

Gram-Negative Toe Web Infections

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Key words: Gram-negative bacteria, toe web infection, toe web intertrigo, *Pseudomonas*

Citation: Waterton KA, Lipner SR. Gram-Negative Toe Web Infections. *Dermatol Pract Concept*. 2024;14(1):e2024059. DOI: <https://doi.org/10.5826/dpc.1401a59>

Accepted: July 9, 2023; **Published:** January 2024

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Funding: None.

Competing Interests: None.

Authorship: Both the authors have contributed significantly to this publication.

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ABSTRACT Gram-negative bacterial toe web infection (GNTWI) is a common dermatologic condition affecting the interdigital spaces. The clinical presentation ranges from mild erythema to exudative maceration of the web spaces that may extend to in other areas of the foot and lead to cellulitis in severe cases. *Pseudomonas aeruginosa* is the most commonly identified etiologic agent. Occlusive and humid environments, pre-existing dermatologic conditions, and fungal infections increase the risk of developing GNTWI. GNTWI has a broad differential diagnosis including erythrasma, tinea pedis, pitted keratolysis, eczematous dermatitis, and malignancies. Diagnosis is performed using bacterial and fungal cultures. There is a lack of a standardized treatment regimen for GNTWI. While GNTWI is fairly common, it may still be under-recognized by dermatologists due to the limited medical literature. This article presents a review of GNTWI, its clinical features, epidemiologic factors, etiologic agents, predisposing factors, diagnostic methods, and therapeutic options.

Introduction

Gram-negative toe web infection (GNTWI) was first described as a distinct dermatological entity by Amonette and Rosenberg in 1973 and is a relatively common disorder characterized by purulent, erythematous macerations in toe web spaces and surrounding areas of the foot such as the plantar region and underneath the toes [1-3]. Patients typically present with pruritis and pain.² Toe web infections may be due to yeast and fungal infections such as *Candida*,

Fusarium, and *Neoscytalidium*, gram-positive bacteria such as *Streptococci* spp, *Staphylococcus aureus*, and *Coryneform* bacteria as well as gram-negative bacteria, most notably *Pseudomonas aeruginosa* [2,4].

Objectives

Despite its prevalence and potential for progression to severe infection and disability, GNTWI has been infrequently discussed in the medical literature. This review aims to provide

a summary of current evidence-based data regarding clinical characteristics, diagnosis, etiologic agents, promoting factors, and treatment of GNTWI.

Methods

A literature search was conducted using the PubMed database with the search term “toe web infection”. Our search was limited to articles published prior to August 31, 2022. A total of 129 articles were retrieved from the original search and an additional 21 articles were included after a review of reference lists of review articles. Of the 150 articles, 53 were excluded if they were non-English, non-full text, and/or duplicates. We further screened the remaining 97 articles for relevance, determined by title and abstract, which excluded an additional 81 articles. We included the remaining 16 articles from this search based on their relevance to the research topic (Figure 1).

Results

Epidemiology

There are few reports on the incidence of GNTWI. A prospective clinical and epidemiologic survey demonstrated an average incidence of 13.6 cases per year with a male/female ratio of 4:1 across 123 patients [5]. Another study showed a similar sex pattern, with 72.5% of 200 GNTWI cases being men [1]. GNTWI typically presents in middle-aged adults but can also present in children and older adults. One retrospective review of 62 cases reported an age range of 10-94 years and a median age of 52.5 years [6]. A cohort study of

200 cases of toe web infections reported similar age distribution with a median age of 51 years and an age range of 11-93 years [1].

Clinical Manifestation

GNTWI presents as an exudative, erythematous maceration with malodorous discharge in the toe web spaces (Figure 2) [7]. There may be accompanying vesicles, pustules, papulovesicles, cracking and fissuring [5,7,8]. The skin may have greenish discoloration in culture-positive pseudomonas toe web infections [6]. With progressive disease, patients may develop a well-demarcated punched-out edge with a hyperkeratotic rim [9]. One case report described a patient who presented with erythematous patches in their toe web spaces, before developing the characteristic maceration [10]. Patients often exhibit symptoms of pain, burning, pruritus, and edema which can become severe and limit mobility [11]. The infection can extend beyond the interdigital spaces and involve both plantar and dorsal regions of the toes and feet [5,9]. GNTWI may also progress to other more severe skin conditions such as erysipelas and cellulitis. One case-control study comparing 114 cases of erysipelas to 208 matched controls, demonstrated a significant independent association between toe web infections and erysipelas of the leg, likely due to disruption of the cutaneous barrier [12]. Another case-control study, with 61 cases of cellulitis and 122 controls, calculated the population-attributable risk (PAR) of independent risk factors, including obesity, skin disruption, history of surgery to the lower limb, and toe-web intertrigo. The authors reported that in comparison to the other risk factors, patients with clinical evidence of toe web infection (mild scaling to an exudative, macerated, or erosive process of the toe web space) had the highest (48.9%) PAR for cellulitis [13].

