest antibiotics can be discontinued when there is no additional need for debridement in stable patients.[59] Patients with perineal infections (FG) had slightly shorter overall duration of antibiotics, at 8.3 days vs 10.6 days, in this study.[51] The specific pattern of de-escalation was not analyzed. A 2017 study of 168 FG patients at a single institution also found significant variation in the duration of antibiotic therapy prescribed for FG, with only 16.7% of patients with a duration of therapy $\leq$7 days, a majority (63.4%) receiving between 8 and 14 days of antibiotics, and a median of 4.85 days of antibiotics after the final debridement.[61] In this study, the duration of antibiotics did not appear to be associated with spread of the infection and/or debridement area or the ability to close the wound.

De-escalation of antimicrobials relies upon close communication between the surgical, and if applicable, the critical care team. Depending on the patient's physiology, de-escalation, and cessation of antibiotics immediately or within 24 hours of the final debridement may be appropriate.[61] Thus, knowing when the surgeons deem debridement complete guides that decision. Antibiotics should be narrowed as soon as surgical cultures are available. For patients debrided at another institution prior to transfer, this may require ongoing communication with the referring hospital to obtain the initial culture results. Negative cultures occur in a minority of NSTI and FG cases, and likely represent anaerobe infections, like *Clostridium*. In the setting of negative cultures, selective de-escalation of antibiotics should be initiated as soon as possible. For example, if there is no MRSA in the wound and the patient is not MRSA positive on nasal or other screening, removal of vancomycin or linezolid should be considered. Persistent fevers, ongoing need for debridement, and persistent leukocytosis are reasons to consider ongoing antibiotic therapy, but in general most patients can have antibiotics de-escalated soon after operative debridement is complete to minimize complications from antibiotic therapy. In 1 study, each additional day of clindamycin therapy was associated with an 6% greater odds of developing a *Clostridium difficile* infection of the intestine while hospitalized.[51]

As discussed above, clindamycin or oxalinates are included in recommended regimens not only for their ability to treat key causative organisms, but also to decrease toxin production and reduce the inflammatory response of the host. In general, this effect is most beneficial in the initial 72 hours of care.[58] Typically, final culture results are available within 48 to 72 hours, thus the timing of de-escalation usually aligns with the duration of the anti-toxic effect. However, if antibiotics are narrowed earlier, providers should consider completing 72 hours of therapy of these agents.

Level of care

Patients suspected of having any NSTI, including FG, should be strongly considered for close monitoring in an ICU. Historically, mortality in these patient populations has reached up to 40%; more recent data suggest that access to critical care resources and early surgical intervention has improved the mortality to between 10% and 20%.[62-64] In addition to local wound infections, NSTIs, including FG, are characterized by a severe, systemic inflammatory response that is frequently associated with multi-organ dysfunction. Retrospective studies evaluating this inflammatory response have identified a trend toward systemic worsening of markers of sepsis over the first 24 hours, followed by gradual improvement.[65] In particular, patients with higher baseline modified Sequential Organ Failure Assessment (mSOFA) scores in that study had elevated risk of multi-organ dysfunction in addition to mortality. In addition to baseline indicators of sepsis and systemic inflammatory response, suspicion for clostridial infection should also prompt strong consideration of ICU admission, as patients can rapidly deteriorate. Clostridial NSTIs, which frequently manifest as "gas gangrene", have been associated with mortality in 70% to 100% of patients, typically in the first several days of hospitalization.[66] For most patients with

suspected or confirmed FG, an ICU level of care is likely appropriate to facilitate close hemodynamic monitoring, active resuscitation, and rapid surgical re-exploration in the event of clinical deterioration.

The physiologic derangements, high-volume fluid resuscitation requirements, and wound care needs common across many patients with NSTI and FG have been compared with the resources utilized by patients with severe burns. Studies suggest improved outcomes for patients transferred to burn centers for management of NSTI.[67] Thus, providers caring for patients with FG should determine if their institution has adequate resources for monitoring and surgical management of the patient and, if not, consider transfer to a burn center capable of providing a high level of surgical critical care.

Because FG patients frequently develop sepsis and require ICU admission, they are at high risk to develop complications during long hospital stays. No guidelines exist that are unique to the FG population to avoid complications like ventilator-associated pneumonia, acute respiratory distress syndrome, catheter-related infection and other organ failure that are common and can be prolonged in patients with sepsis and critical illness from all causes. As such, general best practice guidelines for ICU care should be applied to FG patients as well.

Monitoring of volume status and resuscitation

Several factors contribute to a need for aggressive fluid resuscitation, hemodynamic monitoring, and metabolic support among patients with FG. Postoperative patients frequently have large, open surgical wounds that can result in fluid shifts and insensible losses. Circulating bacterial toxins and immune mediators contribute to capillary leak and loss of intravascular volume; in addition, sepsis from NSTI is associated with the development of severe hypoalbuminemia, which can worsen capillary leak.[68,69] Finally, the impacts of both operative blood loss and hemolysis mediated by bacteria can contribute to anemia. Intensivists caring for patients with NSTIs must pay diligent attention to volume status and hemodynamic changes that may indicate inadequate source control and prompt a return to the operating room. Aggressive fluid resuscitation, including blood products when appropriate, supports end-organ perfusion in these critically ill patients.

Little to no data have been published assessing the appropriate strategy for fluid resuscitation specifically for NSTI or FG patients. Although the choice of resuscitative fluids must be tailored to individual patients; crystalloids are generally accepted as appropriate first-line fluids in patients with FG.[70] Current guidelines generally support an initial crystalloid bolus of 30 cc/kg for patients with suspected or confirmed sepsis; additional fluids will likely be necessary for patients in septic shock. Ongoing assessment of volume status, volume responsiveness, and need for adjuncts to crystalloid resuscitation to maintain appropriate mean arterial pressure must be pursued aggressively. The balance between adequate restoration of intravascular volume and avoidance of volume overload is critical and has prompted investigation into colloid solutions. Albumin is the primary driver of intravascular oncotic pressure; given concerns for capillary leak in sepsis, it has been proposed as an alternative to crystalloids that may maintain intravascular volume.[71] Unfortunately, several studies comparing albumin versus crystalloid fluids for resuscitation have failed to demonstrate consistent mortality benefits in patients with severe sepsis.[72-74] Plasma has also been proposed as a colloid that may be useful in sepsis; however, few studies have evaluated its potential impact on morbidity and mortality in human subjects.

One critical consideration in the early resuscitative phase of NSTI management includes the monitoring and treatment of electrolyte and glycemic derangements. Electrolytes should be corrected initially and monitored serially, especially given the higher rate of renal dysfunction and its association with mortality. In addition, close monitoring and management of elevated blood glucose levels are important during resuscitation. DM is very common in FG patients, although many non-diabetic patients with FG also have hyperglycemia related to infection and sepsis. In-

travenous insulin is frequently required to control blood glucose early in the patient's course. An aggressive approach to volume resuscitation, electrolyte and metabolic derangements, and need for additional intervention are why ICU admission is justified for the majority of patients with FG.

Adjuvant treatments in necrotizing soft tissue infections

Several adjuncts, including hyperbaric oxygen therapy (HBOT), intravenous immunoglobulin (IVIG), and pharmacologic treatments have been proposed for use in severe NSTIs. Although none have been shown to consistently improve outcomes, there are some studies that suggest benefit to some patients, particularly those with severe sepsis. However, these resources are not available at most hospitals, even high volume NSTI centers; thus, availability is another factor in the utility of these interventions.

HBOT theoretically functions by increasing local oxygen concentration in areas where impaired blood flow to infected tissues has created an optimal environment for anaerobic bacteria to grow. HBOT may also improve the neutrophilic response to infections, promote fibroblast proliferation and angiogenesis, and improve the delivery and function of antibiotics.[75] Numerous studies have sought to leverage these benefits in patients with NSTI including FG. These have demonstrated between a 64% and 100% absolute risk reduction in mortality compared to patients who did not receive HBOT. However, these data are limited to retrospective, predominantly single-center studies with small sample sizes and between-group differences that were frequently not accounted for in statistical analyses.[76-81] Furthermore, these results are contradicted by several other small studies that demonstrate no significant difference in survival for patients undergoing HBOT.[81-86] No randomized study has been performed evaluating the impact of HBOT as an adjunct treatment for NSTI of FG. A Cochrane review performed in 2014 did not demonstrate clear evidence that HBOT is effective in improving outcomes for patients with NSTI and current guidelines do not recommend its routine use patients with FG overall.[87]

Pooled IVIG has also been proposed as a potential adjunct treatment for NSTI as it can bind circulating antigens and bacterial toxins that contribute to the worsening physiology in some patients. Similarly to HBOT, the available data are from smaller, observational studies.[85,86] A study of patients with toxic shock syndrome caused by GAS infection found that IVIG infusion reduced the duration of organ failure. However, studies of patients with NSTI have not found similar benefit. This includes a single trial comparing IVIG versus placebo in NSTI treatment which randomized patients to placebo or IVIG, 25 g/day, for 3 consecutive days, beginning immediately after patient admission to an ICU or operating room.[53] In the IVIG group 14% of patients died within 30 days compared to 12% in the placebo group, which was not statistically different. IVIG may benefit patients with GAS infections and can be considered in FG caused by this organism, but is less likely to benefit other types of infections. Recent NSTI guidelines align with this approach, while noting that IVIG does not clearly improve mortality.[45]

The goal to decrease the inflammatory response to minimize end organ injury led to the development of a novel agent, Reltecimod (AB103).[88] This agent blocks superantigen binding on T-cells, specifically at the CD28 receptor. A 2014 phase 2a safety trial of this drug in patients with NSTI found that, at 2 weeks, the drug decreased the modified mSOFA compared to placebo. The authors also found that cytokine levels were decreased in the patients receiving the drug.[88] A subsequent multicenter randomized control trial phase 3 study evaluated a composite outcome of alive at 28 days, no amputation after first operation, <3 debridements by day 14, mSOFA ≤ 1 at day 14, and mSOFA with reduction of ≥ 3 points. NSTI patients who received the drug were significantly more likely to achieve the composite end point compared to placebo (54.3% vs 40.3%). They also found patients that received Reltecimod experienced shorter duration of organ dysfunction and a more favorable disposition

at discharge.[88] This drug has not yet been approved by the United States Food and Drug Administration.

Management of medical comorbidities

Acute kidney injury

Baseline renal impairment has been identified as a risk factor for development of FG, and has been associated with worse morbidity, mortality, and more frequent discharge to a higher level of care.[1,89] In the setting of active infection, AKI impacts from one quarter to more than one half of all patients with FG.[1] The incidence of AKI in this population is associated with severity of early sepsis; in fact, renal impairment is a component of several measures of the severity of NSTIs.[65,90] In a review of 38 studies with nearly 2000 patients, renal failure was associated with an increased risk of mortality from FG.[1]

Early recognition of renal impairment is essential. Urinary catheterization should occur soon after the initial evaluation to monitor renal function and guide fluid resuscitation. Early counseling of patients and families should discuss the possible need for renal replacement therapy when multi-organ dysfunction develops. One study estimated renal recovery at 39% for patients with mSOFA scores greater than 1 at day 14 in their clinical course, although this was not specific to FG patients.[65] Management of fluids and electrolytes, treatment of sepsis, and avoidance of nephrotoxic agents and drug combinations are the foundation of initial treatment. Ultimately, early engagement of nephrology consultants for considering renal replacement therapy in the setting of persistent decline in renal function is necessary.

Diabetes mellitus

DM is a frequent comorbidity for patients with FG, and poorly controlled DM is a risk factor for the development of FG. Rates of DM in FG and other NSTIs range from 30% to 76% of patients.[61,91,92] Poor diabetic control is a major risk factor for the development of NSTI and contributes to poor prognosis among patients with FG.[91,93-96] Patients with DM may present with direct complications of this disease, including diabetic ketoacidosis and hyperosmolar hyperglycemia. In one series of patients presenting with FG, the majority of patients with poorly controlled DM presented in a state of diabetic ketoacidosis.[97] Importantly, ongoing elevated blood glucose, or a worsening of glycemic control after initial improvement, may represent a progression of infection.[98,99] This distinction is critical, and rising blood sugars should be communicated to the surgical team as quickly as possible to facilitate wound inspection and potential further debridement.

Close glucose monitoring, especially in the initial stages of resuscitation and debridement, is required for all patients with FG, not only those with a known history of DM. Insulin infusions are frequently used and are often more effective than an insulin sliding scale at controlling a patient's blood glucose. Hemoglobin A1C levels should be checked on admission for all patients with FG, as this may represent an opportunity both to diagnose DM and to modify outpatient management strategies at discharge. All patients with FG, with or without DM, are at risk for hyperglycemia in the setting of severe infection. One study that evaluated the impact of poor glucose control on clinical outcome in FG did not demonstrate a difference in mortality, or number of debridements among patients who achieved early glucose control, but did note a reduction in length of stay. However, the investigators did note that patients with DM were significantly less likely to achieve glucose control than those without DM.[91,99] A systematic review of 38 articles describing 1990 patients did find that DM was associated with an increased risk of mortality from FG.[1] In summary, blood glucose is an important marker for infection and

early glucose control may reduce length of stay, although this is understandably more difficult to achieve among patients with DM.

Cardiovascular

Unfortunately, cardiovascular comorbidities are also common among patients with FG. Like renal dysfunction, FG patients can have both chronic and acute cardiac concerns. After DM, hypertension is the most common comorbidity for patients with FG (~25%), with approximately 6% of patients presenting with preexisting heart failure, coronary artery disease, and/or peripheral arterial disease.[11] Preexisting heart disease is a risk factor for in-hospital complications and discharge to higher level of care among patients with NSTI.[89] For patients with preexisting cardiovascular disease, early resumption or continuation of home medications—particularly statins, beta blockers and aspirin—may help minimize the risk of myocardial ischemia in the perioperative and critically ill period.[100]

Acute cardiac dysfunction can arise from sepsis induced by FG and can be mediated by cytokines from different organisms. Streptolysin O, a protein produced by streptococcal bacteria common in necrotizing infections, is directly cardiotoxic and impairs myocardial contractility.[57] Targeting production of bacterial antigens by treatment with clindamycin or linezolid is an important adjunct in minimizing these effects, but the primary management of acute myocardial dysfunction is close monitoring of hemodynamic status, especially in patients with sepsis, and maintaining a broad differential when assessing shock etiology. This necessitates reassessment of volume status and cardiac function in the event of worsening hemodynamics.

Immunosuppression

Immunocompromised patients often have an atypical presentation (mild erythema, lack pain out of proportion to findings) of NSTI and therefore a high index of suspicion is imperative when these patients present with sepsis and concern for soft tissue infection. One retrospective cohort study found that patients who were immunocompromised tended to have lower glucose and white blood cell count, important laboratory markers for diagnosis. This cohort had delayed time to diagnosis and initial operative debridement and higher in-hospital mortality.[101] Adherence to the principles of gaining rapid surgical control of infection and early initiation of antibiotic therapy is especially important for this group of patients with FG.

Monitoring for disease progression

A key component of the initial postoperative care after debridement is early detection of patients who require additional debridement to achieve source control. Most patients with necrotizing infections warrant monitoring in the ICU after initial debridement. The exception is patients with small wounds, excellent initial surgical debridement, and no signs of end organ dysfunction like acute kidney injury or sepsis. ICU monitoring facilitates several goals in the early postoperative period, most of which are focused on identifying patients who may need to return to the operating room for additional debridement prior to their planned second-look operation. A planned second-look is typically scheduled 6 to 24 hours after the initial debridement. Timing of planned re-exploration is largely dependent on the extent of debridement, the concern for proximal and/or retroperitoneal extension at the initial operation, and the patient's physiology, and response to treatment.

Especially in patients who present with septic physiology, continuous monitoring of vital signs and renal function are essential to guide postoperative resuscitation. Patients who do not

respond to intravenous volume or who have increasing vasopressor requirements should be urgently and serially re-evaluated by the surgical team to determine whether earlier operative wound exploration is required.

Visual inspection of the wound at regular intervals is an important part of the initial early management as well. The resources of the institution, experience of the nursing team with wound assessment and treatment, and the patient's condition should guide who performs wound assessments and care. Initial postoperative wound care should be within 6 to 12 hours at most after initial debridement to ensure early detection of disease progression.[102] Thus, our practice is to avoid the placement of wound VACs (ie, negative pressure wound therapy [NPWT]) during initial debridement to facilitate early and repeat assessment. We also commonly use Dakin's or chlorhexidine solution as part of our wet-to-dry wound care therapy in the early postoperative hospital course. Additional tissue necrosis noted during wound care prompts rapid evaluation by the surgical team to determine if additional operative debridement is needed. Our NSTI protocol also includes serial monitoring of biochemical markers, specifically leukocyte counts, lactate trends, renal function, and blood glucose. As with the other monitored parameters, failure to improve or worsening despite appropriate resuscitation in any of these laboratory values prompts urgent re-evaluation by the surgical team and consideration of operative re-exploration to ensure adequate debridement. Rapid elevation of the white blood cell count, especially to very high values and in the setting of physiologic deterioration, raises concern for *Clostriudium* spp. infection. In these cases, emergent re-exploration and aggressive debridement is required.

Pain management and wound care

Pain management

Although the extent of debridement varies, large wounds in the perineum with extension to the abdominal wall and lower extremities are common in FG. The high density of nerves in the region and large wound beds can be very painful. Thus, the perioperative care team must develop strategies to help address pain while supporting the wound care imperative for healthy granulation tissue to develop, facilitating eventual closure, and reconstruction.

Pain can be conceptualized as breakthrough, procedural, and background pain, with each type requiring a specific approach.[103] In the acute and immediate postresuscitative phases, short acting opioids such as fentanyl, hydromorphone, and oxycodone are central to the treatment of breakthrough (eg, with mobilization, pain crises) and procedural pain (eg, postoperative, wound care). Providers should work with patients to develop an appropriate dosing strategy. Patients whose comorbidities or complications (eg, AKI) do not preclude the use of acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) are typically treated with these as baseline scheduled medications, given their opioid-sparing and potentially synergistic effects.[104] Other opioid-sparing adjuncts include gabapentin or pregabalin and anxiolytics.[105] Gabapentin is a well-established treatment for neuropathic pain and has also been demonstrated to be effective as an opioid-sparing agent in the acute setting.[106] Additionally, procedural pain related to debridements, wound care, and physical therapy may be augmented by significant anticipatory anxiety for some patients.[107] Relieving periprocedural anxiety with short acting anxiolytics such as midazolam or lorazepam can be critical to the pain control strategy for these patients.

Finally, heightened levels of background pain may be due to preexisting chronic pain conditions or opioid tolerance, whether as a function of substance use disorder or due to protracted wound care. Substance use disorders are commonly seen in patients with necrotizing infections, with studies reporting up to 80% of NSTI cases related to injection drug use. In these populations, background pain may be managed with long-acting opioids. Several studies have demonstrated the use of methadone for acute pain management to mitigate opioid tolerance or coun-

teract progressive difficulty with pain control despite opioid escalation.[108-112] In these cases, addiction specialists and experienced pharmacists are integral components of the multidisciplinary team. For all patients, a detailed weaning protocol should be provided upon discharge, with follow-up scheduled as needed.

