Recognizing Common Skin and Soft Tissue Infections in the Nephrology Clinic

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Abstract

Renal failure patients have an increased risk of infection, including skin and soft tissue infections. This increased susceptibility is multifactorial, due to the conditions causing the renal failure as well as complications of treatment and renal failure's innate effects on patient health. These infections have a significant impact on patient morbidity, increased hospital and procedural demands, and the cost of health care. Many renal failure patients are seen regularly by their nephrology clinic caregivers due to the need for frequent dialysis and transplant monitoring. Familiarity with common skin and soft tissue infections by these caregivers allowing enhanced patient education, optimal infection prevention, and early recognition could significantly reduce the morbidity and cost of these disorders, such as diabetic foot syndrome, necrotizing fasciitis, and herpetic infections.

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Background

End-stage renal disease (ESRD) patients have an increased risk of infection, including skin and soft tissue infections, resulting in increased morbidity, mortality, and medical cost. Causes of this increased risk are multifactorial. Uremia is known to adversely impact innate and adaptive immunity [1]. Renal metabolism of immunologically active proteins is also impacted in ESRD [2]. The replacement of renal function via kidney transplant or dialysis adds to infection risk through factors such as use of immunosuppressive medications, interruption of the cutaneous barrier, and white blood cell and complement dysfunction from dialysis membranes [3], although improvements in biocompatibility of dialysis membranes in recent years have significantly reduced the severity of reactions [4]. Frequent exposure to hospitals and medical facilities carries with it potential increased exposure to pathogens such as methicillin-resistant *Staphylococcus aureus*.

There are many potential causes for the development of ESRD, and many of these underlying disorders them-

selves impart increased infection risk. In the United States, diabetes mellitus (DM) is the most common etiologic factor for development of ESRD [5] and a frequent cause of renal failure worldwide. Immune dysfunction, neurological alterations, and vascular changes in diabetics increase infection risk. Increased risk is seen with other disorders underlying ESRD as well, such as collagen vascular disorders that may require immunosuppressive therapy.

This increased infection risk imparts significant morbidity and mortality, increases medical service utilization, and negatively impacts medical costs. Informed infection prevention techniques and early recognition of infection can reduce all these consequences. ESRD patients with DM and renal transplant recipients are numerous, and they face especially high risk. Due to frequent patient contact required for dialysis provision and transplant monitoring, as well as the external visual presence of most skin and soft-tissue infections, the nephrology clinic medical staff is ideally situated to help reduce the prevalence and risks associated with cutaneous infections in these vulnerable patient populations.

Diabetes Mellitus

Diabetics comprise approximately 40% of new onset renal failure patients [5] and therefore account for a significant proportion of the general nephrology and dialysis patient populations. A number of immunological, vascular, and neurological alterations that occur in diabetics are believed to predispose these patients to multiple disorders including skin and soft tissue infections. Studies suggest these alterations include impaired neutrophil, macrophage, and cytokine function; T-cell malfunction; depression of antioxidant defenses; and impaired tissue nutrition and oxygen supply [6, 7]. Neuropathy and autonomic dysfunction predispose patients to impaired barrier function [8]. Subsequent infections adversely impact diabetic control, which further increases the risk of infection and impaired host response.

There are several cutaneous infections that occur with increased frequency in the diabetic population [9]. These include diabetic foot syndrome, cellulitis, necrotizing fasciitis, and fungal infections. Complications of infection and subsequent hospitalization are more common in diabetics than in the general population increasing morbidity of this vulnerable population. [10].

Diabetic Foot Syndrome

The International Working Group on the Diabetic Foot defines diabetic foot syndrome as ulcerations on the ankle or foot in diabetics that are associated with neuropathy, ischemia, and infection. These ulcerations are quite common worldwide; they affect up to 25% of the over 30 million diabetics in the United States alone and account for 20% of all US hospitalizations [8].

The vast majority of these infections begin with skin ulceration. Diabetics are prone to ulceration of the foot due in part to diabetic neuropathy. Sensory deficits accompanied by abnormal gait developed due to atrophy of intrinsic foot musculature, thick callus formation from an improper loading pattern, and limited joint mobility increase injury risk. Diminished sweating due to neurologic impairment of eccrine glands and increased skin temperature and poor skin perfusion from autonomic dysfunction may lead to dry, fissured feet allowing an entry to infection [11]. Peripheral vascular disease and resultant ischemia contribute to increasing tissue necrosis and impair healing. Approximately 56% of diabetic foot ulcers become infected, resulting in amputation in 20% of these patients [12].