Promoting Factors

Occlusive and Humid Environments

Humid and occlusive environments are risk factors for developing GNTWI. In a review of 123 cases of GNTWIs, Aste and colleagues reported that 14% of patients had either primary or secondary hyperhidrosis. About 10% of cases in the same study reported exposure to wet environments, such as swimming pools, public baths, or public showers [5]. In a survey study by Hope et al. examining 514 coal miners, 61% of those who reported frequent wet feet had gram-negative bacilli cultured, compared with 48% of miners whose feet remained appreciably dry [8]. It is theorized that in wet environments, moisture washes away the protective surface lipids, which then encourages the overgrowth of opportunistic bacteria [14].

Frequent wearing of closed-toe or tight-fitting shoes is common among patients diagnosed with GNTWI. In a case

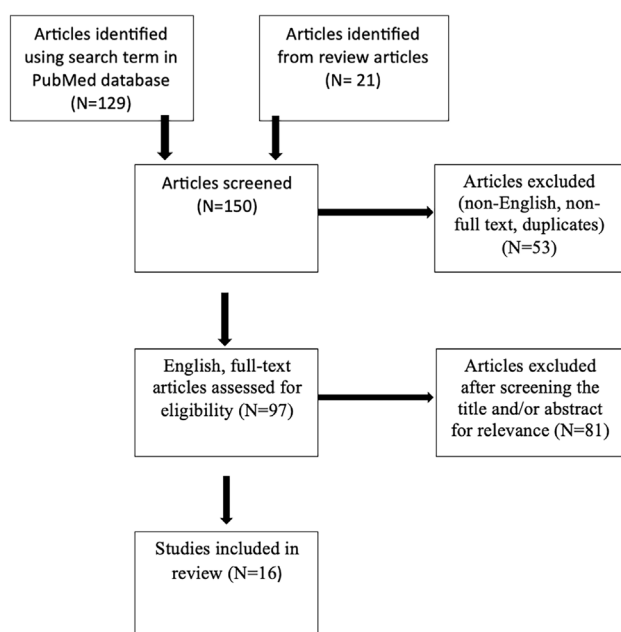


Figure 1. Article selection method.



Figure 2. Clinical manifestations of Gram-negative toe web infection GNTWI. (A,B) The dorsal feet showing erythema and erosions; (C) Plantar feet showing scale and maceration; (D) Third toe web space of the right foot showing maceration and erosions.

report of two individuals with GNTWI, both patients frequently wore steel work boots for occupational purposes [15]. Tight interdigital spaces may cause occlusive environments, which can lead to toe web erosion [4]. In a retrospective multicenter study of 62 patients with GNTWI, Goiset and colleagues reported that 42% of patients were frequently exposed to humidity, occlusion, or both [6].

Pre-existing Dermatologic Conditions

Patients with GNTWI often have histories of other dermatologic conditions and infections. Hassab-El-Naby and colleagues conducted a review of 100 cases of toe web space infections to study common etiological causes. Of the 38 GNTWI patients specifically, 53% had concurrent biopsy-confirmed interdigital eczema [16]. Similarly, a retrospective review of 62 cases of GNTWI identified concomitant or prior interdigital eczema in 66% and psoriasis in 11% of patients. Among the 19 patients with recurrent GNTWI in this same study, 42% were associated with an eczema flare and 16% were associated with a psoriasis flare [6]. Aste et al also reported allergic contact dermatitis in 20% of their patients with GNTWI [5].

Mycosis

Skin maceration secondary to fungal infections has been postulated to promote growth and invasion of gram-negative bacteria, particularly in areas such as the toe web spaces. Leyden and Kligman conducted a study involving several experimental manipulations of the interspace microflora to analyze the interaction of dermatophytes and resident bacteria. In one of their experiments, while all ten subjects had presence of gram-negative bacteria in their toe web spaces, those with dermatophytosis developed considerable hyperkeratosis, erythema, and maceration for an extended period (7-10 days), while those without dermatophytosis had only minor signs and symptoms of infection, such as mild maceration, which normalized within 1-2 days.¹⁷ Thus, they postulated that while gram-negative bacteria alone have a limited capacity to cause disease, in the setting of dermatophytosis, disruption of the integrity of the protective stratum corneum layer may favor invasion of opportunistic bacteria [18].