Wound care

Our institution typically approaches early wound care with frequent wet-to-dry dressing changes using dilute Dakin's solution (0.0125%-0.025% concentration) or chlorhexidine solution. Twice or 3 times daily dressing changes both facilitate wound healing and ensure frequent wound assessments to identify infectious spread early on and expedite additional debridement as needed. The use of Dakin's solution in the resuscitative and immediate postresuscitative phases provides an antiseptic wound environment with low cytotoxicity to fibroblasts.[113] Although little literature exists to support chlorhexidine solution, its cytotoxicity is extremely low. Once granulation has begun and there are no further signs of infection, we transition to wet-to-dry dressings using normal saline at a lower frequency or use a negative-pressure wound dressing. Wound care typically continues for days to weeks until the wound shows no evidence of ongoing infection and is ready for either secondary or delayed primary closure, depending on the available soft tissue, flaps, or skin grafts. In care environments where it is possible, we recommend working closely with reconstructive surgeons in order to determine the need for and timing of reconstruction for large wounds.

Establishing goals of care and palliation

Surgical palliative care is another important adjuvant for caring for the critically ill patient with FG.[114] Palliative care, either by the primary team or with the support of specialty-trained palliative care experts, provides essential support to patients and families who must try to make care decisions that best align with the FG patient's overall goals of care and specific values for their quality of life. In these discussions, it is important to give patients and family members a realistic impression of the best case scenario, the worst case scenario, and the most likely scenario given the patient's clinical course.[115] Patients and families should be informed of the mortality rates (between 10% and 20%), prolonged hospitalizations (an average 2-3 weeks), frequent discharge to non-home destinations, need for multiple operative procedures to achieve cure and reconstruction, and the possibility of needing urinary or fecal diversion.[51,91,99] If clinical findings suggest potential disease extension into the retroperitoneum, we discuss the anatomical limitations of extensive debridement in this area and the low likelihood of achieving surgical control of for this type infectious spread. Because comorbidity rates are high, these discussions should be informed by how pre-existing conditions may impact the patient's course. As with all palliative care discussions, the underlying goal is to engage the patient, if possible, and the family members in shared decision making that ensures care is aligned with the patient's values and can actually help them achieve their stated goals for returning to a meaningful quality of life.[114] When complications arise, critical illness is prolonged, or there are additional interventions needed, these are good points both for the care team and the family to assess whether care continues to be aligned with the patient's goals.

As the majority of patients with FG transfer institutions for care, an appropriate time to initiate conversations with the family and patient, if possible, may be prior to initial transfer.[51] Although it can be difficult to fully assess a patient remotely, providers who receive transfer requests frequently have a sense of the severity of illness, and often an initial expectation of what the patient's overall course may be. Especially when patients have significant preexisting conditions or are not interested in prolonged critical care, multiple operations, or diversion procedures, conversations prior to transfer may help both family and provider determine whether

transfer is appropriate and establish expectations for post-transfer care. Given the challenges in remote assessment and no well-validated tools to predict outcomes with FG, true prognostication, especially without a physical evaluation, may be very challenging. When there is hesitancy, significant uncertainty, or patients or family prefer evaluation at a center with more expertise, the best course of action remains rapid initial debridement with transfer. In our experience, having these conversations prior to transfer can greatly improve the post-transfer communication and expectations of families.

Conclusion

Although the cornerstone of initial treatment of FG is surgical debridement, appropriate early initiation of antibiotic therapy, active resuscitation for patients with sepsis, early recognition of disease progression, management of comorbidities and complications, diligent wound care and pain management, and the use of palliative care to support patients and families are also essential to ensure that patients achieve the best possible outcomes, aligned with their priorities and goals of care.

Surgical therapy for fulminant Fournier's gangrene

-Capt. Tarah Woodle, MD, USAF and E. Charles Osterberg, III, MD

The surgical management of fulminant FG has always been driven by the mantra "time is fascia." Although that focus on timely debridement remains a foundational principle in the management of this disease process, radical debridement is quickly giving way to skin-sparing techniques that facilitate earlier and less complex reconstruction. Furthermore, adjunctive procedures like orchiectomy and fecal diversion are becoming historic considerations in a vast majority of contemporary cases. Although time is still fascia, the current focus of FG debridement centers more around preservation than excision.

Timing of The initial debridement

FG necessitates immediate surgical intervention, requiring timely and thorough surgical debridement of necrotic tissue. Timing is critical as early and urgent surgical debridement has been shown to significantly reduce patient morbidity and mortality.[116-118] The importance of debridement reflects the pathophysiology of the condition whereby necrotic, infected tissue serves as a reservoir for bacteria that cause systemic illness via toxin production. As this tissue has been devitalized by infectious thrombosis of its bloody supply, it is not salvageable with antibiotic therapy because these medications have no tissue penetration without blood supply. Therefore, the only means by which to control the infection is excisional debridement of necrotic tissue.

Previous retrospective studies have attempted to determine the optimal timeframe for surgical debridement from the onset of patient symptoms. In a large single institution retrospective analysis, patients who underwent surgical debridement after 7 days of symptom onset had a 40% higher mortality rate compared to those who were promptly taken for surgical debridement within one week.[117] In their multivariable model, the authors found time to debridement to be an independent predictor of mortality when age and diabetes status were accounted for ($P = 0.001$).

More contemporary series support surgical debridement within a smaller window. In a series of 379 cases of FG, Sugihara and colleagues demonstrated that debridement within 2 days of hospital admission, compared to a delay of 3 to 5 days, led to 38% reduction in patient mortality (odds ratio [OR] = 0.38; $P = 0.031$).[118] Furthermore, a meta-analysis of all NSTIs showed that in 10 included studies, surgical debridement within 6 hours was associated with a mortality rate of

19% compared to 32% for patients undergoing surgery after 6 hours from presentation (OR 0.43; 95% CI 0.26–0.70).[119] Specifically in FG, a retrospective review of 118 cases over 30 years determined that surgical intervention within 14 hours from presentation led to the highest reduction in mortality ($P = 0.039$).[116] Patients receiving early surgical intervention, within 14.35 hours, had a significant reduction in mortality, from 68% to 23%. These findings highlight the need for early and prompt surgical management to achieve improved patient outcomes, which again, is consistent with the pathophysiology of the disease process. No amount or duration of antibiotic therapy will salvage the necrotic tissue in an NSTI; therefore, as soon as a patient is resuscitated enough to undergo anesthesia, he should be taken to the operating room for debridement.

However, while numerous studies have shown time to be of the essence when debriding NSTIs, including FG, studies that report time from onset of symptoms to presentation have not shown an association with patient outcomes.[119] This may be a reflection of the difficulty in obtaining an accurate or precise time of onset in many studies, but it also speaks to the emerging concept of a prodromal state in FG. In a landmark article by Erickson and colleagues, the authors described the pre-FG course of more than 8000 patients who would eventually go on to present with FG.[120] In this cohort, 50% of patients presented with a symptomatically similar diagnosis (cellulitis, genital swelling, urinary tract infection) within 21 days of their FG admission (Fig. 3). Furthermore, patients had an average of 1.8 health care visits for symptomatically similar diagnoses within 90 days of FG diagnosis, with more than 10% of patients having at least 3 such visits. Therefore, while expediting debridement upon presentation with fulminant FG is essential in decreasing mortality and improving clinical outcomes, there is clearly a poorly understood prodromal disease state which is still being explored in the literature.

Techniques for surgical debridement

Surgical debridement is the primary treatment necessary for source control to halt active infection, prevent the local spread of necrosis, and decrease the systemic showering of toxins and inflammatory mediators in FG. Wide radical surgical debridement was historically recommended, and is often still used outside of specialized centers, and includes removal of all necrotic subcutaneous tissue and fascia as well as the skin overlying it. Blunt dissection has been described as an effective means of determining the extent of debridement, as often there is easy separation of involved necrotic tissues from underlying viable deep fascia.[13]

Although radical debridement has long been the standard, there is currently debate regarding whether the boundaries of debridement should be made based on underlying fascia or the overlying skin (Fig. 4). Although some authorities advocate for surgical debridement until bleeding is encountered, there has been a rising interest in reducing the amount of tissue removed during debridement.[13,49,121] This “skin-sparing” strategy prioritizes the initial resection of necrotic tissue but aims to preserve borderline tissue that may declare itself to be ischemic during serial debridements, due to devitalization from loss of its vascular supply, but not overly necrotic and thus not contributing to the systemic illness of the patient (Fig. 5). Skin-sparing technique ideally avoids large, wide excisions which often require multiple debridements, more painful wound care, increased lengths of hospitalization, and result in the need for extensive and often complex surgical reconstruction including skin grafting.[49] In an attempt to reduce the morbidity of patients undergoing treatment of FG, several authors have proposed strategies to reduce the extent of resection at the time of initial debridement by utilizing skin-sparing incisions.[49,50,121]

Skin-sparing techniques were first developed by classifying tissues into 3 “zones” according to the degree and location of skin infection and necrosis.[121] The 3 zones of tissue were defined as: zone 1, containing necrotic tissue that is non-salvageable and is at the epicenter of the infection; zone 2, characterized by tissue that displays erythema and initial signs of infection but may be salvageable; and zone 3, described as healthy, viable tissue that remains uninvolved by the infection.

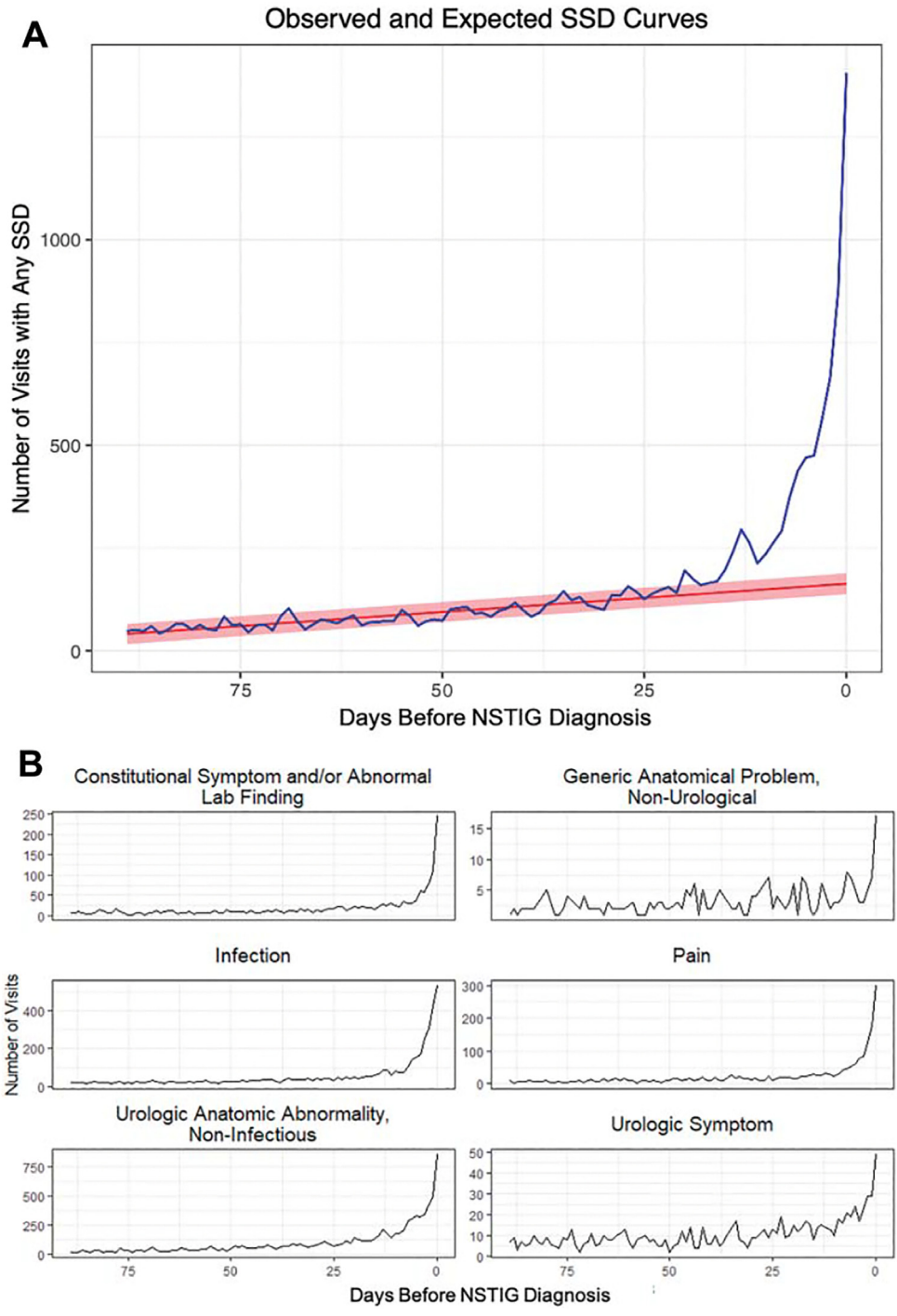

Fig. 3. (A) Symptomatically similar diagnosis (SSD) visits prior to index diagnosis of necrotizing soft tissue infection of the genitalia (NSTIG) with expected trend observed SSD-associated visits (blue) vs the expected trend (red). (B) SSD visits prior to index diagnosis by SSD category. Adapted from Erickson et al. 2021).

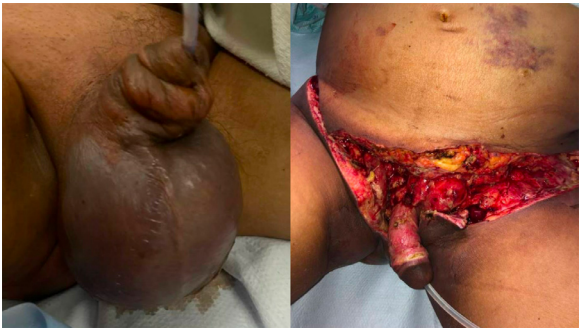

Fig. 4. Radical debridement of scrotal Fournier's gangrene.

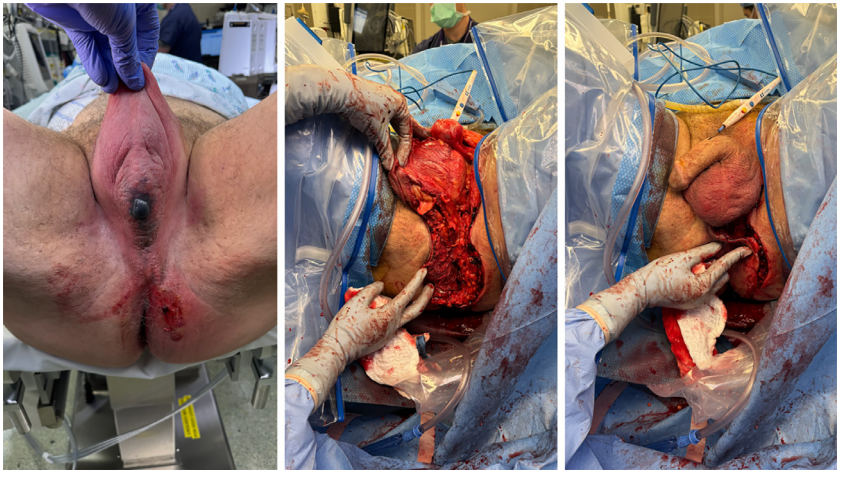

Fig. 5. Skin-sparing debridement of scrotal Fournier's gangrene.

Wong and colleagues advocated for performing a blunt dissection along the deep fascia to delineate the perimeters of infected fascia and demarcate the overlying tissue that should be removed. In the experience of these authors, the edges of the debridement often fall within the area between zone 2 and zone 3. Ideally, this technique allows for the preservation of a greater amount of surrounding tissue, which can later facilitate delayed primary closure of the wound.

Describing a similar technique, Perry and colleagues reported on a retrospective cohort of 17 patients who underwent skin-sparing debridement.[48] Their surgical approach involved assessing the skin and soft tissue for gross evidence of microvascular thrombosis. If present, the tissue was resected, however, if bleeding vessels were identified, even in tissue that appeared to have cellulitis, the overlying skin was salvaged. A NPWT device was then placed over the wound and the patient was later returned to the operating room for delayed primary closure. The authors found that by utilizing this technique, 100% of patients could be closed prior to discharge with only 2 of 17 (11.8%) requiring skin grafting.

Skin-sparing techniques have also been validated histologically. Alyanak and colleagues examined histologic changes between the deep subcutaneous tissues and the overlying epidermal skin layer at the edges of skin-sparing debridements in 15 patients diagnosed with FG.[122] This analysis revealed that the outermost layer of the skin remained unaffected, in contrast to the necrotic subcutaneous tissue beneath. This is the only pathologic evidence to date supporting

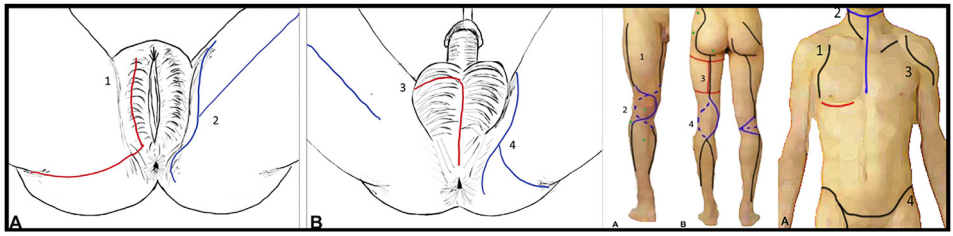

Fig. 6. Skin-sparing incision maps.

the validity of skin-sparing techniques, but coupled with the ever-growing clinical results, is a reassuring basic science correlate for the technique.

Further refinements in skin-sparing techniques for NSTIs have been developed by Tom and colleagues.[49] These authors, in collaboration with plastic surgery and general surgery colleagues, created incisional diagrams designed to both preserve vascular perforators on initial debridement as well as to minimize radical debridement of difficult to cover areas like flexor surfaces and bony prominences (Fig. 6). These incisional maps allow for debridement of underlying tissue while preserving skin that can then be used for delayed primary closure rather than necessitating skin grafting. The authors argue that the vascular arcades within the skin have shunting mechanisms that allow for blood flow redistribution, even when main vascular pedicles are compromised. This “choke vessel” phenomenon takes up to 48 hours to redistribute vascular flow, meaning that skin spared using this technique can be reassessed during repeat debridements to ensure viability.[49] The authors do acknowledge that there must be special care taken to evaluate patients for worsening infection in the instance that preserved tissues develop necrosis and result in worsening clinical condition. In the initial case series presented by this group, the authors were able to perform delayed primary closure in 10 of 11 patients without skin grafting. In a follow-up study, the authors compared 230 patients undergoing traditional radical debridement of NSTIs with 257 patients who underwent skin-sparing debridement.[50] In this large series, the authors found huge improvements in the ability to close wounds primarily (0% vs 50%, $P < 0.0001$) as well as to avoid skin grafts (90% grafted vs 20% grafted, $P < 0.0001$) both favoring the skin-sparing group. Equally impressive was the similar mortality rate of 10% for both groups, signifying equivalent infectious outcomes with vastly improved wound outcomes. These results have been validated in both NSTIs overall, and in FG specifically. Most recently a meta-analysis by Suijker and colleagues showed improved rates of delayed primary closure (75% vs 38%, $P = 0.002$) and decreased length of stay (26 vs 46 days, $P = 0.02$) in favor of skin-sparing.[123] Overall, skin-sparing has consistently proven to be a viable strategy for debriding FG and should be utilized at high volume centers with the resources needed for close monitoring and serial debridement.