Appropriate foot management in diabetics can significantly reduce morbidity and amputation in diabetic foot syndrome. Basic ulcer prevention techniques include regular skin examination and identification of at risk patients. Family and caregiver involvement in cutaneous examinations may be necessary due to frequent retinopathy and resultant visual compromise in this patient population. Monthly foot checks in diabetic hemodialysis patients have been demonstrated to reduce the risk of amputation [13]. Due to neuropathy and ischemia, patients may also be unable to recognize proper shoe fit. Patient, family, and caregiver education and use of appropriate footwear are key prevention strategies. Shoes must be neither too tight nor loose and length should be 1–2 cm longer than the foot. Shoes should have an adequate internal width and height so they do not compress the foot at the metatarsal phalangeal joint nor at the toes. Shoe fittings should be performed preferably after a prolonged period of standing [11].

Sensory nerve function assessment, peripheral vascular evaluation, and foot/ankle examination are essential to identify patients at risk for diabetic foot syndrome. Simple neurological tests include the Semmes-Weinstein monofilament test and assessment of tuning fork vibration [11]. Vascular compromise may be suspected in patients with lower extremity claudication, decreased foot pulses, dependent rubor or pallor on leg elevation, skin

atrophy, or decreased lower extremity hair [8]. Further evaluation may include testing such as ankle brachial pressure index or Doppler ultrasound [12].

Ulcer infection may present with local erythema, warmth, induration, edema, pain, or purulent or malodorous drainage. Secondary signs of infection such as fever, chills, anorexia, nausea/vomiting or night sweats may occur. However, many times these signs may not be obvious in a diabetic or renal failure patient. Other signs may include a change in mental status, worsening glyce-mic control, or delayed wound healing. Of note, many patients with diabetic foot syndrome are unable to mount an elevated white blood cell response to infection [8].

Adequate wound debridement is essential in ulcer evaluation and management. All necrotic tissue and cal-lus should be removed, and the ulcer probed with a sterile blunt instrument to determine structural involvement [13]. Osteomyelitis should be suspected in patients with visible or palpable bone at the ulcer base, elevated CRP, elevated ESR, delayed healing, skin breakdown, and sig-nificant exudate production. Plain X-ray films are use-ful to assess for structural deformity, bony involvement, foreign body, and soft tissue emphysema, although spec-ificity and sensitivity for osteomyelitis are low. Magnetic resonance imaging, bone scans, or radiolabelled leuko-cyte scans may be necessary for accurate osteomyelitis recognition [8, 14].

Optimal treatment of diabetic foot syndrome includes restoration of adequate skin perfusion, maintenance of glycemic control and treatment of patient comorbidities, debridement of ulcerations, and antimicrobial agents tai-lored to infecting organisms. Of note, studies suggest up to 25% of diabetic foot infection patients harbor deep fun-gal infection with or without bacterial organisms [15].

Many options for dressings and avoidance of pressure over ulcerations are available; the gold standard for plan-tar diabetic neuropathic ulcers is total contact casting [12]. Adjunctive therapies such as negative pressure wound therapy, antibiotic impregnated beads, and hy-perbaric oxygen therapy may be of benefit for some pa-tients [8].

Cellulitis and Necrotizing Fasciitis

Bacterial skin and soft tissue infections are more com-mon in diabetics than in the general population. These infections include erysipelas, cellulitis, follicular/perifol-licular infections, and necrotizing fasciitis. Many of these infections are caused by common skin flora such as *Staph-ylococcus* and *Streptococcus* species, but polymicrobial in-fections, anaerobic infections, and infections with unusu-

al organisms also occur not infrequently in both diabetics and ESRD patients in general. Methicillin-resistant staph-ylococcal infection is not infrequent both in the commu-nity and in medical facilities. These factors must be con-sidered in determination of appropriate antimicrobial therapy, especially as culture is frequently unsuccessful in cellulitis and other soft-tissue infections [16].

Cellulitis is a skin infection involving the dermis and subcutaneous tissue. Erysipelas is considered by many to be a subset of cellulitis and is more superficial, involving the upper dermis and epidermis. Although generally bac-terial, cellulitis may be caused by mycobacterial, viral, or fungal infection. Typically, patients with both cellulitis and erysipelas present with an edematous, indurated, and erythematous plaque that is warm and tender. Regional adenopathy and fever may be present. Margins are often especially well demarcated in erysipelas, and lymphatic spread with obvious streaking apparent on visual inspec-tion is common. An obvious entry portal to infection, such as a puncture wound, dry, fissured skin, or inter-digital fungal infection, may be present in some cases of cellulitis or erysipelas but is not always apparent.