In addition, dermatophytes produce penicillin and streptomycin-like substances, which disrupt the bacterial flora and create an environment that preferentially selects for antibiotic-resistant bacteria [6,19]. Antibiotic-resistant

gram-negative bacteria then proliferate, promoting progression to GNTWI [18]. Though tinea pedis is frequently suspected in patients with GNTWI, dermatophytes are often not identified on fungal culture [6]. The paradoxical decrease in dermatophyte presence with clinical progression of macerated toe web spaces may be due to prior application of antifungal agents or production of an inhibitory substance by some gram-negative bacteria [5,6,20,21].

Etiology

The surface of the human foot, especially the toe web space has a diverse microbiome and a substantially greater fungal biodiversity when compared to other skin areas [22]. In a study examining the toe web spaces of 77 patients, the microbial ecology of normal toe webs was compared to toe webs with erythema and/or inflammation, maceration, severe fissures, malodor, and erosions. Among the normal interspaces, a polymicrobial flora primarily composed of coagulase-negative staphylococci, micrococci, and coryneform organisms, as well as smaller numbers of gram-negative rods, yeasts, and dermatophytes were identified [18,23]. While gram-positive bacteria have been identified as the predominant colonizers of healthy toe web spaces, Hope et al isolated over 30 distinct gram-negative species from men with affected toe webs [8,25]. *Pseudomonas aeruginosa* is the most common etiologic agent identified in GNTWI though it is often found in the presence of other gram-negative bacteria [6].

Aste et al. isolated *Pseudomonas aeruginosa* (46.4%) among other pathogens (*Escherichia coli* (13.8%), *Proteus mirabilis* (7.8%), *Morganella morganii* (7.1%), *Enterobacter cloacae* (7.1%), *Klebsiella pneumoniae* (6.2%), *Acinetobacter* spp (5.5%), *Serratia marcescens* (3.1%), and *Alcaligenes faecalis* (3.1%)) at lesser frequencies, among 123 cases of GNTWI. Furthermore, fungal species were present in 6% of cases and gram-positive bacteria were present in 17% of cases where gram-negative bacteria were isolated [5].

In a case series of 17 patients with 32 TWI episodes, including recurrences, Lin et al reported growth of gram-negative bacteria in 86% of their cultures. *Pseudomonas aeruginosa* (55%), *Enterococcus faecalis* (41%), *Staphylococcus aureus* (41%), and coagulase-negative staphylococci were the most frequently isolated species. The rate of multi-organism infection was 93%, with *Pseudomonas aeruginosa* being the most common concomitant pathogen. A similar *Pseudomonas aeruginosa* predominance was reported in several other studies, with frequency as high as 84.5% [1,4,6].

Diagnosis

Toe web infections are diagnosed by performing bacterial and fungal cultures of the affected area. Potassium hydroxide preparations (KOH), or Wood lamp examination may

also be used to provide further information regarding the etiologic agents, as well as guide appropriate treatment [14,16]. A KOH preparation will show the presence of hyphae indicative of a fungal infection [16]. A Wood lamp examination may help identify *Pseudomonas* infections, showing characteristic green fluorescence [24].

Differential Diagnoses

GNTWI may present similarly to various infectious and noninfectious conditions that involve the toe web spaces. Therefore, several diagnoses should be considered before treatment [7].

Erythrasma

Interdigital erythrasma is a superficial, localized, mild infection due to *Corynebacterium minutissimum*. This bacterium typically affects the stratum corneum in warm and wet areas of the skin such as interdigital regions [26]. Erythrasma may present with maceration with fissuring or scaling [27]. Wood lamp examination shows characteristic coral-pink fluorescence. Confirmation of the diagnosis is performed with gram stains or cultures [26].

Fungal Infections

Tinea pedis is a common dermatophyte infection of the feet that may also be suspected in patients who present with scaling, maceration, erosion, and erythema of the interdigital skin [28]. Candidal intertrigo of the toe web spaces can similarly present with erythema, desquamation, erosion, malodor, and maceration [24]. Tinea pedis and candidal intertrigo may be confirmed by KOH with microscopy or culture of skin scrapings [24,28]. However, macerated toe webs that persist despite appropriate antifungal therapies should be further investigated for other etiologies such as gram-negative bacterial infections.