Executing a successful skin-sparing debridement centers around understanding the difference between necrotic tissue and infected tissue. In FG, necrotic tissue serves as a nidus for disseminated infection and sheds bacterial toxins which compromise patient stability. Necrotic tissue is not salvageable with antibiotic therapy. By contrast, infected tissue still receives blood flow and thus antibiotics, and may still survive after the necrotic nidus has been excised. A good skin-sparing debridement therefore starts with excision of the necrotic skin (Fig. 7). The skin incision is then extended longitudinally in order to access any necrotic subcutaneous tissue, muscle, or fascia without having to remove any potentially viable skin. It is important to remember that skin-sparing technique should not be an incision-sparing technique. A wide incision is often necessary to attain source control and can easily be closed in the future once the infection has been treated (Fig. 8). Furthermore, it is essential to be mindful of the potentially distorted anatomy that large skin-sparing incisions can cause. Finally, skin-sparing technique relies on thoughtful debridement and incisions should be designed with the final reconstruction in mind.

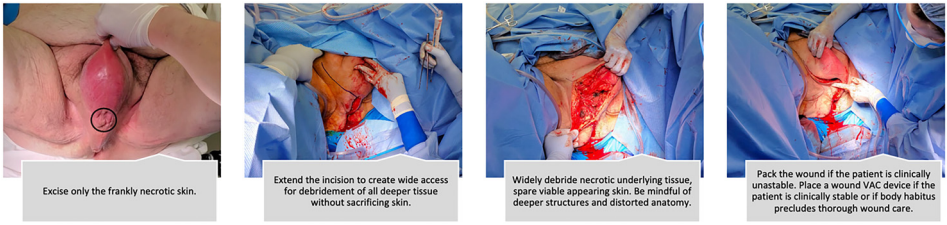

Fig. 7. How to perform skin-sparing debridement.

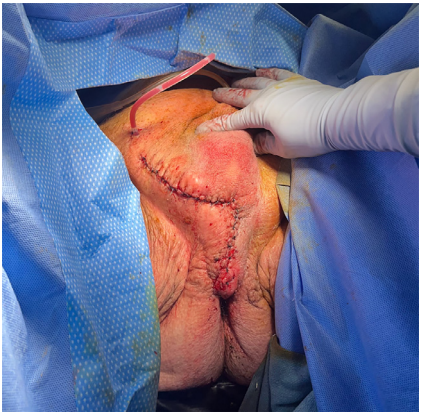

Fig. 8. Closed skin-sparing incision.

Repeat debridement

Serial debridement is an essential part of the surgical treatment of FG. The "second look" debridement is usually performed within 24 to 48 hours of the initial one. While the initial debridement is focused on removal of necrotic, nonviable tissue, repeat debridements provide the surgeon with an opportunity for aggressive wound care and wound inspection, as well as debridement of ischemic tissue that has declared itself as nonviable and prepping the wound bed for closure. In the case that some necrotic tissue was missed during the initial debridement, it should be excised during serial debridement.

In the era of skin-sparing debridements, serial debridement also allows the surgeon the ability to remove only what is necrotic or overtly ischemic during each procedure. With traditional radical debridement, viable tissues were removed if they were overlying the infected tissue due to the concern that they would not survive because of a compromised blood supply. In contrast, after a skin-sparing debridement, all potentially viable tissue can be left in place because it can be serially inspected during repeat debridements. In this fashion, the most possible skin can be left at each debridement until final closure is attempted.

The number of debridements required for each patient varies, with some studies reporting as few as 2 debridements prior to closure whereas others report as many as 5 debridements.[124,125] However, most studies report an average of 2 to 3 debridements.[126] Higher numbers of reported debridements may reflect more aggressive NSTIs, but they may also reflect utilization of the operating room for vacuum-assisted wound closure device application and replacement. Chawla and colleagues found that within their cohort, patients who survived were more likely to undergo fewer debridements compared to patients who did not survive.[124] Specifically, survivors had an average of 2.4 debridements, whereas non-survivors underwent an average of 5.2 debridements. The authors speculated that either the survivors benefited from an

aggressive initial debridement, resulting in decreased need for subsequent interventions or that non-survivors may have had a more severe disease process, involving larger surface areas, necessitating a greater number of debridements. Although serial debridements do offer the opportunity for more thorough wound care and facilitate the use of vacuum-assisted wound closure devices, they are associated with an increased length of stay. Yucel and colleagues demonstrated that patients who underwent a vacuum-assisted wound closure had a higher number of debdriements (2.8 vs 1.7, $P = 0.004$) as well as longer hospital length of stay (26.4d vs 12.6d, $P = 0.048$).

Clearly the number of debridements a patient undergoes is influenced by disease severity and surgeon preference and aggressiveness, as well as wound care strategy, making this statistic a difficult one to draw conclusions from in the literature. At our institution, the goal of serial debridements is not just for wound cleaning, but to progress the patient's wound forward. For example, during the first serial debridement we may begin a staged closure whereby we close a portion of the wound over a vacuum-assisted closure device or drain. The strategy can help create a "landing zone" of skin, facilitating a better seal with the vacuum-assisted closure device. We may also raise tissue flaps or place the testicles in thigh pouches. By using each debridement as a step in a staged closure, even if the entire wound is not ready for closure, we have found that we are able to incrementally reduce the size of patient wounds without negatively impacting our secondary wound infection rate.

Adjunctive procedures

There are a variety of adjunctive surgical procedures that may be required at the time of the initial or serial debridements. Although these procedures are often not necessary in modern practice, they may be considered for severe, aggressive infections with profound tissue loss. These include orchiectomy, urinary diversion, and fecal diversion.

Orchiectomy

The rates of orchiectomy performed during surgical debridement are variable. From pathophysiologic and anatomic standpoints, it should rarely be necessary as the testicles and their blood supply reside within a distinct fascial layer not in direct continuity with infected superficial fascia. Although some particularly aggressive infections will penetrate deeply and affect testicular tissue, this is rare. A systematic review of 11,096 patients with FG reflected this principle, with only 2.6% of patients undergoing orchiectomy.[11] Orchiectomy is typically not associated with increased risk of mortality in most studies, however in a large population-based database, interestingly, it was associated with a 70% decreased risk in mortality (OR 0.31, 95%CI 0.61-0.58).[117,118,127]

Smaller studies report much higher rates of orchiectomy, reaching up to 35%.[128] It is possible that this adjunctive procedure is more commonly performed at smaller local hospitals than at tertiary referral centers or teaching hospitals, secondary to a relative lack of exposure to FG at these institutions.[125,127] It also may be possible that orchiectomy is being used to decrease the reconstructive burden of patients not treated by a urologist, plastic surgeon, or general surgeon comfortable with thigh pouch creation, tissue flap coverage, or skin grafting in the perineum. Regardless, multiple recent small series of patients who underwent orchiectomy during debridement for FG found that 100% of testicles removed were viable and free of necrosis on pathologic analysis.[129,130] In the rare event that testicular tissue is involved, this represents retroperitoneal spread of infection and repeat imaging, wound reassessment, and debridement may be required ensure complete excision of all necrotic tissue. Although no current clinical guidelines recommend orchiectomy, given the typically unaffected nature of the testicular tissue, data show that it is being utilized in some capacity. We would, however, advocate

for sparing the testicles in all cases of FG with transfer of the patient to a high volume center for reconstruction in cases in which the testicles represent a significant obstruction to wound closure.

Urinary diversion

Urinary diversion can be achieved by either urethral catheterization or suprapubic cystostomy, at the time of initial debridement procedure or during subsequent debridements.[126] This adjunctive procedure was historically thought to aid in maintaining the hygiene of the recently debrided surgical field as well as facilitate dressing changes. In the cases where infection is secondary to urethral stricture, suprapubic cystotomy can also be used to bypass the obstruction if urethral catheter placement isn't feasible.[13] Rates of cystostomy in the literature range greatly from 2% to as high as 61% and the decision to perform cystostomy is often driven by surgeon preference.[130,131] A retrospective analysis identified cystostomy as a significant predictive factor of mortality, indicating that this procedure is more likely performed in patients with extensive disease. Although it may be necessary in some cases, it is our institutional practice to utilize urethral catheterization for urinary tract management in FG whenever possible, and to reserve cystostomy tube placement for severe cases in which a urethral catheter provides inadequate drainage or is unable to be placed, as in urethral necrosis or obliterative urethral strictures.

Fecal diversion

The benefit of fecal diversion is controversial in the treatment of FG. The rationale behind considering fecal diversion as a preventative measure is to reduce the level of fecal contamination of the debrided wound. However, a retrospective review comparing debridement without fecal diversion to colostomy in fecally continent patients found that there was no difference in mortality, surgical complications, or number of required debridements.[132] In contrast, several other retrospective studies have found that there is a significant correlation between diverting colostomy and poor prognosis.[133] Korkut and colleagues reported a significant univariable increase in mortality in up to 38% of patients who underwent fecal diversion versus 7% in those without diversion. Yet on multivariate analysis, fecal diversion was no longer significantly associated with mortality when controlled for diabetes and time to intervention.[117] This may indicate that fecal diversion in these patients is simply a surrogate for disease severity and not an independent predictor of outcomes. Furthermore, patients who undergo colostomy for fecal diversion often do not have colostomy reversal in long-term follow-up.[134–136] Thus, the possibility of permanent stoma should be discussed with patients, especially in individuals with many comorbidities. When bowel diversion is necessary, a laparoscopic diverting loop colostomy is often a feasible option.

Given this heterogeneity in the data, and in patient presentation with FG, careful consideration should be given to the decision to perform fecal diversion. Bowel diversions are associated with their own complications including prolonged ileus, parastomal hernias, stomal stenosis, and wound infections.[137] However, bowel catheters are a less morbid option for fecal diversion without the need for a major surgical intervention. In a retrospective study by Eray and colleagues, there was no difference in mortality between patients who underwent bowel catheter placement versus colstomy.[138] However, it was observed that patients who underwent surgical diversion experienced prolonged hospital courses, resulting in increased overall cost. These findings were substantiated by a recent meta-analysis conducted by Sarofim and colleagues, which concluded that there was no association between colostomy creation and mortality, however surgical diversion was associated with an increased number of operations and cost of hospitalization.[139] In summary, with little data to support its practice, our institutional standard is to avoid colostomy

creation except in cases of necrosis of the rectum, but with a low threshold for bowel diversion with a bowel catheter in patients with recurrent fecal stooling of their debrided wounds.

Conclusion

Patients should be debrided as soon as possible upon presenting with FG. Skin-sparing techniques with excisional debridement of only overtly necrotic tissue should be attempted during the first debridement. Surgeons should have a low threshold to return to the operating room for a second-look debridement in patients who may not have had adequate source control when skin-sparing techniques are utilized. Repeat debridements should progress wounds toward closure whenever possible. Orchiectomy is almost never indicated in FG and bowel and urinary diversion should be accomplished with minimally invasive catheters whenever possible.

Novel adjuncts to wound care in Fournier's gangrene

-Lindsay A. Hampson, MD, MAS and Brian P. Dick, MD

The mainstays of FG treatment are rapid initiation of resuscitation, broad-spectrum antibiotics, and surgical debridement.[140] However, the importance of good wound care cannot be overstated as it helps prepare patients for closure and reconstruction. In this section, we review some novel techniques in the management of FG wounds that aim to decrease the morbidity and mortality for these patients.

Skin-sparing debridement

FG is a necrotizing soft tissue infection that usually spreads along fascial planes. Skin becomes infected and then secondarily necrotic due to microvascular thrombosis with resultant local bacterial spread into compromised tissue. En bloc debridement is the most common surgical approach and consists of removing all infected subcutaneous, fascial, and muscle tissue, as well as all overlying skin, which often leaves broad defects that may require skin grafting or prolonged wound management. Although skin-sparing techniques have been discussed above, we will quickly review this topic here as it has major implications on patient wound care.

Skin-sparing debridement is an approach by which skin is only resected if grossly necrotic, with the hope that limiting the skin defect will reduce the complexity of future reconstruction.[123] The feasibility of this approach has borne out on histologic examination. Alyanak and colleagues retrospectively reviewed tissue histology from 15 patients treated with skin-sparing debridement for FG at their institution, looking specifically at tissue necrosis in subcutaneous and epidermal layers.[122] These investigators found that histology slides from macroscopically intact skin had preservation of the epidermis. Additionally, they noted preserved epidermal layers overlying areas with subcutaneous necrosis which supports the idea that skin can be spared even if the underlying tissue is dead. The authors note that progressive ischemia in spared skin can always be removed at future debridements.[122]

This approach may raise the concern that skin-sparing debridement does not provide adequate source control and could lead to increased morbidity and mortality, however the literature suggests that this is a safe approach. Suijker and colleagues identified 10 studies in their systematic review of skin-sparing debridement for necrotizing soft tissue infections.[123] They found that skin-sparing debridement had no increased risk of mortality, length of stay, or complication when compared to en bloc debridement. Furthermore, skin-sparing debridement was associated with higher rates of delayed primary closure compared to en bloc debridement (75% vs 38%, $P = 0.002$), and may result in the decreased need for skin grafting.

Table 3
Cytotoxic and bactericidal properties of medicated dressings.

Author	1% povidone-iodine	0.001% povidone-iodine	0.5% Dakin's solution	0.025% Dakin's solution	0.005% Dakin's solution	0.25% acetic acid	3% hydrogen peroxide	0.003% hydrogen peroxide
Lineaweaver[16] (1985)	Fb = Bac	Bac only	Fb = Bat	NT	Bac only	Fb Bar	Fb > Bac	Bar > Fb
Bennett[14] (2001)	Fb=Bac	NT	NT	Fb> Bac	NT	Fb Bac	Bac > Fb	NT
Heggers[15] (1991)	NT	NT	NT	Bac only	NT	NT	NT	NT

Bac, Bacterial toxicity; Fb, Fibroblast toxicity; NT, Nontested.

Following skin-sparing debridement, wound care adjuncts may improve tissue viability and facilitate reconstruction. The 3 most well-studied adjuncts are medicated wet-to-dry dressings, NPWT, and HBOT.

Medicated wet-to-dry dressings

Dakin's solution (0.012%-0.5% sodium hypochlorite) was first introduced as a wound care adjunct in 1915 by Henry D. Dakin and Alexis Carrel because of its bactericidal effects on *Staphylococcus aureus* in their research on battlefield wounds.[141] Between World War I and World War II, Dakin's solution became a common wound irrigation solution in United States hospitals, but it quickly fell out of favor as the antibiotics sulfanilamide and penicillin became widely used. After the 1960s it made a resurgence with surgeons for wound care.

Dakin's solution continues to play an important role in wound care for NSTIs. Although some authors argue that it may be cytotoxic, most believe that at currently used concentrations it stimulates fibroblast recruitment to the wound while also killing bacteria. A review of Dakin's solution by Ueno and colleagues reported the cytotoxic and bactericidal properties of various concentrations of Dakin's, solution povidone-iodine, acetic acid, and hydrogen peroxide showing that even dilute concentrations of Dakin's solution retain bactericidal properties while protecting tissues from cytotoxic effects (Table 3).[141]

Acetic acid and hydrogen peroxide are not routinely used in modern practice, and mafenide is used mainly in burn patients. However, povidone-iodine and Dakin's solution are both commonly used in the post-debridement wound care regimens of NSTI patients.[142] However, very few studies have examined the efficacy of these adjuncts compared to saline for NSTIs. Altunoluk and colleagues compared outcomes in a series of 14 patients with FG, 6 of whom were dressed with povidone-iodine and 8 of whom were dressed with Dakin's solution. These authors found that the length of stay was significantly less (13 vs. 8.9 days, $P < 0.05$) for patients treated with Dakin's solution compared with povidone-iodine.[142] Chlorhexedine irrigation solutions have also become more utilized in FG as they become commonplace in urologic surgery as a whole, although there is little evidence to support this practice.[143] Although most surgeons argue that the risk vs. benefit favors medicated dressings for FG, more research is still needed as these adjuncts can be easily and cheaply integrated into the care of FG patients if found to be effective.

Negative-pressure wound therapy

NPWT has emerged as another wound care adjunct that may help optimize FG wounds for reconstruction (Fig. 9). NPWT both encourages vascularization and wound healing and reduces the frequency of wound care, and thus, the pain and anesthetic requirements associated with dressing changes.[144,145] NPWT relies on the combination of suction, a foam dressing to

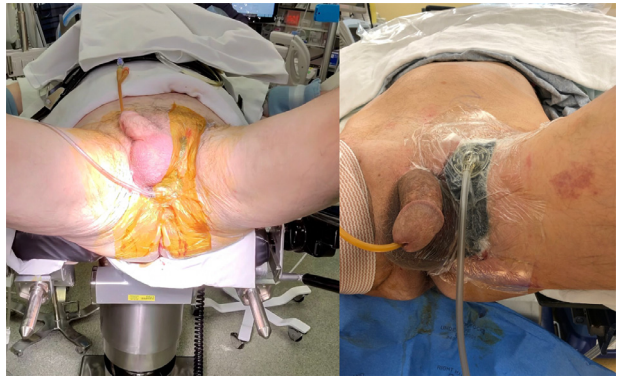

Fig. 9. Negative-pressure wound therapy in Fournier's gangrene.

Table 4
Negative-pressure wound therapy effects on healing tissue.

Physical Effects	Macro-deformation
	Micro-deformation
	Fluid removal
	Environmental protection
Physiologic Effects	Cell proliferation
	Granulation tissue formation
	Inflammation modulation
	Protein and peptide synthesis

evenly distribute negative pressure across a wound, and a tape or barrier to keep the foam in place and create a vacuum seal.[146] There are several types of foam that can be used. The most common foam used for subcutaneous wounds is "black foam," which is made of hydrophobic polyurethane and is typically lighter (pore size of 400-600 μm). "White foam" is used for deeper wounds and is made of hydrophilic polyvinyl and is typically denser.[147] The increased density of white foam limits growth of tissue into the dressing and is recommended for use in tunneling tracts, painful wounds, and in areas where there is concern for hypergranulation.[148]

NPWT is thought to work by using physical forces to induce physiologic changes in healing tissue (Table 4). These changes include macro-deformation of the tissue, in which edges of the wound are brought closer together, micro-deformation of the tissue in which cells undergo stretching, fluid removal from the wound, and maintenance of a warm, moist, and insulated wound environment.[149,150] These physical effects induce a variety of physiologic responses including granulation tissue formation, cell proliferation, inflammation modulation, peptide formation, and changes in bacterial levels.[146] The majority of these effects are driven by mechanotransduction, however the physiologic details of wound healing are outside the scope of this review and well-reported elsewhere in the literature.[151]

NPWT is initiated after surgical debridement of the necrotic tissue, once disease progression has been halted and the wound is overall stable. This can sometimes be performed even after the initial debridement. It offers several benefits over conventional wet-to-dry dressings. Ozturk and colleagues compared 5 patients treated with NPWT to 5 patients undergoing conventional treatment and reported that NPWT was associated with less pain, fewer skipped meals, greater mobility, and decreased hands-on physician treatment time.[152] A retrospective study by Yanaral and colleagues reported on 54 patients who underwent treatment for FG and grouped them based on whether they had conventional dressings or vacuum assisted closure (VAC), a type of NPWT. Compared to the conventional group, the VAC group had less pain, less analgesic use, and increased mobilization.[153]

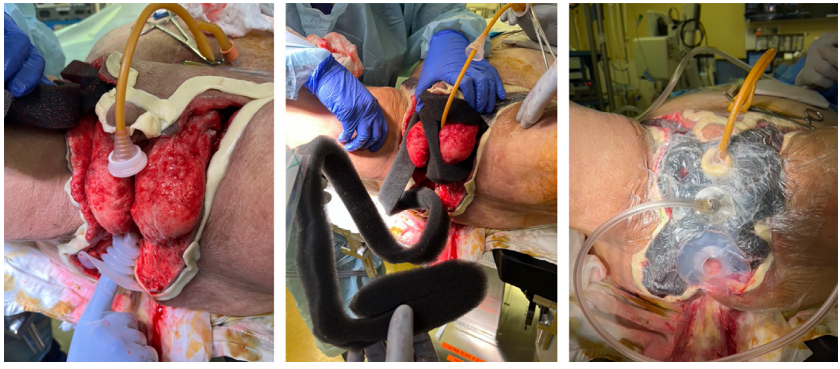

Fig. 10. Complex negative-pressure wound therapy placement.