The differential diagnosis of cellulitis is extensive. Sig-nificant pain, skin slough, cutaneous hemorrhage, and anesthesia of the skin may indicate a more extensive in-fection such as necrotizing fasciitis. Rapid progression, violaceous discoloration, and bullae may indicate serious systemic involvement with organisms such as *Vibrio vul-nificans* or *Streptococcus pneumonia*. Crepitus suggests infection with gas-forming organisms such as *Clostridi-um perfringens*. One of the more common disorders mis-taken for cellulitis is stasis dermatitis; lower extremities are often erythematous, but in stasis dermatitis involve-ment is generally bilateral and chronic, and erythema usually diminishes with passive leg elevation.

Necrotizing fasciitis is a rare soft tissue infection with a mortality rate of approximately 40%. Seventy percent of affected patients are diabetics [7]. Infection is rapidly pro-gressive and is characterized by necrosis of the fascia and subcutaneous tissue. Initial presentation may be decep-tively mild. Early in disease progression, most patients ex-hibit erythema of the skin and low-grade fever. Intense pain is common, followed by bulla formation, subsequent skin ulceration, and malodorous drainage. Gas, as noted on radiograph or by the presence of crepitus may develop within the tissue. Rapid diagnosis and extensive surgical debridement with appropriate antibiotic coverage and ad-equate hemodynamic stabilization are crucial to prevent mortality. In diabetics, these infections are usually poly-microbial with both aerobic and anaerobic organisms [7].

Fournier's gangrene is a subset of necrotizing fasciitis that affects the external genitalia, perineum and perirectal areas. The majority of affected patients are male diabetics. Risk factors include concomitant hemodialysis-dependent renal failure, alcoholism, chronic use of corticosteroids, advanced age, and malnutrition. Akin to necrotizing fasciitis, it is generally a polymicrobial infection [17].

Fungal Infection

Superficial fungal infections are common in ESRD patients [18]. Diabetics with ESRD have an even higher risk both due to the favorable conditions of fungal growth inherent in an environment with higher glucose levels and to the innate and cellular immune dysfunction common in diabetics [19]. Invasive fungal infection is also of increased risk in diabetics, particularly in lower extremity wounds or at catheter sites – where there is loss of skin integrity or direct percutaneous access of organisms to deeper structures – as well as via mucosal surfaces and inhalation. The majority of cutaneous infections in this population are superficial: cutaneous candidiasis, tinea versicolor, and dermatophytosis.

Most candida infections are due to *Candida albicans*, but infection due to other candida species, such as *C. tropicalis* and *C. glabrata*, occur. *Candida albicans* favors warm, moist environments, such as intertriginous areas and mucosal surfaces. Oral candidiasis, also known as thrush, commonly presents as localized, firmly adherent, irregular white plaques that can be removed by scraping, generally leaving behind an eroded base. Involvement of the tongue is common, and the infection can extend to the esophagus and trachea. Microscopic examination of the plaque reveals pseudohyphae. Other presentations include glossitis, in which the tongue is smooth, shiny, erythematous and painful, and angular cheilitis, also known as perleche, which presents with erythematous, eroded fissures at the angles of the mouth.

Vulvovaginitis and balanitis are also common presentations of candidiasis. Vulvovaginitis may be acute or chronic. It most commonly presents as irregular white plaques akin to oral candidiasis, and like oral candidiasis, painful, erosive, erythematous plaques may also occur. Infection may spread to the perineum and perirectal regions and may develop as satellite lesions of erythematous, tender plaques studded with papules on the inner thighs. Balanitis occurs most commonly in the uncircumcised male. It is often tender with white plaques, erosions or ulcerations, and pustules. Phimosis (a condition in which the foreskin is unable to be retracted) may occur.

Paronychia, characterized by painful swelling and erythema of the proximal or lateral nailfold, and interdigital web space infections are not infrequently caused by candida infection. Intertriginous candidiasis occurs at body folds and presents most commonly as tender erythematous plaques and pustules with fissure formation at folds. Pustules often extend beyond the erythematous areas.