Pitted Keratolysis

Pitted keratolysis (PK) is a superficial, skin infection due to gram-positive bacteria, including *Corynebacterium* spp, *Actinomyces* spp, *Dermatophilus* sp., and *Kytococcus sedentarius* [29]. PK primarily affects the stratum corneum and may present as pits that coalesce into erosions on the plantar feet [30]. Though it is primarily diagnosed clinically, dermoscopy and histopathological examination may aid in diagnosis. The dermatoscopic findings are pits with interrupted dermatoglyphic lines and scattered arrangements while histopathologic features include the presence of pits, bacteria, and color alteration of keratin [29].

Eczematous Dermatitis

Eczematous dermatitis may present on plantar feet and interdigital spaces such as toe webs [16,18]. While eczematous

dermatitis is typically diagnosed clinically, a skin biopsy may be performed in equivocal cases, and patch testing may be used to rule out allergic contact dermatitis [31]. In a study of etiological causes of toe web intertrigo among 100 patients, Hassab-El-Naby et al identified biopsy-proven interdigital eczema in 52% of patients. However, patients with macerated toe web spaces who do not respond to treatment for allergic dermatitis, irritant contact dermatitis, or dyshidrotic atopic eczema should undergo a workup for GNTWI [16].

Malignancy

Malignancy should be considered in the differential diagnosis of GNTWI. Pempinello et al reported a case of a 74-year-old man with plantar verrucous carcinoma that was initially diagnosed as a skin infection. He had an ulcer for 6-years that was unsuccessfully treated with multiple excisions and targeted parenteral antibiotic therapy before receiving the correct diagnosis [32]. In another case report, a 77-year-old man with a 6-month history of hyperkeratosis in the third and fourth web spaces of his left foot, initially diagnosed as intractable toe web intertrigo and treated with oral and topical therapies, was later diagnosis as verrucous carcinoma [33]. Therefore, malignancy may be amongst several diagnoses considered for GNTWI that are refractory to treatment.

Management

To date, there are no treatment guidelines for GNTWI. When Amonette and Rosenberg first described GNTWI in 1972, they concluded that there was no single or simple therapeutic agent that was regularly effective. They used combinations of 0.5% silver nitrate solution, Castellani paint, and gentamicin sulfate to treat 12 patients with GNTWI and none produced consistent results across patients. Only 9 of 12 patients had complete resolution of their toe web infection with combination therapy. They reported that the remaining three patients initially had no response to therapy, but achieved adequate improvement after persistent use, however they did not define length of treatment [3].

Topical

As polymicrobial toe web infections are common with GNTWI, treatment often requires topical antibacterial, antiseptic, antifungal, and/or steroidal therapies in combination with systemic treatment. In Goiset et al retrospective study of 62 patients with GNTWI, 54.8% were treated with topicals and 45.2% were treated with both systemic antibiotics and topical treatment. The length of treatment was not described in this study. The topical regimens varied by the patient and included hydrogen peroxide, boric acid, silver sulfadiazine, gentamicin, or topical steroids. Dosing and length of treatment were not specified [6].

In their review of 123 cases of GNTWI, Aste et al utilized a combination of topical antiseptics and antibiotics. Toe webs were cleaned and debrided and treated with a combination of amikacin 5% gel and application of hot compresses with 2% to 5% solutions of acetic acid daily for 15 days [5]. Similarly, Lin et al treated their 17 GNTWI patients with antiseptic solutions, including aluminum chloride, potassium permanganate, povidone-iodine, and gentamicin in addition to systemic antibiotics twice daily. After one to two weeks of this combination therapy, all patients experienced a significant reduction in pruritus and pain, as well as maceration [18].

Foot soaking has been reported for treatment for GNTWI. In their case series, Rozenblat et al treated ten patients with evidence of Pseudomonal GNTWI and concomitant fungal infection patients with acetic acid 1% immersion for 20 minutes between 10 days and 3 weeks. In addition to the acetic acid 1% immersion, six (60%) patients were treated with bifonazole gel, two (20%) were treated with local clotrimazole, one (10%) was treated with oral terbinafine, and one (10%) with oral itraconazole. All were treated for 10-14 days but the daily regimen was not mentioned. They reported that 80% of their patients had full resolution, while the remaining 20% achieved a partial response [34]. In a case report, Tan et al also treated a 53-year-old man, with a twice-daily foot soak containing an herbal decoction (Rhei radix et rhizome; Scutellariae radix; Coptidis rhizome; Phellodendrichinensis cortex) along with ciprofloxacin intravenously daily for seven days and reported resolution of maceration and infection within two weeks [10].