Franco-Buenaventura and colleagues reviewed these studies, and several others in a 2021 systematic review of FG and NPWT.[145] Of the studies that reported mortality, 2 reported significantly higher mortality in patients treated with conventional bandaging compared to the NPWT group and one reported no difference. Of note, NPWT was not superior to standard dressing changes in any measured variable. NPWT was, however, associated with longer hospital stays, longer ICU stays, more surgical debridements, and a longer time from initial debridement to wound closure. The authors were unable to perform a meta-analysis due to methodologic heterogeneity between the studies. Additionally, many of the reviewed studies were limited by their retrospective nature. As of now, there are no randomized controlled trails for NPWT in FG treatment registered with clinicaltrials.gov.

Although the accumulated retrospective data regarding NPWT in FG are low-quality and inconclusive, difficulties in consistent successful placement of NPWT device in the perineum likely contributes to decreased utilization and efficacy at centers that do not frequently treat patients with FG. Applying a leak-free NPWT device is difficult in FG because of the complex tissue surfaces and creases around the penis, scrotum, and perineum as well as the need from effective drainage of urine for the penis and stool from the anus. Stoma paste and barrier dressings, skin barrier and adhesive solutions, iodine impregnated wound barrier tape, and urethral and bowel catheters can all be used to help attain and maintain an effective NPWT seal (Fig. 10). Furthermore, cutting the VAC sponge into a more versatile shape like a long strip, stapling it in place, and creating a large flat surface for the VAC tubing to adhere can also help with NPWT device placement. Finally, temporary skin closure of a large wound over NPWT foam can give increased surface area for tape to be placed and maintain a good seal (Fig. 11).

Hyperbaric oxygen therapy

HBOT is a treatment in which patients breathe 100% oxygen in a pressurized environment in order to increase the partial pressure of oxygen dissolved in the blood. There are single-patient "monoplace" chambers, as well as "multiplace" chambers which accommodate more than one person at a time (Fig. 12). Pressures in these chambers range between 1.4 and 3 atmospheres.[154] The increased atmospheric pressure raises the amount of oxygen that is dissolved in the liquid phases of blood and body fluids. HBOT is thought to benefit wounds and wound healing via increased oxygen delivery to tissues. Animal studies offer insight into possible additional mechanisms through which HBOT may reduce inflammation and enhanced white cell activation.[155-157]

Outside of oxygen delivery, the increased pressure experienced by the body during HBOT "dives" has additional beneficial effects on wound healing. These include peripheral vasoconstriction, slowed heart rate, release of red blood cells sequestered in the spleen, and mobilization

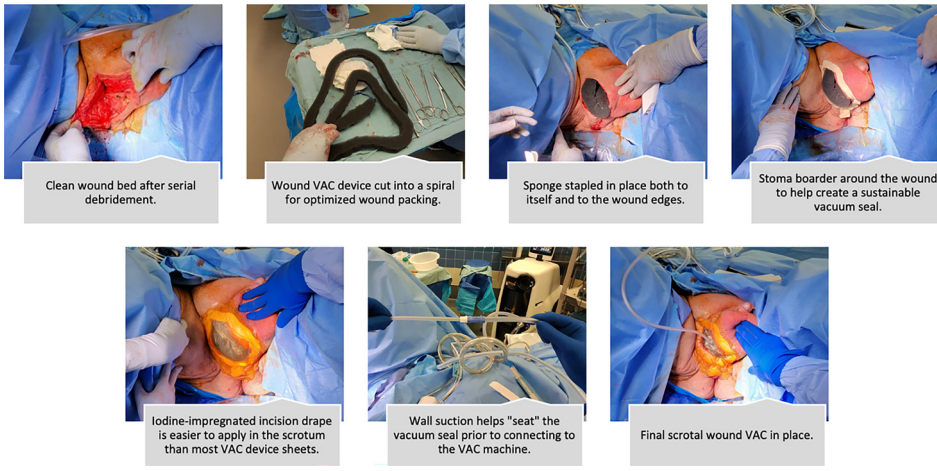

Fig. 11. How to place a scrotal wound VAC.

Fig. 12. Hyperbaric oxygen chamber.

of third-spaced fluid back into circulation.[154] Clinicians should be aware of this fluid shift as it may exacerbate congestive heart failure due to increased cardiac load. Other practical considerations include lowered blood glucose during HBOT, increased seizure risk, and complications related to air pockets in the lung (ie, pneumothoraces, blebs, or bullae) (Table 5). In addition to use in NSTIs, HBOT can be used to treat decompression sickness, carbon monoxide poisoning, severe anemias, chronic osteomyelitis, delayed radiation wounds, burn injuries, and crush injuries.[154] Urologists may be most familiar with HBOT as a treatment for radiation cystitis/hematuria.

Although HBOT should not delay surgical debridement of FG patients, it can be offered as an adjuvant wound treatment following, and between, debridements. A growing body of evidence suggests that HBOT may be associated with decreased mortality in FG. Hung and colleagues reviewed records from 2007 to 2015 and identified 60 patients who were treated at their facility for FG, 12 of whom underwent HBOT.[158] The mortality rate was 0% among patients who underwent HBOT vs. 33.3% among patients who did not get HBOT ($P = 0.025$). All patient deaths were

Table 5
Considerations for hyperbaric oxygen therapy (HBOT).

HBOT effect	Precautions
Increased cardiac load from third-space fluid re-entering vascular system	EKG, ECHO, cardiac clearance in patients with CHF
Decreased blood sugar and seizure threshold	Interrupt use of oxygen every 5-10 minutes during treatment
Complication of air collections in lung	Screening CXR

CHF, congestive heart failure; CXR, chest radiograph; ECHO, echocardiogram; EKG, electrocardiogram.

due to septic shock. Although detractors of this analysis argue that there is a high likelihood of selection bias in this retrospective study as less critically ill patients can more easily undergo HBOT, neither the age nor the FGSI was statistically different between those groups who did and did not undergo HBOT. Interestingly, 7 of the HBOT patients experienced septic shock with a survival rate of 100% vs a 22% survival rate of 18 non-HBOT patients who developed septic shock demonstrating that these critically ill patients were still able to undergo HBOT treatments in his study.[158] However, although HBOT may have offered some benefit via its ability to modulate inflammation, these results require prospective validation. Furthermore, as most HBOT facilities are not easily accessible from inpatient units, this treatment may be impractical for critically ill patients at most centers.

Raizandha and colleagues performed a systematic review and meta-analysis of the use of HBOT in FG and identified 10 retrospective studies with a total of 268 patients who underwent HBOT and 389 who had not.[140] Compared to non-HBOT patients, the HBOT group had significantly lower mortality (11% vs 32%, $P = 0.005$). There were no significant differences in length of hospital stay or number of debridements. As noted with individual studies, the meta-analysis was limited by the retrospective, observational nature of the studies included.[140] Although there are 2 clinical trials listed on clinicaltrials.gov based in Denmark designed to examine the role of HBOT in FG, no results are currently published in the literature.

Conclusion

Wound care adjuncts such as medicated dressings, NPWT, and HBOT all hold the potential for optimized wound care in FG. The aim of theses adjunct therapies is to expedite wound cleaning and wound bed health in order to allow for earlier primary wound closure, minimizing the need for skin grafting. As the data for all of these therapies are low-quality, more research is sorely needed in this space in FG. Innovations in wound care remain an excellent potential research landscape in FG.

Postdebridement reconstruction following Fournier's gangrene

-Lindsey Teal, MD, MPH and Jeffrey B. Friedrich, MD, MC

After the infection has been adequately controlled, the next step is coverage of the remaining wound. There are several techniques used to close a surgical wound after debridement, including primary closure, local tissue rearrangement, skin grafting, and flap reconstruction. Given that these patients are at high risk of complication due to multiple comorbidities, the simplest option that provides adequate coverage and function is preferred.[159] Single-stage reconstruction is also preferred, if possible. Smaller defects are amenable to healing by secondary intention, delayed primary closure, or local tissue rearrangement. Larger defects require skin grafting or a flap for reconstruction.

Healing by secondary intention

Small defects and patients at high anesthetic risk are amenable to healing secondarily. Scrotal defects that involve less than 50% of the scrotum can heal by secondary intention.[160,161] However, these wounds take longer to heal and result in longer hospitalizations when compared to delayed primary closure.[162] Aesthetically, healing with secondary intention also results in higher rates of contracture. A 10-year study in the United Kingdom found that 15% of wounds from FG were able to successfully heal by secondary intention.[163] In the authors' experience, secondary healing of the perineal body specifically is preferred, both due to its healing capacity, and the difficulty with pressure and shearing in the area that can compromise soft tissue reconstruction.

To facilitate healing by secondary intention, we recommend using NPWT as an adjunct. This results in fewer dressing changes for the patient and a shorter hospital stay.[164] NPWT can also be used after initial debridement to promote granulation tissue prior to reconstruction. An adequate seal in the perineum can be challenging to maintain given the risk of soiling, therefore foley catheter and fecal management systems may be necessary.

Primary closure

Both the complex angles of the perineum and genital organs as well as their variable functionality can make primary closure difficult. Primary closure is preferred if there is no tension over the wound and closure does not distort the anatomy.[165] Patients who undergo delayed primary closure report higher quality of life compared to those who undergo healing by secondary intention.[166] The wound should be closed in layers with appropriate approximation of muscle, fascia, and subcutaneous tissue to avoid dead space. Closed suction drains can also help to suction down potential dead space under tissue flaps. If the wound cannot be closed without tension, more advanced coverage techniques should be employed. An algorithm that can be used to cover perineal defects when primary closure is not feasible is shown in Figure 13.

Local tissue rearrangement

Local tissue rearrangement recruits healthy tissue adjacent to the wound to close the defect. Due to the elasticity of the scrotum, scrotal advancement flaps can be used for coverage of scrotal defects when the defect involves less than 50% of the scrotum (Fig. 14).[167,168] Local tissue rearrangement is a simple technique that replaces "like with like," can be performed as a single-stage procedure, and has minimal donor site morbidity. This is accomplished by undermining the subcutaneous tissue around the scrotum and advancing the elastic scrotal skin until a tension-free closure is achieved. It is imperative the closure is without tension to prevent scrotal skin necrosis. Additionally, scrotal advancement flaps can be used for penile reconstruction in the setting of an isolated penile defect without involvement of the scrotum.

Skin grafting

Skin grafting, particularly split thickness skin grafting, is a popular option for coverage of genital/perineal wounds, as it is a relatively simple procedure and can be performed in a single-stage approach. Skin grafting should only be undertaken in wound beds with healthy granulation tissue that are cleared of infection. This procedure carries minimal donor site morbidity and yields adequate functional and aesthetic outcomes. Risks associated with the use of skin grafting include contraction over time and potential for skin graft loss due to infection, seroma, hematoma, or shearing.[160] However, given the simplicity of the procedure and minimal donor site morbidity, skin grafting is a key component of reconstruction for FG.

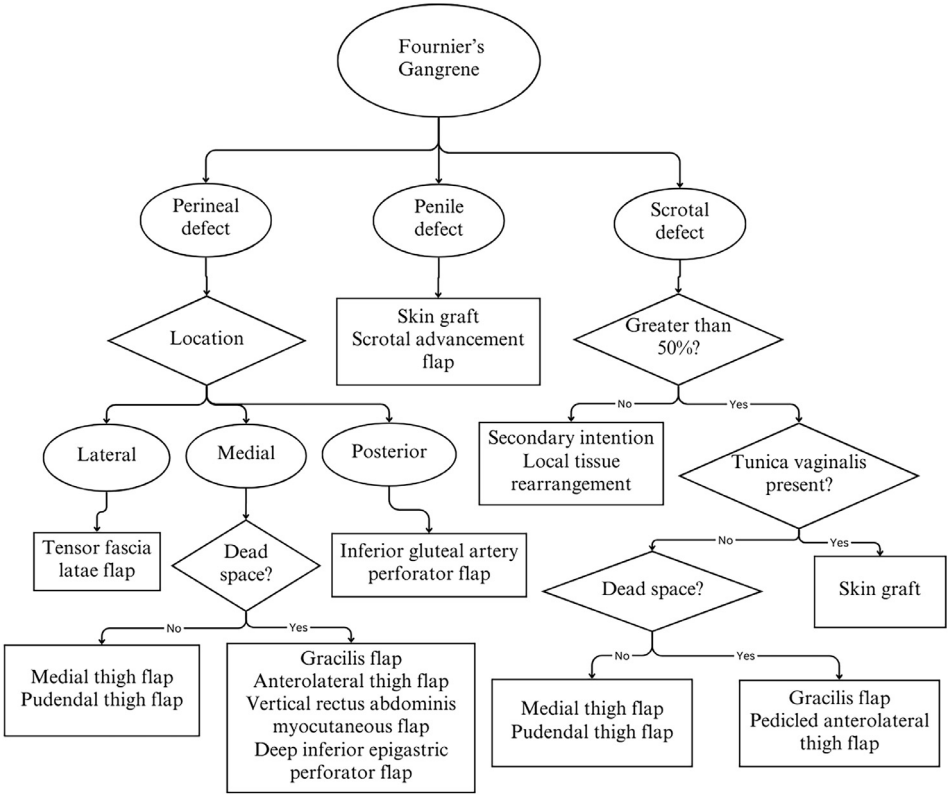

Fig. 13. The algorithm for reconstruction of perineal, penile, and scrotal defects resulting from Fournier's gangrene.

In scrotal reconstruction, skin grafting is an appropriate reconstruction option for scrotal defects greater than 50% (Fig. 15). The thin skin from a split thickness skin graft is similar to the scrotal skin, contours well to the surface of the testes, and maintains the lower temperature needed by the testes. However, there is concern for pain due to tightness and lack of mobilization between skin graft and testes.[169] Some have reported that tunica vaginalis and ideally some dartos muscle must be preserved in order for the skin graft to appropriately take, although this is not a universal experience.[170] Many surgeons will mesh scrotal grafts to decrease donor site morbidity with improved coverage. Of note, midline orchiopexy is recommended to allow grafting of the testicles as a unit. The orchiopexy can be undertaken at the same time as skin grafting or even during prior debridements once the infection around the testicles has been controlled. It is important not to wait too long for the orchiopexy because the testicles can retract superiorly and become very difficult to bring back down to a normal anatomic position below the penis (Fig. 16).

In penile reconstruction, full or split thickness skin grafts may be used. When compared to full thickness grafts, split thickness skin grafts have a lower incidence of graft failure and cause less donor site morbidity, and therefore are used more frequently.[171] Penile skin grafts tend not to be meshed in order to improve cosmesis, but if donor site morbidity is of importance then meshing is acceptable.[172] Ideally, these grafts are placed on dartos muscle overlying Buck's fascia as opposed the fascia itself, as they may have improved sexual function and pliability if not directly on the fascia.

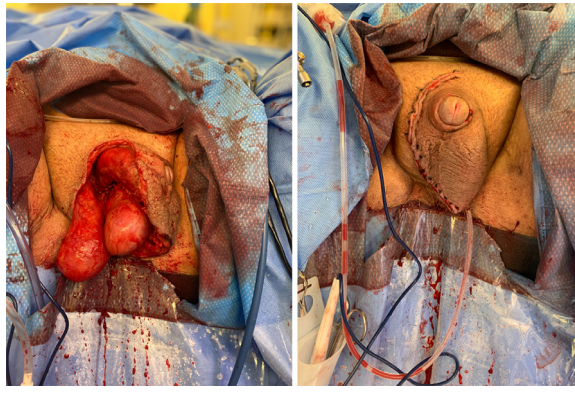

Fig. 14. Local tissue rearrangement.

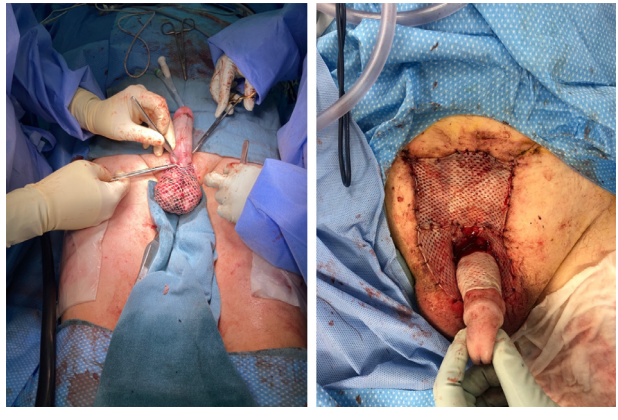

Fig. 15. Skin grafting after Fournier's gangrene.

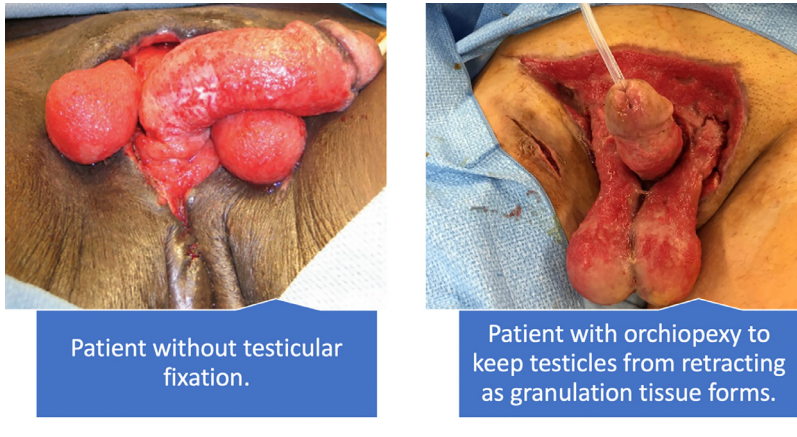

Fig. 16. The importance of orchiopexy.

In perineal reconstruction, skin grafting is not optimal given the high bacterial load in the perineal body area with high risk of infection leading to loss of skin graft.[173] Additionally, due to pressure from sitting and shearing forces from walking, graft take can be poor. However, when the defect extends superiorly to the abdomen, skin grafting can be used to cover defects in this area.