Most superficial candidiasis can be managed with topical antifungal therapy. Intertriginous areas should be kept dry and paronychial abscess drained.

Tinea versicolor is a superficial infection of *Pityrosporum* yeast. It is generally found at the trunk and consists of multiple patchy circular papules with fine scale. Patches may be hypopigmented, hyperpigmented, or erythematous. They generally enlarge over time.

Dermatophyte infections are named by body area of occurrence, such as tinea pedis (feet), tinea unguium (nails), tinea manuum (hands), tinea cruris (groin), tinea capitis (scalp), and tinea corporis (trunk). Typically, these occur as erythematous plaques with fine scale. Accentuated borders are often seen; vesiculation occurs predominately at the foot. Secondary infection with bacteria may occur. Most infections may be treated with topical antifungals, but more aggressive infection may require systemic therapy.

Kidney Transplant

Skin infections are a common cause of morbidity after kidney transplantation. Studies suggest that the interval since transplantation and specific immunosuppressive therapy impact the likely infections present at various intervals post-transplantation [20]. Cutaneous bacterial infections have been reported to occur in approximately 2–28% of renal transplant recipients. Viral infection is common, particularly human papilloma virus and human herpes viruses (HHV). Oncogenic viruses, including HHV-8 (causing Kaposi's Sarcoma), are also present in greater numbers than in the general population [21]. Superficial fungal infections are present in up to 25% of patients [20].

Human Papilloma Virus

Studies report that the frequency of human papilloma virus, or viral warts, in renal transplant recipients is 11–53%. Wart frequency tends to increase with duration of time post-transplant. Most are found in sun-exposed areas. Severity is also increased with transplant patients; multiple lesions and transformation to cancer are more frequent [21].

Herpes Simplex and Varicella Zoster

Herpes simplex virus 1 (HSV1) seroprevalence in the general population is approximately 60% [22]. Because primary infection is not cleared and virus remains latent in nerve ganglia, it is not surprising that reactivation frequently occurs in immunosuppressed patients. Additionally, HSV-naïve patients may seroconvert when receiving a positive allograft. For these reasons, prophylaxis is recommended. When HSV occurs in renal transplant recipients, most patients develop oral or genital mucocutaneous lesions consisting of grouped vesicles on an erythematous base. Vesicles ulcerate with progression, leaving a “punched-out” ulcer. Complications of infection are seen with increased frequency and include bacterial superinfection, pneumonitis, tracheo-bronchitis, esophagitis, hepatitis, and disease dissemination. Acyclovir, adjusted for renal failure as needed, is the most common therapy, although other antivirals may also be used. Rarely, acyclovir-resistant HSV has been reported [23].

Varicella zoster virus (HHV-3) seropositivity occurs in 90% of solid organ transplant patients. Reactivation is a significant risk post-transplantation as is seroconversion of Varicella zoster virus -naïve patients. Infection results in shingles, a painful erythematous plaque in a dermatomal distribution with grouped vesicles. As with herpes simplex, prophylaxis is recommended. Complications include disease dissemination, disseminated intravascular coagulation, hepatitis, pneumonitis, pancreatitis, and central nervous system infection [23].

Kaposi's Sarcoma

Kaposi's sarcoma (KS) is a vascular neoplasm associated with HHV-8 infection. There are several subtypes involving variable severity and patient populations. Immunosuppression-associated KS has been reported post renal transplant and affects up to 5% of patients. Onset is most frequent about 20 months post transplant [24]. Cutaneous involvement with violaceous macules and plaques as well as red/purple nodules is common, however, lymphatic and visceral tumor involvement are especially frequent. Studies suggest immunosuppression plays a critical role in KS development. Treatment with proliferation signal inhibitors, such as the immunosuppressant Sirolimus, inhibits KS progression and may result in apparent resolution [25].

Key Messages

Cutaneous infections are a significant cause of morbidity and mortality in renal failure patients. Subgroups of these patients, such as those with DM and transplant recipients, face especially high risks of infection. These patients generally also require frequent appointments in nephrology clinics, providing an excellent opportunity for close monitoring of potential skin and soft tissue infections and solidification of patient and caregiver education. Awareness of the importance of monitoring the skin for rashes, ulcerations, and pigmentary change, and maintenance of cutaneous integrity and barrier function can reduce infection severity and limit complications of cutaneous disorders. Prevention, early recognition, and prompt treatment can dramatically reduce patient morbidity and mortality.

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