Systemic

The most commonly reported systemic treatment for GNTWI is oral ciprofloxacin [5,7,18]. In a case report of a 47-year-old male with GNTWI caused by *Pseudomonas aeruginosa* with autosensitization dermatitis, there was gradual improvement following two weeks of 250 mg oral ciprofloxacin twice daily with gauze dressings and topical application of tobramycin [7]. Aste et al also demonstrated complete eradication after 10 days of 500 mg oral ciprofloxacin twice daily for patients presenting with severe cases of GNTWI (number of patients treated not specified) [5]. Other systemic therapies used to treat GNTWI included fluconazole, terbinafine, prednisone, amoxicillin/clavulanic acid, cephalosporin, clindamycin, penicillin, oxacillin, ampicillin trimethoprim-sulfamethoxazole, tigecycline, and other fluoroquinolones. The dosage, length of treatment, and number of patients treated were not reported in these studies [1,18]. Patients with multi-drug-resistant *Pseudomonas aeruginosa* present additional management challenges. A 39-year-old male with GNTWI caused by *Acinetobacter baumannii*, was successfully treated with oral trimethoprim-sulfamethoxazole (160-800 mg/q12h) for 14 days.

A 53-year-old male with a complicated hospital course secondary to multi-drug resistant *Pseudomonas aeruginosa* showed improvement after 7 days of IV tigecycline (50mg/q12h) and a 6-month course of oral terbinafine (250 mg/d) [15]. While some studies have demonstrated success with the use of topical therapies for GNTWI, most of the literature supports utilizing systemic therapies or a combination of systemics and topicals [5]. Therefore, topical therapies may be attempted first, followed by systemic therapy alone or as an adjunct topical therapy for severe and persistent cases [5,10,18].

Recurrence of GNTWI

Recurrence of GNTWI has been reported in several studies. In a prospective clinical trial of 123 cases of GNTWI collected over a 10-year period, 7% of patients had recurrences [5]. In a case series of 17 GNTWI outpatient cases collected over a 5-year period, 53% of patients had recurrences, which the authors attributed to an underlying dermatophyte infection or eczema [18]. This notion is congruent with other studies that have suggested an association between eczema, dermatophyte infection, and other skin conditions due to their tendency to disrupt the cutaneous barrier [6,16,17]. In a retrospective study evaluating 62 GNTWI patients, 39 patients had available long-term follow-up data for a median of 31 months after the first clinical episode (range: 8 to 73 months). Of those 39 patients, 49% experienced recurrences and reported eczema, psoriasis, and wearing occlusive footwear. Control of these associated factors was associated with the absence of recurrence ($P < 0.0001$) [6].

Treatment Recommendations

Oral ciprofloxacin (250-500 mg bid) for 10-14 days is frequently effective for patients presenting with GNTWI [5,7,18]. Utilization of other systemic antibiotic treatments for this disorder has not been extensively studied. Topical antibiotics, such as gentamicin may also be appropriate treatment for mild forms of GNTWI [6,18]. To address recurrences, it is imperative to manage underlying dermatological conditions that may impair the skin barrier, such as eczema, psoriasis, and tinea pedis [5,6,18]. It is necessary to educate patients on reducing predisposing factors, such as moisture, occlusion, fungal infections, and pre-existing dermatological conditions [6]. Patients can be counseled on strategies such as blow-drying the feet after contact with water and avoidance of poor-fitting shoes to reduce moisture and friction, respectively.

Conclusions

Despite GNTWI causing functional impairment and carrying the risk of progressing to erysipelas and cellulitis, it remains a poorly studied condition. The scarcity of epidemiological

data on GNTWI precludes an accurate estimation of incidence and prevalence. The therapeutic management of GNTWI can be quite challenging due to the risk of antibiotic resistance and the lack of standardization of treatment methods. Treatment involves general measures such as mitigating risk factors, treating underlying dermatologic diseases, and keeping the feet and web spaces dry. Topical gentamicin may be appropriate for management of mild GNTWI, while oral ciprofloxacin is preferred for moderate to severe cases. Further research is needed to provide evidence-based data to support treatment guidelines, reduction of predisposing factors and recurrences, and ultimately, improved outcomes for patients.

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