Flap reconstruction

Larger scrotal wounds and perineal wounds are often treated with flap reconstruction. For areas without dead space, thinner fasciocutaneous flaps are chosen. If the infection caused significant soft tissue loss creating a dead space, myocutaneous flaps can be used to add bulk to replace the soft tissue defect. Pedicled or free flaps can be used to cover the defects, depending on the tissue involvement and the area that must be covered.

In scrotal reconstruction, scrotal wounds greater than 50% can be treated with local (non-scrotal) flap reconstruction as opposed to skin grafting, specifically if the tunica vaginalis has been removed. If there is no dead space present, fasciocutaneous flaps, such as medial thigh flaps or pudendal thigh flaps can be used. A benefit of these flaps compared to skin grafting and local tissue rearrangement is the recruitment of well vascularized and often sensate tissue outside the area of infection to replace the defect. Although the tissue recruited for fasciocutaneous flaps is more similar to scrotal skin than a myocutaneous flap, it is still bulkier than native scrotal skin. Additionally, the increased subcutaneous tissue recruited with these flaps increases the temperature of the testes and can impair spermatogenesis.[169] If dead space must be filled, gracilis flaps or pedicled anterolateral thigh flaps may be used.

In perineal wounds, flaps are needed for wounds that cannot be closed primarily or with local tissue rearrangement. There are multiple options to consider based on the location. For medial defects without dead space, fasciocutaneous flaps can be used, such as the medial thigh flaps and pudendal thigh flaps. If dead space is present, medial defects can be closed by using thigh-based flaps (gracilis flaps, anterolateral thigh flaps) or abdominal-based flaps (vertical rectus abdominis myocutaneous flaps, deep inferior epigastric perforator flaps). Lateral and posterior defects can also be present, often in conjunction with medial defects. Therefore, coverage of these defects is often combined with previously mentioned flaps for medical coverage. For lateral hip/groin defects, tensor fascia lata flaps can be used. For posterior defects, such as the buttock, gluteal flaps can be used, such as inferior gluteal artery perforator flaps.

Local fasciocutaneous flaps

Local fasciocutaneous flaps are based on local perineal perforators that should be assessed preoperatively with Doppler ultrasound. Local flaps require more advanced surgical techniques than skin grafting or primary closure, but they can be used in a single-stage approach and often result in minimal donor site morbidity. The medial thigh is a common donor site for fasciocutaneous flaps used for perineal and scrotal reconstruction.

Medial thigh fasciocutaneous flaps

The medial thigh fasciocutaneous flaps are based on the external pudendal, superficial femoral, and medial circumflex femoral perforators and can be used to cover scrotal or perineal defects. The flap is elevated longitudinally along the medial thigh in a distal to proximal direction along the subfascial plane (Fig. 17). The flap can be rotated 90 degrees medially to cover the defect. The thin fasciocutaneous flaps resemble the scrotal tissue more than bulkier flaps.[174] The donor site is primarily closed and hidden along the medial thigh.

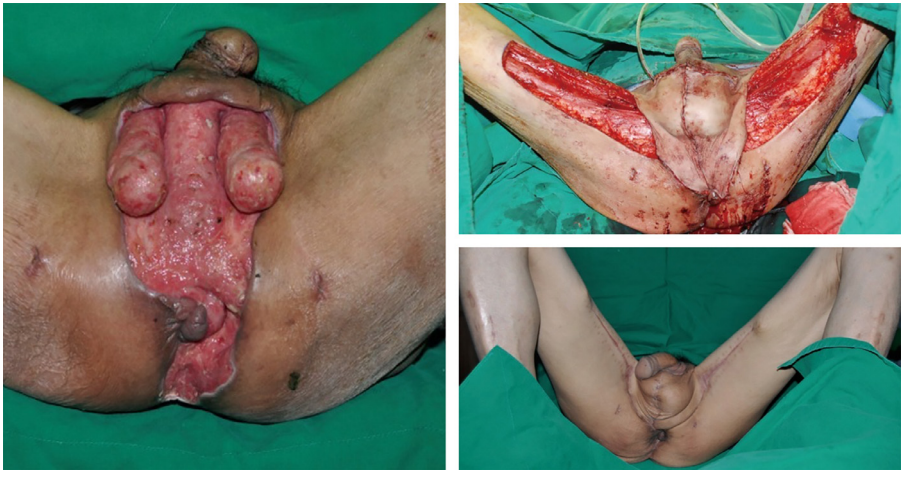

Fig. 17. Medial thigh fasciocutaneous flaps.

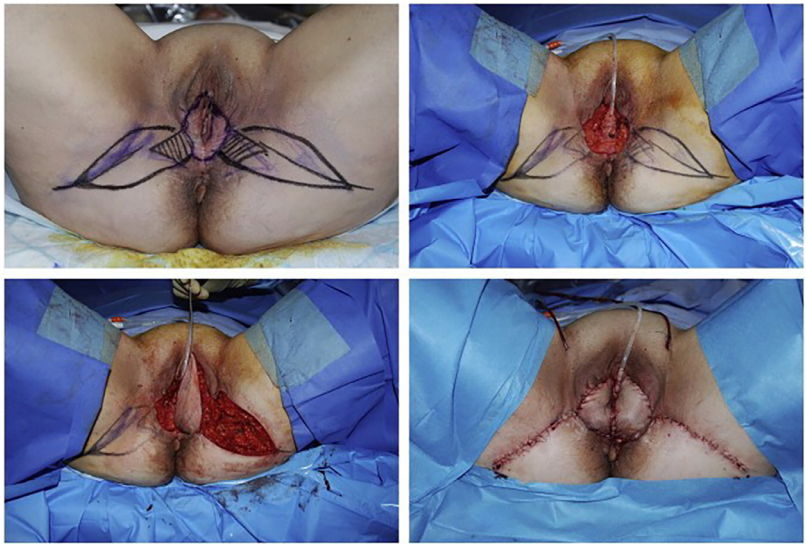

Fig. 18. Lotus petal flap.

Pudendal thigh flaps

There are 2 common sensate flaps used for perineal and scrotal reconstruction based on the internal pudendal artery, the lotus petal flap and the Singapore flap. The Singapore flap is traditionally a true fasciocutaneous flap, whereas the lotus petal flap is raised in a suprafascial plane.[175] In a Singapore flap, tissue is raised in a subfascial plane lateral to the labia majora or scrotum from anterior to posterior direction, being mindful to keep the internal pudendal perforators intact. The lotus petal flap is also based on the internal pudendal artery but can be raised in multiple different axes. When all possible axes are drawn together, it resembles a lotus petal. As this flap does not include the fascia, it is thinner and more malleable, making it an optimal choice for scrotal reconstruction (Fig. 18).[176]

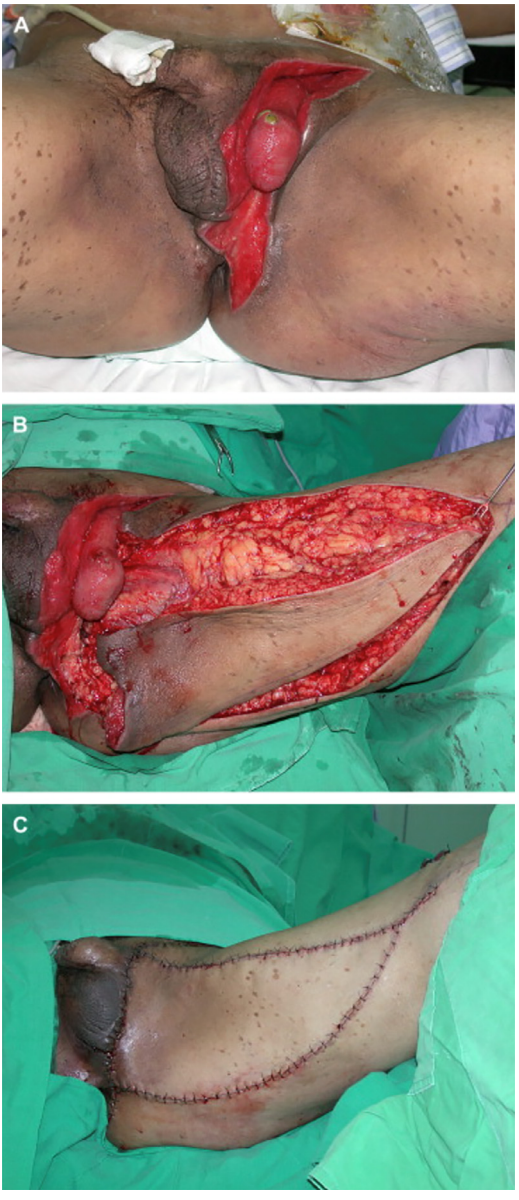

Fig. 19. Gracilis myocutaneous flap.

Local pedicled flaps

Thigh flaps

Gracilis flap. The gracilis flap is a workhorse myocutaneous flap in perineal and scrotal reconstruction (Fig. 19). This flap allows for coverage of large and deep wounds.[177] The gracilis flap is a reliable flap that has one dominant pedicle based on the medial femoral circumflex vessels

and several minor vascular pedicles arising from the superficial femoral artery. The muscle is released from its distal musculotendinous junction and elevated longitudinally along the medial thigh in a distal to proximal direction. This can be used to cover scrotal and perineal defects when there is dead space present. The gracilis muscle is expendable and most patients do not notice a functional deficit. The site is also able to be closed primarily and therefore there is little donor site morbidity.

Anterolateral thigh flap. The anterolateral thigh (ALT) flap is a robust flap that can be used for large perineal and scrotal defects. The ALT flap is a versatile flap with a large cutaneous skin paddle, covering defects up to 8×25 cm.[97,178] The blood supply is from the descending branch of the lateral circumflex femoral artery, and it can be raised as a fasciocutaneous or a myocutaneous flap, depending on the level of volume needed to close the defect. It can also be harvested as a pedicled flap or a free flap, depending on the location of the defect. When used as a pedicle flap for scrotal or perineal reconstruction, the ALT flap almost always should be passed deep to the rectus femoris muscle in order for it to adequately reach the defect without pedicle tension. Even though it is robust in size, the donor site at the anterolateral thigh can be often closed primarily and causes low donor site morbidity. This is one of the more complex and technically demanding procedures offered for perineal reconstruction but can be accomplished in a single stage. The primary disadvantage of this flap is its bulkiness, thus myocutaneous flaps should only be used in areas where there is significant soft tissue loss.[169]

Tensor fascia latae. The tensor fascia latae flap incorporates skin, muscle, and fascia from the lateral thigh and can be used for lateral defects, including the inguinal region.[179] It is large and can be raised to cover a 10×30 cm defect.[180] The blood supply is based on the ascending branch of the lateral circumflex femoral artery. It is elevated along the longitudinal lateral thigh from a distal to proximal direction. ALT flaps are often used in conjunction with tensor fascia latae flaps to provide medial coverage for perineal reconstruction.[181]

Gluteal flaps

Inferior gluteal artery perforator flap. The inferior gluteal artery perforator flap (IGAP) is a simple perforator flap harvested from the lower buttock for posterior perineal reconstruction. It is dissected from lateral to medial and the gluteus maximus muscle is spared, therefore there is low donor morbidity.[182] These flaps are typically raised bilaterally and advanced medially and the donor sites are closed in a V-Y fashion. Intraoperative positioning should be considered, as a patient will need to be placed in either the prone or lateral decubitus position for harvesting. The primary disadvantage to this flap is it requires patients to lie flat for several weeks postoperatively to prevent dehiscence.[180]

Abdominal flaps

Vertical rectus abdominis myocutaneous flaps. The vertical rectus abdominis myocutaneous (VRAM) flap or oblique rectus abdominis myocutaneous (ORAM) is the primary abdominal flap used for perineal reconstruction. The vertical or oblique terminology refers to the orientation of the skin paddle in relation to the rectus abdominis muscle. This is an ideal flap to use when bulk and a large skin paddle are needed. The flap can be raised on a vertical or oblique cutaneous skin paddle, covering up to 10×20 cm (Fig. 20).[180] The flap consists of skin, subcutaneous tissue, and rectus abdominus muscle based on the deep inferior epigastric vessels. The flap is harvested by transecting the rectus abdominus muscle superiorly at the costal margin and tunneling the rectus inferiorly through the perineum to cover the defect. The primary disadvantage of this flap is the donor site defect, with an abdominal wall hernia rate of 15.6%, with 3.8% requiring repair for symptomatic hernias.[183] Donor site bulges have also been found at a rate of 12%, with 6% being symptomatic and requiring surgery.[184]

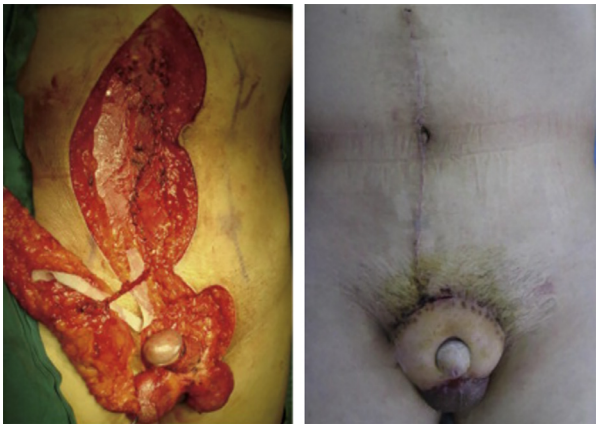

Fig. 20. Vertical rectus abdominis myocutaneous flaps.

Deep inferior epigastric perforator flap. The pedicled or free deep inferior epigastric perforator (DIEP) flap is another abdominally based flap that offers similar cutaneous coverage as the VRAM flap, but with less donor site morbidity as it spares the rectus muscle.[185] The DIEP flap is also based on the deep inferior epigastric vessels but spares the rectus abdominis muscle itself. The dissection for this flap can be challenging, as the perforators often course through tendinous inscriptions in the rectus muscles. The main disadvantage to the DIEP flap is the bulkiness of the flap, which may ultimately require debulking.[186]

Conclusion

In summary, source control of FG often requires extensive debridement resulting in open wounds to the external genitalia and perineum. There are many factors to consider when selecting the best reconstructive option, including patient comorbidities, size and location of the defect, volume of dead space, patient preference, and surgeon expertise. There are many options for reconstruction spanning the entirety of the reconstructive ladder, from delayed primary closure to free flaps. A single-stage reconstruction that replaces the soft tissue defect with similar tissue and creates minimal donor site morbidity should be prioritized.

Considerations for special populations in Fournier's gangrene

-George E. Koch, MD and Judith C. Hagedorn, MD, MHS

Although a majority of FG cases are diagnosed in men and associated with obesity and poorly controlled DM, several conditions like immunosuppression from malignancy or its treatment and spinal cord injury can present unique challenges and considerations in the care of FG patients. Similarly, FG in female patients is less common and delays in diagnosis can lead to more fulminant cases.

Spinal cord injury

There are very few reports in the literature of spinal cord injury patients developing FG, presumably because the differentiation and management of a super-infected chronic pressure

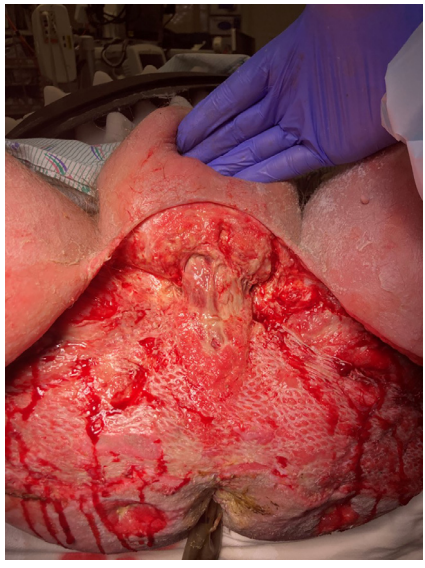

Fig. 21. Urethral involvement in Fournier's gangrene secondary to a pressure ulcer.

ulcer and a severe skin and soft tissue infection of the perineum is not clinically meaningful. However, the disease process in this population can differ significantly from typical FG.

There is only one published comparative study of spinal cord injury patients with FG, a retrospective cohort study which describes a strong association between preexisting pressure ulcers and the development of FG for these patients.[187] Backhaus and colleagues reported that in a group of 3991 spinal cord injury patients, the relative risk of developing FG was 2.9 (95% CI 2.1-3.4) for patients with a pressure ulcer compared to those without. Interestingly, the FG patients in this study did not resemble classic FG patients. Spinal cord injury patients that developed FG were younger (median age of 43 years, range 23-67) than the 50 to 60 years described by most epidemiological FG studies.[7,127] Furthermore, only 2 of the 16 FG patients described had comorbid DM. Finally, there were no mortalities in the 16 patients described. Therefore, although pressure ulcers may put spinal cord injury patients at risk for FG, their relative age and different comorbidities may also contribute to a lower mortality rate.

Although pressure ulcers may replace local skin trauma as the gateway insult for the development of a NSTI in spinal cord injury patients, they may also cause a divergence from the typical fascial spread of the infection. Classically, these NSTIs spread along the fascia, deep to the dermis and epidermis, causing secondary injury to those superficial structures by thrombosing perforating blood vessels. This results in the preservation of deeper structures of the perineum like the penis, deep to Buck's Fascia, and the testicles, deep to the tunica vaginalis. However, it has been observed in spinal cord injury patients that deeper structures may be infected and necrotic, potentially due to preexisting erosive damage through the fascia from pressure ulcers (Fig. 21). Spinal cord injury patients, therefore, require a thorough examination of the urethra and may require debridement deep to traditionally spared boundaries.

Although little has been published about FG in spinal cord injury patients, better understood aspects of their physiology can inform medical and surgical management. Spinal cord injury patients often require either intermittent or indwelling catheterization for neurogenic bladder management with resulting colonization by different organisms than neurologically intact patients.[188-190] Furthermore, patients with neurogenic bladder secondary to spinal cord injuries and requiring catheterization in some form are also at risk for traumatic catheterization, which has been identified as a potential inciting injury in some case reports on FG in the spinal cord

injury population.[191,192] Even outside of a traumatic catheterization, spinal cord injury patients can suffer from bladder neck and urethral erosions from long-term pressure from a catheter, which can further lead to urine extravasation and subsequent soft tissue infection.[193] Although this is most often described in women, we have seen erosions at our institution in men as well. In 1 patient who had undergone a previous sphincterotomy abroad, his bladder neck erosion led to constant urine leakage into his perineum, precipitating infection of sacral ulcers.

Spinal cord injury patients are not only more susceptible to infection due to decreased or damaged physical barriers, but they are also immunosuppressed secondary to their injury.[192,194] Although immunosuppression thought to be caused directly by neurologic dysfunction and hypofunction in spinal cord injuries patients is not yet well understood, it likely plays a role in the susceptibility of this population to infection. Both of these risk factors, chronic catheterization and immunosuppression, must be considered when triaging spinal cord injury patients who may have a NSTI.

Following the debridement and source control for spinal cord injury patients, the integrity of the lower urinary tract needs to be evaluated when planning reconstructions. Equally as important, the functionality of the bladder, urethra and sphincter complexes must be assessed. For patients with large urethral or sphincteric injuries, but with a functional bladder, bladder neck closure and suprapubic cystostomy should be considered. For patients with a non-functional bladder, urinary diversion should be strongly considered.

Women

FG in women is comparatively more rare, although the exact rate of FG and even the definition are debated. A 2009 review of United States Inpatient Databases by Sorenson and colleagues reported that only 39 of 1,680 cases of FG occurred in women in their sample, representing 2.3% of the entire cohort.[127] Notably, this analysis identified patients using the ICD-9 diagnosis coding system, under which the code specific to FG is found under the “male genital organs” section. Given this limitation, examining FG in female patients using large administrative datasets remains difficult.

Maybe the most granular and comprehensive data on female FG patients comes from a comparative analysis of male and female patients with FG that was described by Beecroft and colleagues in 2021.[6] In this study, female patients had a larger body mass index (42.1 vs 33.7, $P = 0.003$) but similar age, FGSI, length of hospital stay, and number of debridements. Interestingly, wound culture results did not differ between sexes, although this may be due to the analysis being broken down only by gram stain as opposed to specific bacterial species. There was also no statistical difference in the percentage of men (23%) versus women (18%) who underwent definitive reconstruction during their index hospitalization. Given that the scrotum theoretically offers more abundant tissue for reconstruction, this lack of a difference in outcomes is surprising, however the lack of testicles requiring coverage may balance the advantage of more scrotal skin. Although this analysis by Beecroft was only a single institution series, it provides a great deal of detailed data that is likely much more precise than the large administrative datasets that had previously been used to describe the prevalence of FG in women.

A scoping review of FG in women written in 2023 by Khalid and colleagues included 134 female patients from 22 studies published between 2004 and 2022.[195] Similar to Beecroft and colleagues, the age and comorbidities of female patients was similar to that of male patients, however the authors identified a much higher mortality rate among women at 20% than the 5% to 10% reported in most contemporary series of FG patients.[6,196] Unfortunately, it is difficult to account for the causes of such a difference in mortality rate in this systematic review, however the authors postulate that it may be secondary to delayed diagnosis given that FG in women is less common and may be underrecognized. At our institution, the urology service treats most male FG patients whereas the general surgery and gynecology services treat the female FG patients. Therefore, it is possible that there are systematic differences in the way the 2 different patient cohorts are treated at varying institutions around the county.

Malignancy

Patients with concomitant malignancy and FG represent another population with special considerations. Creta and colleagues described 44 patients with hematologic malignancy presenting with FG from 1983 to 2021.[197] Fifty percent of patients in this series were undergoing either chemotherapy or a stem-cell transplant, signaling that immunosuppression may have played a role in the progression of the infection for these patients. Although the mortality rate reported for this cohort was 11.3%, the average hospitalization for these patients was 81.6 days. Therefore, although immunosuppression likely predisposes these patients to fulminant infection, it also inhibits wound healing in massive skin and soft tissue loss.

Unlike hematologic malignancy in which patients are predisposed to FG from immunosuppression, colorectal malignancy has also been associated with FG in multiple series, with the infection heralding the diagnosis of malignancy. These patients often present with superinfection of the mass or a skin and soft tissue infection secondary to locally invasive bowel cancer.[198,199] Regardless of the malignancy, this patient population requires antibiotic therapy and prompt debridement as in other cases of FG with a multidisciplinary approach to each patient's individual malignancy after stabilization.

The need for a multidisciplinary approach for these patients cannot be overstated because they not only require reconstruction after stabilization, but they also require a reconstructive plan that takes into account their potential need for additional extirpative surgery, radiation, or chemotherapy. Engagement with the surgical oncology and/or oncology services is essential and a patient's final reconstruction should be delayed until this multidisciplinary plan is finalized. NPWT can be used to manage wounds while final pathology and treatment plans are obtained and formulated. Skin grafts and complex reconstructions should be avoided for patients who will require short interval chemotherapy, immunotherapy, or radiation and wound simplification with thigh pouches or even orchiectomy may be indicated in these special circumstances.

Medication-associated and deep penetrating Fournier's gangrene

Two other special populations that require mention, but without much published data are medication-associated FG and invasive FG. The most common medications associated with FG are the sodium-glucose transport protein 2 (SGLT2) inhibitors, which are used to treat DM.[200] SGLT2 inhibitors work by blocking glucose reabsorption in the kidney, thus lowering blood glucose levels via increased urine glucose levels.[201] This increase in urine glucose helps create a more favorable environment for bacterial overgrowth and has been associated with both urinary tract infections and skin and soft tissue infections of the perineum. Although this sub-type of FG should be treated like any other, it is important to take these patients off this antihyperglycemic medication during their recovery.[202]

Classically, FG infections do not invade into the deeper tissues of the penis or testicles, however isolated case reports of penile involvement do populate the literature (Fig. 22).[203–205] These case reports often involve patients with end-stage vascular disease that compromises deeper tissues, or even dry gangrene like penile calciphylaxis that serves as a nidus of infection prior to the development of FG.[206] Although these cases are not typical, they serve as a reminder to carefully and serially examine deeper structures during FG debridements as these patients often have severe and end-stage contributing comorbidities. For patients with these deeper tissue infections, more complex reconstructions may be necessary, but it is important to understand the patients' comorbidities and appropriateness for complex reconstructive procedures. For urethral erosion, a suprapubic tube, with or without urethral closure, may be more judicious than an augmentation urethroplasty. Urinary diversion is sometimes required instead of attempting major salvage reconstructions.

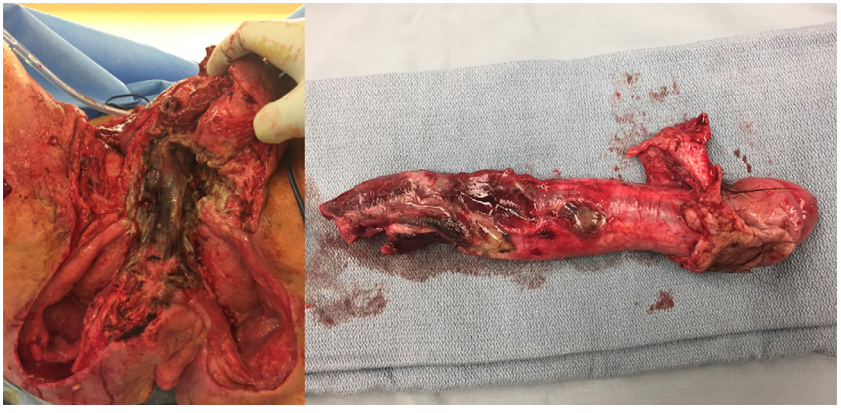

Fig. 22. Penile and urethral involvement of Fournier's gangrene.

Conclusion

Although much about the diagnosis, treatment, and reconstruction of FG is consistent across the literature, the special cases and considerations described above remind the treating urologist and general surgeon that there is more nuance to FG than often appreciated. These special patient populations require further study and individualized approaches to care.

References

1. El-Qushayri AE, Khalaf KM, Dahy A, et al. Fournier's gangrene mortality: a 17-year systematic review and meta-analysis. *Int J Infect Dis*. 2020;92:218–225. doi:10.1016/j.ijid.2019.12.030.
2. Jean-Alfred Fournier 1832-1914. *Dis Colon Rectum*. 1988;31(12):984–988. doi:10.1007/BF02554904.
3. Sorensen MD, Krieger JN, Rivara FP, et al. Fournier's gangrene: population based epidemiology and outcomes. *J Urol*. 2009;181(5):2120–2126. doi:10.1016/j.juro.2009.01.034.
4. Furr J, Watts T, Street R, Cross B, Slobodov G, Patel S. Contemporary trends in the inpatient management of Fournier's gangrene: predictors of length of stay and mortality based on population-based sample. *Urology*. 2017;102:79–84. doi:10.1016/j.urology.2016.09.021.
5. Eke N. Fournier's gangrene: a review of 1726 cases. *Br J Surg*. 2002;87(6):718–728. doi:10.1046/j.1365-2168.2000.01497.x.
6. Beecroft NJ, Jaeger CD, Rose JR, et al. Fournier's gangrene in females: presentation and management at a Tertiary Center. *Urology*. 2021;151:113–117. doi:10.1016/j.urology.2020.05.056.
7. Sorensen MD, Krieger JN. Fournier's gangrene: epidemiology and outcomes in the general US population. *Urol Int*. 2016;97(3):249–259. doi:10.1159/000445695.
8. Wróblewska M, Kuzaka B, Borkowski T, Kuzaka P, Kawecki D, Radziszewski P. Fournier's gangrene–current concepts. *Pol J Microbiol*. 2014;63(3):267–273.
9. Kuo CF, Wang WS, Lee CM, Liu CP, Tseng HK. Fournier's gangrene: ten-year experience in a medical center in northern Taiwan. *J Microbiol Immunol Infect*. 2007;40(6):500–506.
10. Desai R, Batura D. A contemporaneous narrative review of Fournier's gangrene. *Urol J*. 2023;90(2):201–208. doi:10.1177/03915603231165067.
11. Huayllani MT, Cheema AS, McGuire MJ, Janis JE. Practical review of the current management of Fournier's gangrene. *Plast Reconstr Surg Glob Open*. 2022;10(3):e4191. doi:10.1097/GOX.0000000000004191.
12. Cipriani C, Iacovelli V, Sandri M, et al. The microbiological profile of patients with Fournier's gangrene: A retrospective multi-institutional cohort study. *Urologia Journal*. 2022;89(3):437–443. doi:10.1177/03915603211018441.
13. Hagedorn JC, Wessells H. A contemporary update on Fournier's gangrene. *Nat Rev Urol*. 2017;14(4):205–214. doi:10.1038/nrurol.2016.243.
14. Chia L, Crum-Cianflone NF. Emergence of multi-drug resistant organisms (MDROs) causing Fournier's gangrene. *J Infect*. 2018;76(1):38–43. doi:10.1016/j.jinf.2017.09.015.
15. Huang KF, Hung MH, Lin YS, et al. Independent predictors of mortality for necrotizing fasciitis: a retrospective analysis in a Single Institution. *J Trauma*. 2011;71(2):467–473. doi:10.1097/TA.0b013e318220d7fa.
16. Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas A. Current concepts in the management of necrotizing fasciitis. *Front Surg*. 2014;1:36. doi:10.3389/fsurg.2014.00036.
17. Akilov O, Pompeo A, Sehrt D, Bowlin P, Molina WR, Kim FJ. Early scrotal approximation after hemiscrotectomy in patients with Fournier's gangrene prevents scrotal reconstruction with skin graft. *Can Urol Assoc J*. 2013;7(7-8):481. doi:10.5489/cuaj.1405.

18. Şahin H, Aflay U, Kılınç N, Bircan MK. Coagulation parameters in the patients with Fournier's gangrene. *Int Urol Nephrol*. 2005;37(4):733–737. doi:10.1007/s11255-005-8437-y.
19. Montrief T, Long B, Koyfman A, Auerbach J. Fournier gangrene: a review for emergency clinicians. *J Emerg Med*. 2019;57(4):488–500. doi:10.1016/j.jemermed.2019.06.023.
20. Hejase MJ, Simonin JE, Bihrle R, Coogan CL. Genital fournier's gangrene: experience with 38 patients. *Urology*. 1996;47(5):734–739. doi:10.1016/S0090-4295(96)80017-3.
21. Bowen D, Juliebø-Jones P, Somani BK. Global outcomes and lessons learned in the management of Fournier's gangrene from high-volume centres: findings from a literature review over the last two decades. *World J Urol*. 2022;40(10):2399–2410. doi:10.1007/s00345-022-04139-4.
22. Ngugi P, Magoha G, Nyaga P. Fournier's gangrene in the HIV era. *Afr Health Sci*. 2015;14(4):1063. doi:10.4314/ahs.v14i4.38.
23. Osbun N, Hampson LA, Holt SK, Gore JL, Wessells H, Voelzke BB. low-volume vs high-volume centers and management of Fournier's gangrene in Washington State. *J Am Coll Surg*. 2017;224(3):270–275. doi:10.1016/j.jamcollsurg.2016.11.012.
24. Clayton MD, Fowler JE, Sharifi R, Pearl RK. Causes, presentation and survival of fifty-seven patients with necrotizing fasciitis of the male genitalia. *Surg Gynecol Obstet*. 1990;170(1):49–55.
25. Baskin LS, Carroll PR, Cattolica EV, McAninch JW. Necrotising soft tissue infections of the perineum and genitalia: bacteriology, treatment and risk assessment. *Br J Urol*. 1990;65(5):524–529. doi:10.1111/j.1464-410X.1990.tb14801.x.
26. Benizri E, Fabiani P, Migliori G, et al. Gangrene of the perineum. *Urology*. 1996;47(6):935–939. doi:10.1016/S0090-4295(96)00058-1.
27. Laor E, Palmer LS, Tolia BM, Reid RE, Winter HI. Outcome prediction in patients with Fournier's gangrene. *J Urol*. 1995;154(1):89–92.
28. Corcoran AT, Smaldone MC, Gibbons EP, Walsh TJ, Davies BJ. Validation of the Fournier's Gangrene Severity Index in a large contemporary series. *J Urol*. 2008;180(3):944–948. doi:10.1016/j.juro.2008.05.021.
29. Ozden Yeniyol C, Suelozgen T, Arslan M. Riza Ayder A. Fournier's gangrene: experience with 25 patients and use of Fournier's gangrene severity index score. *Urology*. 2004;64(2):218–222. doi:10.1016/j.urology.2004.03.049.
30. Uluğ M, Gedik E, Girgin S, Çelen MK, Ayaz C. The evaluation of microbiology and Fournier's gangrene severity index in 27 patients. *Int J Infect Dis*. 2009;13(6):e424–e430. doi:10.1016/j.ijid.2009.01.021.
31. Yilmazlar T, Ozturk E, Ozguc H, Ercan I, Vuruskan H, Oktay B. Fournier's gangrene: an analysis of 80 patients and a novel scoring system. *Tech Coloproctol*. 2010;14(3):217–223. doi:10.1007/s10151-010-0592-1.
32. Yalçınkaya S, Yıldız A, Yüksel M, et al. Can we predict mortality in patients with Fournier's gangrene using questionnaires? A pilot study with eighty-seven patients. *Journal of Urological Surgery*. 2019;6(2):118–124. doi:10.4274/jus.galenos.2018.2327.
33. García Marín A, Turégano Fuentes F, Cuadrado Ayuso M, Andueza Lillo JA, Cano Ballesteros JC, Pérez López M. Factores predictivos de mortalidad en la gangrena de Fournier: serie de 59 casos. *Cir Esp*. 2015;93(1):12–17. doi:10.1016/j.ciresp.2014.03.017.
34. Yasri S, Re Wiwanitkit V. Simplified Fournier's gangrene severe index score (SFGSI). *Int Braz J Urol*. 2018;44(1):204. doi:10.1590/s1677-5538.ibju.2017.0535.
35. Sumisławski P, Kołecki J, Piotrowska M, Kotowski M, Szemitko M, Sieńko J. Utility of diagnostic imaging in the early detection and management of the Fournier gangrene. *Diagnostics*. 2022;12(10):2320. doi:10.3390/diagnostics12102320.
36. Fernando SM, Tran A, Cheng W, et al. Necrotizing soft tissue infection: diagnostic accuracy of physical examination, imaging, and LRINEC score. *Ann Surg*. 2019;269(1):58–65. doi:10.1097/SLA.0000000000002774.
37. Ballard DH, Mazaheri P, Raptis CA, et al. Fournier gangrene in men and women: appearance on CT, ultrasound, and MRI and what the surgeon wants to know. *Can Assoc Radiol J*. 2020;71(1):30–39. doi:10.1177/0846537119888396.
38. Ballard DH, Raptis CA, Guerra J, et al. Preoperative CT findings and interobserver reliability of Fournier gangrene. *Am J Roentgenol*. 2018;211(5):1051–1057. doi:10.2214/AJR.18.19683.
39. McGillicuddy EA, Lischuk AW, Schuster KM, et al. Development of a computed tomography-based scoring system for necrotizing soft-tissue infections. *J Trauma*. 2011;70(4):894–899. doi:10.1097/TA.0b013e3182134a76.
40. Chennamsetty A, Khourdaji I, Burks F, Killinger KA. Contemporary diagnosis and management of Fournier's gangrene. *Ther Adv Urol*. 2015;7(4):203–215. doi:10.1177/1756287215584740.
41. Chaudhry AA, Baker KS, Gould ES, Gupta R. Necrotizing fasciitis and its mimics: what radiologists need to know. *Am J Roentgenol*. 2015;204(1):128–139. doi:10.2214/AJR.14.12676.
42. de Miguel Criado J, del Salto LG, Rivas PF, et al. MR imaging evaluation of perianal fistulas: spectrum of imaging features. *Radiographics*. 2012;32(1):175–194. doi:10.1148/rg.321115040.
43. Wongwaisayawan S, Krishna S, Haroon M, Nisha Y, Sheikh A. Fournier gangrene: pictorial review. *Abdomin Radiol*. 2020;45(11):3838–3848. doi:10.1007/s00261-020-02549-9.
44. Gelbard RB, Ferrada P, Yeh DD, et al. Optimal timing of initial debridement for necrotizing soft tissue infection: a practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg*. 2018;85(1):208–214. doi:10.1097/TA.0000000000001857.
45. Sartelli M, Guirao X, Hardcastle TC, et al. 2018 WSES/SIS-E consensus conference: recommendations for the management of skin and soft-tissue infections. *World J Emerg Surg*. 2018;13:58. doi:10.1186/s13017-018-0219-9.
46. Ingraham AM, Jung HS, Liepert AE, Warner-Hillard C, Greenberg CC, Scarborough JE. Effect of transfer status on outcomes for necrotizing soft tissue infections. *J Surg Res*. 2017;220:372–378. doi:10.1016/j.jss.2017.06.006.
47. Rüfenacht MS, Montaruli E, Chappuis E, Posfay-Barbe KM, La Scala GC. Skin-sparing débridement for necrotizing fasciitis in children. *Plast Reconstr Surg*. 2016;138(3):489e–497e. doi:10.1097/PRS.0000000000002478.
48. Perry TL, Kranker LM, Mobley EE, Curry EE, Johnson RM. Outcomes in Fournier's gangrene using skin and soft tissue sparing flap preservation surgery for wound closure: an alternative approach to wide radical debridement. *Wounds*. 2018;30(10):290–299.

49. Tom LK, Wright TJ, Horn DL, Bulger EM, Pham TN, Keys KA. A skin-sparing approach to the treatment of necrotizing soft-tissue infections: thinking reconstruction at initial debridement. *J Am Coll Surg*. 2016;222(5):e47–e60. doi:10.1016/J.JAMCOLLSURG.2016.01.008.
50. Tom LK, Maine RG, Wang CS, Parent BA, Bulger EM, Keys KA. Comparison of traditional and skin-sparing approaches for surgical treatment of necrotizing soft-tissue infections. *Surg Infect (Larchmt)*. 2020;21(4):363–369. doi:10.1089/sur.2019.263.
51. Horn DL, Chan JD, Li K, et al. Defining the optimal antibiotic duration in necrotizing skin and soft tissue infections: clinical experience from a Quaternary Referral Center. *Surg Infect (Larchmt)*. 2023;24(8):741–748. doi:10.1089/sur.2022.294.
52. Mallikarjuna MN, Vijayakumar A, Patil VS, Shivswamy BS. Fournier's gangrene: current practices. *ISRN Surg*. 2012;2012:942437. doi:10.5402/2012/942437.
53. Madsen MB, Hjortrup PB, Hansen MB, et al. Immunoglobulin G for patients with necrotising soft tissue infection (INSTINCT): a randomised, blinded, placebo-controlled trial. *Intensive Care Med*. 2017;43(11):1585–1593. doi:10.1007/s00134-017-4786-0.
54. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Crit Care Med*. 2018;46(6):997–1000. doi:10.1097/CCM.0000000000003119.
55. Castillejo Becerra CM, Jaeger CD, Rose JR, et al. Microorganisms and antibiogram patterns in Fournier's gangrene: contemporary experience from a Single Tertiary Care Center. *J Urol*. 2020;204(6):1249–1255. doi:10.1097/JU.0000000000001194.
56. Koch GE, Launer BM, Li AN, Johnsen NV. A disease-specific antibiogram to evaluate empiric coverage patterns in Fournier's gangrene. *Urology*. 2023;178:162–166. doi:10.1016/j.urology.2023.05.014.
57. Stevens DL, Bryant AE, Goldstein EJ. Necrotizing soft tissue infections. *Infect Dis Clin North Am*. 2021;35(1):135–155. doi:10.1016/j.idc.2020.10.004.
58. Campbell AJ, Dotel R, Blyth CC, Davis JS, Tong SYC, Bowen AC. Adjunctive protein synthesis inhibitor antibiotics for toxin suppression in Staphylococcus aureus infections: a systematic appraisal. *J Antimicrob Chemother*. 2019;74(1):1–5. doi:10.1093/jac/dky387.
59. Bryant AE, Bayer CR, Aldape MJ, McIndoo E, Stevens DL. Emerging erythromycin and clindamycin resistance in group A streptococci: efficacy of linezolid and tedizolid in experimental necrotizing infection. *J Glob Antimicrob Resist*. 2020;22:601–607. doi:10.1016/j.jgar.2020.04.032.
60. Blears EE, Morris J, Popp D, Lee JO, Norbury WB. Kidney injury in critically ill patients treated with vancomycin and zosyn or an alternative: a systematic review and meta-analysis. *Surg Infect (Larchmt)*. 2022;23(6):516–524. doi:10.1089/sur.2022.128.
61. Lauerman MH, Kolesnik O, Sethuraman K, et al. Less is more? Antibiotic duration and outcomes in Fournier's gangrene. *J Trauma Acute Care Surg*. 2017;83(3):443–448. doi:10.1097/TA.0000000000001562.
62. Kao LS, Lew DF, Arab SN, et al. Local variations in the epidemiology, microbiology, and outcome of necrotizing soft-tissue infections: a multicenter study. *Am J Surg*. 2011;202(2):139–145. doi:10.1016/j.amjsurg.2010.07.041.
63. Faraklas I, Yang D, Eggerstedt M, et al. A multi-center review of care patterns and outcomes in necrotizing soft tissue infections. *Surg Infect (Larchmt)*. 2016;17(6):773–778. doi:10.1089/sur.2015.238.
64. Anaya DA, McMahon K, Nathens AB, Sullivan SR, Foy H, Bulger E. Predictors of mortality and limb loss in necrotizing soft tissue infections. *Arch Surg*. 2005;140(2):151–157 discussion 158. doi:10.1001/archsurg.140.2.151.
65. Bulger EM, May A, Bernard A, et al. Impact and progression of organ dysfunction in patients with necrotizing soft tissue infections: a multicenter study. *Surg Infect (Larchmt)*. 2015;16(6):694–701. doi:10.1089/sur.2015.098.
66. Stevens DL, Bryant AE. Necrotizing soft-tissue infections. *N Engl J Med*. 2017;377(23):2253–2265. doi:10.1056/NEJMra1600673.
67. Endorf FW, Klein MB, Mack CD, Jurkovich GJ, Rivara FP. Necrotizing soft-tissue infections: differences in patients treated at burn centers and non-burn centers. *J Burn Care Res*. 2008;29(6):933–938. doi:10.1097/BCR.0b013e31818ba112.
68. Kurian GP, Korula PJ, Jacob JM, Desha AMK, Karuppusami R, Kandasamy S. Patient characteristics and outcomes in necrotizing soft-tissue infections: results from a prospective cohort study in a Tertiary Care Center Intensive Care Unit in South India. *Indian J Crit Care Med*. 2022;26(4):452–456. doi:10.5005/jp-journals-10071-24153.
69. Tsai YH, Hsu RWW, Huang KC, Huang TJ. Laboratory indicators for early detection and surgical treatment of vibrio necrotizing fasciitis. *Clin Orthop Relat Res*. 2010;468(8):2230–2237. doi:10.1007/s11999-010-1311-y.
70. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. 2021;47(11):1181–1247. doi:10.1007/s00134-021-06506-y.
71. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *Br J Anaesth*. 2012;108(3):384–394. doi:10.1093/bja/aer515.
72. Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ*. 2014;349:g4561. doi:10.1136/bmj.g4561.
73. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med*. 2014;370(15):1412–1421. doi:10.1056/NEJMoa1305727.
74. Finfer S, McEvoy S, et al.SAFE Study Investigators Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med*. 2011;37(1):86–96. doi:10.1007/s00134-010-2039-6.
75. Capelli-Schellpfeffer M, Gerber GS. The use of hyperbaric oxygen in urology. *J Urol*. 1999;162(3 Pt 1):647–654. doi:10.1097/00005392-199909010-00002.
76. Shaw JJ, Psoinos C, Emhoff TA, Shah SA, Santry HP. Not just full of hot air: hyperbaric oxygen therapy increases survival in cases of necrotizing soft tissue infections. *Surg Infect (Larchmt)*. 2014;15(3):328–335. doi:10.1089/sur.2012.135.

77. Li CQ, Gerson S, Snyder B. Case report: hyperbaric oxygen and MRI findings in radiation-induced optic neuropathy. *Undersea Hyperb Med*. 2014;41(1):59–63.
78. Mehl AA, Nogueira Filho DC, Mantovani LM, et al. Management of Fournier's gangrene: experience of a university hospital of Curitiba. *Rev Col Bras Cir*. 2010;37(6):435–441. doi:10.1590/s0100-69912010000600010.
79. Krenk L, Nielsen HU, Christensen ME. Necrotizing fasciitis in the head and neck region: an analysis of standard treatment effectiveness. *Eur Arch Otorhinolaryngol*. 2007;264(8):917–922. doi:10.1007/s00405-007-0275-3.
80. Ayan F, Sunamak O, Paksoy SM, et al. Fournier's gangrene: a retrospective clinical study on forty-one patients. *ANZ J Surg*. 2005;75(12):1055–1058. doi:10.1111/j.1445-2197.2005.03609.x.
81. Wilkinson D, Doolette D. Hyperbaric oxygen treatment and survival from necrotizing soft tissue infection. *Arch Surg*. 2004;139(12):1339–1345. doi:10.1001/archsurg.139.12.1339.
82. Mindrup SR, Kealey GP, Fallon B. Hyperbaric oxygen for the treatment of fournier's gangrene. *J Urol*. 2005;173(6):1975–1977. doi:10.1097/01.ju.0000158129.56571.05.
83. George ME, Rueth NM, Skarda DE, Chipman JG, Quickel RR, Beilman GJ. Hyperbaric oxygen does not improve outcome in patients with necrotizing soft tissue infection. *Surg Infect (Larchmt)*. 2009;10(1):21–28. doi:10.1089/sur.2007.085.
84. Massey PR, Sakran J V, Mills AM, et al. Hyperbaric oxygen therapy in necrotizing soft tissue infections. *J Surg Res*. 2012;177(1):146–151. doi:10.1016/j.jss.2012.03.016.
85. Linnér A, Darenberg J, Sjölin J, Henriques-Normark B, Norrby-Teglund A. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. *Clin Infect Dis*. 2014;59(6):851–857. doi:10.1093/cid/ciu449.
86. Norrby-Teglund A, Muller MP, Mcgeer A, et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. *Scand J Infect Dis*. 2005;37(3):166–172. doi:10.1080/00365540410020866.
87. Levett D, Bennett MH, Millar I. Adjunctive hyperbaric oxygen for necrotizing fasciitis. *Cochrane Database Syst Rev*. 2015;1(1):CD007937. doi:10.1002/14651858.CD007937.pub2.
88. Bulger EM, May AK, Robinson BRH, et al. A novel immune modulator for patients with necrotizing soft tissue infections (NSTI): results of a multicenter, phase 3 randomized controlled trial of reltecimod (AB 103). *Ann Surg*. 2020;272(3):469–478. doi:10.1097/SLA.0000000000004102.
89. Collins CM, McCarty A, Jalilvand A, et al. Outcomes of patients with necrotizing soft tissue infections: a propensity-matched analysis using the national inpatient sample. *Surg Infect (Larchmt)*. 2022;23(3):304–312. doi:10.1089/sur.2021.317.
90. Maine RG, Bulger EM . Infections of skin, muscle, and necrotizing soft tissue infections. In: Vincent JL, Moore FA, Bellomo R, Marini JJ, eds. *Textbook of Critical Care*. 8th ed. Amsterdam, Netherlands: Elsevier; 2022:932–938.
91. Nisbet AA, Thompson IM. Impact of diabetes mellitus on the presentation and outcomes of Fournier's gangrene. *Urology*. 2002;60(5):775–779. doi:10.1016/s0090-4295(02)01951-9.
92. Singh A, Ahmed K, Aydin A, Khan MS, Dasgupta P. Fournier's gangrene. A clinical review. *Arch Ital Urol Androl*. 2016;88(3):157–164. doi:10.4081/aiua.2016.3.157.
93. Goh T, Goh LG, Ang CH, Wong CH. Early diagnosis of necrotizing fasciitis. *Br J Surg*. 2014;101(1):e119–e125. doi:10.1002/bjs.9371.
94. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10–e52. doi:10.1093/cid/ciu444.
95. Ioannidis O, Kitsikosta L, Tatsis D, et al. Fournier's gangrene: lessons learned from multimodal and multidisciplinary management of perineal necrotizing fasciitis. *Front Surg*. 2017;4:36. doi:10.3389/fsurg.2017.00036.
96. Phan HH, Cocanour CS. Necrotizing soft tissue infections in the intensive care unit. *Crit Care Med*. 2010;38(9 Suppl):S460–S468. doi:10.1097/CCM.0b013e3181ec667f.
97. Bhatnagar AM, Mohite PN, Suthar M. Fournier's gangrene: a review of 110 cases for aetiology, predisposing conditions, microorganisms, and modalities for coverage of necrosed scrotum with bare testes. *N Z Med J*. 2008;121(1275):46–56.
98. Tran KK, Kibert JL, Telford ED, Franck AJ. Intravenous insulin infusion protocol compared with subcutaneous insulin for the management of hyperglycemia in critically ill adults. *Ann Pharmacother*. 2019;53(9):894–898. doi:10.1177/1060028019841363.
99. Beauchamp LC, Mostafavifar LG, Evans DC, Gerlach AT. Sweet and sour: impact of early glycemic control on outcomes in necrotizing soft-tissue infections. *Surg Infect (Larchmt)*. 2019;20(4):305–310. doi:10.1089/sur.2018.182.
100. Rothenberg FG, Clay MB, Jamali H, Vandivier-Pletsch RH. Systematic review of β blocker, aspirin, and statin in critically ill patients: importance of severity of illness and cardiac troponin. *J Investig Med*. 2017;65(4):747–753. doi:10.1136/jim-2016-000374.
101. Keung EZ, Liu X, Nuzhad A, Adams C, Ashley SW, Askari R. Immunocompromised status in patients with necrotizing soft-tissue infection. *JAMA Surg*. 2013;148(5):419–426. doi:10.1001/jamasurg.2013.173.
102. Windsor C, Hua C, De Roux Q, et al. Healthcare trajectory of critically ill patients with necrotizing soft tissue infections: a multicenter retrospective cohort study using the clinical data warehouse of Greater Paris University Hospitals. *Ann Intensive Care*. 2022;12(1):115. doi:10.1186/s13613-022-01087-5.
103. Patterson DR, Hofland HWC, Espey K, Sharar S. Nursing committee of the international society for burn injuries. Pain management. *Burns*. 2004;30(8):A10–A15. doi:10.1016/j.burns.2004.08.004.
104. Dahl JB, Nielsen R V, Wetterslev J, et al. Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. *Acta Anaesthesiol Scand*. 2014;58(10):1165–1181. doi:10.1111/aas.12382.
105. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg*. 2007;104(6):1545–1556 table of contents. doi:10.1213/01.ane.0000261517.27532.80.

106. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clin Ther*. 2003;25(1):81–104. doi:10.1016/s0149-2918(03)90011-7.
107. Woo KY. Unravelling nocebo effect: the mediating effect of anxiety between anticipation and pain at wound dressing change. *J Clin Nurs*. 2015;24(13-14):1975–1984. doi:10.1111/jocn.12858.
108. Frazee BW, Fee C, Lynn J, et al. Community-acquired necrotizing soft tissue infections: a review of 122 cases presenting to a single emergency department over 12 years. *J Emerg Med*. 2008;34(2):139–146. doi:10.1016/j.jemermed.2007.03.041.
109. Chen JL, Fullerton KE, Flynn NM. Necrotizing fasciitis associated with injection drug use. *Clin Infect Dis*. 2001;33(1):6–15. doi:10.1086/320874.
110. Jones GM, Porter K, Coffey R, et al. Impact of early methadone initiation in critically injured burn patients: a pilot study. *J Burn Care Res*. 2013;34(3):342–348. doi:10.1097/BCR.0b013e3182642c27.
111. Kim DE, Pruskowski KA, Ainsworth CR, Linsenbardt HR, Rizzo JA, Cancio LC. A review of adjunctive therapies for burn injury pain during the opioid crisis. *J Burn Care Res*. 2019;40(6):983–995. doi:10.1093/jbcr/irz111.
112. Williams PI, Sarginson RE, Ratcliffe JM. Use of methadone in the morphine-tolerant burned paediatric patient. *Br J Anaesth*. 1998;80(1):92–95. doi:10.1093/bja/80.1.92.
113. McCullough M, Carlson GW. Dakin's solution: historical perspective and current practice. *Ann Plast Surg*. 2014;73(3):254–256. doi:10.1097/SAP.0b013e3182a634f7.
114. Voordeckers M, Noels J, Brognet M, Salaouatchi MT, Mesquita M. Localized Fournier's gangrene in "end-stage" renal failure: multidisciplinary approach and integration of palliative care. *Case Rep Nephrol*. 2020;2020:8868993. doi:10.1155/2020/8868993.
115. Taylor LJ, Nabozny MJ, Steffens NM, et al. A framework to improve surgeon communication in high-stakes surgical decisions: best case/worst case. *JAMA Surg*. 2017;152(6):531–538. doi:10.1001/jamasurg.2016.5674.
116. Lin TY, Cheng IH, Ou CH, et al. Incorporating simplified Fournier's Gangrene Severity Index with early surgical intervention can maximize survival in high-risk Fournier's gangrene patients. *Int J Urol*. 2019;26(7):737–743. doi:10.1111/iju.13989.
117. Korkut M, Içöz G, Dayangaç M, et al. Outcome analysis in patients with Fournier's gangrene: report of 45 cases. *Dis Colon Rectum*. 2003;46(5):649–652. doi:10.1007/s10350-004-6626-x.
118. Sugihara T, Yasunaga H, Horiguchi H, et al. Impact of surgical intervention timing on the case fatality rate for Fournier's gangrene: an analysis of 379 cases. *BJU Int*. 2012;110(11 Pt C):E1096–E1100. doi:10.1111/j.1464-410X.2012.11291.x.
119. Nawijn F, Smeeing DPJ, Houwert RM, Leenen LPH, Hietbrink F. Time is of the essence when treating necrotizing soft tissue infections: a systematic review and meta-analysis. *World J Emerg Surg*. 2020;15:4. doi:10.1186/s13017-019-0286-6.
120. Erickson BA, Miller AC, Warner HL, et al. Understanding the prodromal period of necrotizing soft tissue infections of the genitalia (Fournier's gangrene) and the incidence, duration, and risk factors associated with potential missed opportunities for an earlier diagnosis: a population-based longitudinal study. *J Urol*. 2022;208(6):1259–1267. doi:10.1097/JU.0000000000002920.
121. Wong CH, Yam AKT, Tan ABH, Song C. Approach to debridement in necrotizing fasciitis. *Am J Surg*. 2008;196(3):e19–e24. doi:10.1016/j.amjsurg.2007.08.076.
122. Alyanak A, Cakici OU, Turkmen YA. Skin-sparing approach in the management of Fournier's gangrene: the initial histological evidence and results of a tertiary health-care center. *ANZ J Surg*. 2022;92(1-2):128–131. doi:10.1111/ANS.17387.
123. Suijker J, Zheng KJ, Pijpe A, Nasroe F, Meij-de Vries A. The skin-sparing debridement technique in necrotizing soft-tissue infections: a systematic review. *J Surg Res*. 2021;264:296–308. doi:10.1016/J.JSS.2021.03.001.
124. Chawla SN, Gallop C, Mydlo JH. Fournier's gangrene: an analysis of repeated surgical debridement. *Eur Urol*. 2003;43(5):572–575. doi:10.1016/s0302-2838(03)00102-7.
125. Osbun N, Hampson LA, Holt SK, Gore JL, Wessells H, Voelzke BB. Low-volume vs high-volume centers and management of Fournier's gangrene in Washington State. *J Am Coll Surg*. 2017;224(3):270–275. doi:10.1016/j.jamcollsurg.2016.11.012.
126. Nnabugwu II, Onumaegbu OO, Okolie LT. Fournier's gangrene: a retrospective review of management outcomes and seasonal variations of clinical presentation. *African J Urol*. 2021;27(1):66. doi:10.1186/s12301-021-00168-4.
127. Sorensen MD, Krieger JN, Rivara FP, et al. Fournier's Gangrene: population based epidemiology and outcomes. *J Urol*. 2009;181(5):2120–2126. doi:10.1016/j.juro.2009.01.034.
128. Wetterauer C, Ebbing J, Halla A, et al. A contemporary case series of Fournier's gangrene at a Swiss tertiary care center-can scoring systems accurately predict mortality and morbidity? *World J Emerg Surg*. 2018;13:25. doi:10.1186/s13017-018-0187-0.
129. Elbakry AA, Wasef K, Pettit A, et al. Testicular involvement in fournier's gangrene: is orchiectomy overutilized? *J Urol*. 2023;209(4S).
130. Yanar H, Taviloglu K, Ertekin C, et al. Fournier's gangrene: risk factors and strategies for management. *World J Surg*. 2006;30(9):1750–1754. doi:10.1007/s00268-005-0777-3.
131. Kuzaka B, Wróblewska MM, Borkowski T, et al. Fournier's gangrene: clinical presentation of 13 cases. *Med Sci Monit*. 2018;24:548–555. doi:10.12659/msm.905836.
132. Akcan A, Sözüer E, Akyildiz H, Yilmaz N, Küçük C, Ok E. Necessity of preventive colostomy for Fournier's gangrene of the anorectal region. *Ulus Travma Acil Cerrahi Derg*. 2009;15(4):342–346.
133. Erol B, Tuncel A, Hanci V, et al. Fournier's gangrene: overview of prognostic factors and definition of new prognostic parameter. *Urology*. 2010;75(5):1193–1198. doi:10.1016/j.urology.2009.08.090.
134. Ortega Ferrete A, López E, Juez Sáez LD, et al. Fournier's gangrene and fecal diversion. When, in which patients, and what type should I perform? *Langenbecks Arch Surg*. 2023;408(1):428. doi:10.1007/s00423-023-03137-3.
135. Mahmood BA, ElSayed EH, Ali SA. Effect of colostomy on treatment outcome in Fournier gangrene: a prospective comparative study. *Plast Surg (Oakv)*. 2023;31(1):24–28. doi:10.1177/22925503211024757.

136. Rosen DR, Brown ME, Cologne KG, Ault GT, Strumwasser AM. Long-term follow-up of Fournier's gangrene in a tertiary care center. *J Surg Res*. 2016;206(1):175–181. doi:10.1016/j.jss.2016.06.091.
137. Ge Z, Zhao X, Liu Z, et al. Complications of preventive loop ileostomy versus colostomy: a meta-analysis, trial sequential analysis, and systematic review. *BMC Surg*. 2023;23(1):235. doi:10.1186/s12893-023-02129-w.
138. Eray IC, Alabaz O, Akcam AT, et al. Comparison of diverting colostomy and bowel management catheter applications in fournier gangrene cases requiring fecal diversion. *Indian J Surg*. 2015;77(Suppl 2):438–441. doi:10.1007/s12262-013-0868-6.
139. Sarofim M, Di Re A, Descallar J, Toh JWT. Relationship between diversional stoma and mortality rate in Fournier's gangrene: a systematic review and meta-analysis. *Langenbecks Arch Surg*. 2021;406(8):2581–2590. doi:10.1007/s00423-021-02175-z.
140. Raizandha MA, Hidayatullah F, Kloping YP, Rahman IA, Djatisoesanto W, Rizaldi F. The role of hyperbaric oxygen therapy in Fournier's gangrene: a systematic review and meta-analysis of observational studies. *Int Braz J Urol*. 2022;48(5):771–781. doi:10.1590/S1677-5538.IBJU.2022.0119.
141. Ueno CM, Mullens CL, Luh JH, Wooden WA. Historical review of Dakin's solution applications. *J Plast Reconstr Aesthet Surg*. 2018;71(9):e49–e55. doi:10.1016/j.bjps.2018.05.023.
142. Altunoluk B, Resim S, Efe E, et al. Fournier's gangrene: conventional dressings versus dressings with Dakin's solution. *ISRN Urol*. 2012;2012:762340. doi:10.5402/2012/762340.
143. Griggs R, Karpman E, Jones L, Twomey C, Henry G. Effect of 0.05% chlorhexidine gluconate in water on the hydrophilic inflatable penile prosthesis: biocompatibility, adherence, and dip time. *J Sex Med*. 2023;20(1):113–117. doi:10.1093/jsxmed/qdac007.
144. Xie X, McGregor M, Dendukuri N. The clinical effectiveness of negative pressure wound therapy: a systematic review. *J Wound Care*. 2010;19(11):490–495. doi:10.12968/jowc.2010.19.11.79697.
145. Franco-Buenaventura D, HA G-P. Vacuum-assisted closure device in the postoperative wound care for Fournier's gangrene: a systematic review. *Int Urol Nephrol*. 2021;53(4):641–653. doi:10.1007/s11255-020-02705-6.
146. Orgill DP, Bayer LR. Negative pressure wound therapy: past, present and future. *Int Wound J*. 2013;10 Suppl 1(Suppl 1):15–19. doi:10.1111/iwj.12170.
147. Medical devices; general and plastic surgery devices; classification of the negative pressure wound therapy device for reduction of wound complications. Published online December 10, 2021:70373–70375.
148. KCI V.A.C. Therapy clinical guidelines. In; 2015:1–72.
149. McNulty AK, Schmidt M, Feeley T, Kieswetter K. Effects of negative pressure wound therapy on fibroblast viability, chemotactic signaling, and proliferation in a provisional wound (fibrin) matrix. *Wound Repair Regen*. 2007;15(6):838–846. doi:10.1111/j.1524-475X.2007.00287.x.
150. Saxena V, Hwang CW, Huang S, Eichbaum Q, Ingber D, Orgill DP. Vacuum-assisted closure: microdeformations of wounds and cell proliferation. *Plast Reconstr Surg*. 2004;114(5):1086–1096 discussion 1097-8. doi:10.1097/01.prs.0000135330.51408.97.
151. Morykwas MJ, Simpson J, Punger K, Argenta A, Kremers L, Argenta J. Vacuum-assisted closure: state of basic research and physiologic foundation. *Plast Reconstr Surg*. 2006;117(7 Suppl):121S–126S. doi:10.1097/01.prs.0000225450.12593.12.
152. Ozturk E, Ozguc H, Yilmazlar T. The use of vacuum assisted closure therapy in the management of Fournier's gangrene. *Am J Surg*. 2009;197(5):660–665 discussion 665. doi:10.1016/j.amjsurg.2008.04.018.
153. Yanaral F, Balci C, Ozgor F, et al. Comparison of conventional dressings and vacuum-assisted closure in the wound therapy of Fournier's gangrene. *Arch Ital Urol Androl*. 2017;89(3):208–211. doi:10.4081/aiua.2017.3.208.
154. Kirby JP, Snyder J, Schuerer DJE, Peters JS, Bochicchio GV. Essentials of hyperbaric oxygen therapy: 2019 review. *Mo Med*. 2019;116(3):176–179.
155. Rinaldi B, Cuzzocrea S, Donniacuo M, et al. Hyperbaric oxygen therapy reduces the toll-like receptor signaling pathway in multiple organ failures. *Intensive Care Med*. 2011;37(7):1110–1119. doi:10.1007/s00134-011-2241-1.
156. Hunt TK, Linsey M, Grislis H, Sonne M, Jawetz E. The effect of differing ambient oxygen tensions on wound infection. *Ann Surg*. 1975;181(1):35–39. doi:10.1097/00000658-197501000-00009.
157. Knighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic. The effect of inspired oxygen on infection. *Arch Surg*. 1984;119(2):199–204. doi:10.1001/archsurg.1984.01390140057010.
158. Hung MC, Chou CL, Cheng LC, et al. The role of hyperbaric oxygen therapy in treating extensive Fournier's gangrene. *Urol Sci*. 2016;27(3):148–153.
159. Karian LS, Chung SY, Lee ES. Reconstruction of defects after Fournier gangrene: a systematic review. *Eplasty*. 2015;15:e18.
160. Carvalho JP, Hazan A, Cavalcanti AG, Favorito LA. Relation between the area affected by Fournier's gangrene and the type of reconstructive surgery used. A study with 80 patients. *Int Braz J Urol*. 2007;33(4):510–514. doi:10.1590/s1677-55382007000400008.
161. Akilov O, Pompeo A, Sehrt D, Bowlin P, Molina WR, Kim FJ. Early scrotal approximation after hemiscrotectomy in patients with Fournier's gangrene prevents scrotal reconstruction with skin graft. *Can Urol Assoc J*. 2013;7(7-8):E481–E485. doi:10.5489/cuaj.1405.
162. Sam P, Zilavy A, Ice C, Gallegos M . Primary closure is superior to secondary intention for treating Fournier gangrene. *J Urol*. 2022;207(Supplement 5).
163. Biju NE, Sadiq M, Raj S, et al. Fournier's gangrene reconstruction: A 10-year retrospective analysis of practice at Guys and St Thomas's NHS Foundation Trust. *J Plast Reconstr Aesthet Surg*. 2023;80:13–15. doi:10.1016/j.bjps.2023.02.030.
164. Zens Y, Barth M, Bucher HC, et al. Negative pressure wound therapy in patients with wounds healing by secondary intention: a systematic review and meta-analysis of randomised controlled trials. *Syst Rev*. 2020;9(1):238. doi:10.1186/s13643-020-01476-6.

165. Sandberg JM, Warner HL, Flynn KJ, et al. Favorable outcomes with early component separation, primary closure of necrotizing soft tissue infections of the genitalia (Fournier's gangrene) debridement wound defects. *Urology*. 2022;166:250–256. doi:10.1016/j.urology.2022.03.042.
166. Palka J, Comb W, Begun E, Soto-Aviles O. Comparison of delayed primary closure versus secondary intention healing in Fournier's gangrene. *J Urol*. 2019;201(Supplement 4).
167. Chen SY, Fu JP, Chen TM, Chen SG. Reconstruction of scrotal and perineal defects in Fournier's gangrene. *J Plast Reconstr Aesthet Surg*. 2011;64(4):528–534. doi:10.1016/j.bjps.2010.07.018.
168. Hofer M, Dumanian G, Felício J, Martins F. Updates in the management of benign and malignant scrotal conditions: issues on surgical ablation and reconstruction. *AME Med J*. 2020;5:27. doi:10.21037/amj.2020.03.08.
169. Maurya R, Mir MA, Mahajan S. Various options for scrotal reconstruction: a prospective observational study. *Cureus*. 2022;14(2):e22671. doi:10.7759/cureus.22671.
170. Tiwari IN, Seth HP, Mehdiratta KS. Reconstruction of the scrotum by thigh flaps. *Plast Reconstr Surg*. 1980;66(4):605–607. doi:10.1097/00006534-198010000-00019.
171. Triana Junco P, Dore M, Nuñez Cerezo V, et al. Penile reconstruction with skin grafts and dermal matrices: indications and management. *European J Pediatr Surg Rep*. 2017;5(1):e47–e50. doi:10.1055/s-0037-1606282.
172. Black PC, Friedrich JB, Engrav LH, Wessells H. Meshed unexpanded split-thickness skin grafting for reconstruction of penile skin loss. *J Urol*. 2004;172(3):976–979. doi:10.1097/01.ju.0000133972.65501.44.
173. Ferreira PC, Reis JC, Amarante JM, et al. Fournier's gangrene: a review of 43 reconstructive cases. *Plast Reconstr Surg*. 2007;119(1):175–184. doi:10.1097/01.prs.0000244925.80290.57.
174. Yang J, Ko SH, Oh SJ, Jung SW. Reconstruction of a perineoscrotal defect using bilateral medial thigh fasciocutaneous flaps. *Arch Plast Surg*. 2013;40(1):72–74. doi:10.5999/aps.2013.40.1.72.
175. Bodin F, Weitbruch D, Seigle-Murandi F, Volkmar P, Bruant-Rodier C, Rodier JF. Vulvar reconstruction by a "supra-fascial" lotus petal flap after surgery for malignancies. *Gynecol Oncol*. 2012;125(3):610–613. doi:10.1016/j.ygyno.2012.03.029.
176. Warrier SK, Kimble FW, Blomfield P. Refinements in the lotus petal flap repair of the vulvo-perineum. *ANZ J Surg*. 2004;74(8):684–688. doi:10.1111/j.1445-1433.2004.03119.x.
177. Hsu H, Lin CM, Sun TB, Cheng LF, Chien SH. Unilateral gracilis myofasciocutaneous advancement flap for single stage reconstruction of scrotal and perineal defects. *J Plast Reconstr Aesthet Surg*. 2007;60(9):1055–1059. doi:10.1016/j.bjps.2006.09.005.
178. Spyropoulou GA, Jeng SF, Demiri E, Dionyssopoulos A, Feng KM. Reconstruction of perineoscrotal and vaginal defects with pedicled anterolateral thigh flap. *Urology*. 2013;82(2):461–465. doi:10.1016/j.urology.2013.04.044.
179. Akhtar MS, Khurram MF, Khan AH. Versatility of pedicled tensor fascia lata flap: a useful and reliable technique for reconstruction of different anatomical districts. *Plast Surg Int*. 2014;2014:846082. doi:10.1155/2014/846082.
180. Mughal M, Baker RJ, Muneer A, Mosahebi A. Reconstruction of perineal defects. *Ann R Coll Surg Engl*. 2013;95(8):539–544. doi:10.1308/rcsann.2013.95.8.539.
181. Koshima I, Fukuda H, Utunomiya R, Soeda S. The anterolateral thigh flap; variations in its vascular pedicle. *Br J Plast Surg*. 1989;42(3):260–262. doi:10.1016/0007-1226(89)90142-2.
182. Nico Albano M, Louro JM, Brito I, Ramos S. Perineal reconstruction using an inferior gluteal artery perforator flap after abdominoperineal resection. *BMJ Case Rep*. 2019;12(9):e228613. doi:10.1136/bcr-2018-228613.
183. Banuelos J, Kreutz-Rodrigues L, Mills AM, et al. Vertical rectus abdominis myocutaneous flap to reconstruct thigh and groin defects: a retrospective cohort and systematic review. *J Plast Reconstr Aesthet Surg*. 2022;75(6):1893–1901. doi:10.1016/j.bjps.2022.01.015.
184. Parrett BM, Winograd JM, Garfein ES, Lee WPA, Hornicek FJ, Austen WG. The vertical and extended rectus abdominis myocutaneous flap for irradiated thigh and groin defects. *Plast Reconstr Surg*. 2008;122(1):171–177. doi:10.1097/PRS.0b013e3181774330.
185. Pividori M, Gangloff D, Ferron G, et al. Outcomes of DIEP flap reconstruction after pelvic cancer surgery: a retrospective multicenter case series. *J Plast Reconstr Aesthet Surg*. 2023;85:242–251. doi:10.1016/j.bjps.2023.07.005.
186. rong Fang B, H Ameet, fang Li X, et al. Pedicled thinned deep inferior epigastric artery perforator flap for perineal reconstruction: a preliminary report. *J Plast Reconstr Aesthet Surg*. 2011;64(12):1627–1634. doi:10.1016/j.bjps.2011.04.013.
187. Backhaus M, Citak M, Tilkorn DJ, Meindl R, Schildhauer TA, Fehmer T. Pressure sores significantly increase the risk of developing a Fournier's gangrene in patients with spinal cord injury. *Spinal Cord*. 2011;49(11):1143–1146. doi:10.1038/sc.2011.75.
188. Groah SL, Pérez-Losada M, Caldovic L, et al. Redefining healthy urine: a cross-sectional exploratory metagenomic study of people with and without bladder dysfunction. *J Urol*. 2016;196(2):579–587. doi:10.1016/j.juro.2016.01.088.
189. Fouts DE, Pieper R, Szpakowski S, et al. Integrated next-generation sequencing of 16S rDNA and metaproteomics differentiate the healthy urine microbiome from asymptomatic bacteriuria in neuropathic bladder associated with spinal cord injury. *J Transl Med*. 2012;10:174. doi:10.1186/1479-5876-10-174.
190. Kinnear N, Barnett D, O'Callaghan M, Horsell K, Gani J, Hennessey D. The impact of catheter-based bladder drainage method on urinary tract infection risk in spinal cord injury and neurogenic bladder: a systematic review. *Neurourol Urodyn*. 2020;39(2):854–862. doi:10.1002/nau.24253.
191. Vaidyanathan S, Soni BM, Hughes PL, et al. Localised necrosis of scrotum (Fournier's gangrene) in a spinal cord injury patient - a case report. *BMC Fam Pract*. 2002;3:20. doi:10.1186/1471-2296-3-20.
192. Nigam V, Halim TA, Chhabra HS. Fournier's gangrene in a female with spinal cord injury: a case report. *Spinal Cord*. 2010;48(3):268–269. doi:10.1038/sc.2009.127.
193. Vaidyanathan S, Soni BM, Brown E, Singh G. Erosion of urethra in female patients with spinal cord injury. *Spinal Cord*. 2005;43(7):451. doi:10.1038/sj.sc.3101728.
194. Kopp MA, Meisel C, Liebscher T, et al. The spinal cord injury-induced immune deficiency syndrome: results of the SCIentinel study. *Brain*. 2023;146(8):3500–3512. doi:10.1093/brain/awad092.

195. Khalid A, Devakumar S, Huespe I, Kashyap R, Chisti I. A comprehensive literature review of Fournier's gangrene in females. *Cureus*. 2023;15(5):e38953. doi:10.7759/cureus.38953.
196. Koch GE, Johnsen NV. The diagnosis and management of life-threatening urologic infections. *Urology*. 2021;156:6–15. doi:10.1016/j.urology.2021.05.011.
197. Creta M, Sica A, Napolitano L, et al. Fournier's gangrene in patients with oncohematological diseases: a systematic review of published cases. *Healthcare (Basel)*. 2021;9(9):1123. doi:10.3390/healthcare9091123.
198. Yoshino Y, Funahashi K, Okada R, et al. Severe Fournier's gangrene in a patient with rectal cancer: case report and literature review. *World J Surg Oncol*. 2016;14(1):234. doi:10.1186/s12957-016-0989-z.
199. Mann AJ, Reinoso DB, Genuit T, Jimenez J. Fournier's gangrene in the setting of underlying carcinoma: a case report and review of the literature. *Cureus*. 2020;12(9):e10317. doi:10.7759/cureus.10317.
200. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes.; 2018.
201. Chowdhury T, Gousy N, Bellamkonda A, et al. Fournier's gangrene: a coexistence or consanguinity of SGLT-2 inhibitor therapy. *Cureus*. 2022;14(8):e27773. doi:10.7759/cureus.27773.
202. Kasbawala K, Stamatiades GA, Majumdar SK. Fournier's gangrene and diabetic ketoacidosis associated with sodium glucose co-transporter 2 (SGLT2) inhibitors: life-threatening complications. *Am J Case Rep*. 2020;21:e921536. doi:10.12659/AJCR.921536.
203. Temiz MZ, Yuruk E, Aykan S, Tuken M, Kandirali E. Isolated penile Fournier's gangrene presenting with glans penis involvement. *J Coll Physicians Surg Pak*. 2015;25(Suppl 2):S140–S141. doi:10.2015/JCPSP.S140141.
204. Pandey S, Sharma D, Aggarwal A, Sharma A. Isolated Fournier's gangrene of the penis with penile autoamputation. *BMJ Case Rep*. 2018;2018(bcr2018226862). doi:10.1136/bcr-2018-226862.
205. De S, Belsante MJ, Tausch TJ, Simhan J. A case of Fournier's gangrene necessitating total penectomy. *Can J Urol*. 2015;22(6):8108–8111.
206. So A, Bell D, Metcalfe P, Gupta R. Calciphylaxis of the penis: a unique cause of Fournier's gangrene. *Can J Urol*. 2001;8(5):1377–1379.
207. Creta M, Longo N, Arcaniolo D, et al. Hyperbaric oxygen therapy reduces mortality in patients with Fournier's Gangrene. Results from a multi-institutional observational study. *Minerva Urol Nefrol*. 2020;72(2):223–228. doi:10.23736/S0393-2249.20.03696-6.
208. Tenório CEL, Lima SVC, de Albuquerque AV, Cavalcanti MP, Teles F. Risk factors for mortality in Fournier's gangrene in a general hospital: use of simplified Founier gangrene severe index score (SFGSI). *Int Braz J Urol*. 2018;44(1):95–101. doi:10.1590/s1677-5538.ibju.2017.0193.
209. Kim SY, Dupree JM, Le BV, Kim DY, Zhao LC, Kundu SD. A contemporary analysis of Fournier gangrene Using the National Surgical Quality Improvement Program. *Urology*. 2015;85(5):1052–1057. doi:10.1016/j.urology.2014.08.063.
210. Sugihara T, Yasunaga H, Horiguchi H, et al. Impact of surgical intervention timing on the case fatality rate for Fournier's gangrene: an analysis of 379 cases. *BJU Int*. 2012;110(11c):E1096–E1100. doi:10.1111/j.1464-410X.2012.11291.x.