

GRAM-NEGATIVE BACTERIAL TOE WEB INTERTRIGO

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ABSTRACT

Gram-negative infection of the toe web space is less frequent than dermatophytes and yeasts, but it is more challenging, especially with the involvement of *Pseudomonas aeruginosa* in relation to antibiotic resistance and the increased risk of potentially lethal complications. Many conditions, other than infections, might initially present with the same clinical features, recognising the common initial damage (intertrigo), due to skin-on-skin rubbing in a moist environment with air entrapment, which is typical of interdigital spaces. Conditions such as contact eczema, atopic dermatitis, and inverse psoriasis, frequently predispose to, and are maintained by, the intertrigo, triggering a vicious circle. The dermatologist is in a lead position to address the correct assessment and management. A careful screening for predisposing factors is necessary: overweight, diabetic, but also athletes or people attending swimming pools, gyms, public showers/dressing rooms, and thermal baths are also at an increased risk of intertrigo of the toe web spaces. Occupational activities other than recreational might be relevant, such as the use of safety shoes or working in wet warm conditions. Incongruous therapy for tinea pedis or contact dermatitis, frequently auto-prescribed, might be among promoting factors altering the microbial ecosystem balance. The aim of this review is to evaluate the main epidemiologic and clinical features of Gram-negative bacteria intertrigo, the role of promoting factors, and the measures taken to treat and prevent this disorder. Appropriate treatment and patient education are crucial to prevent further infection and relapses.

Keywords: Toe web intertrigo, skin and soft tissue infections, Gram-negative infection, multidrug resistance.

INTRODUCTION

The term 'intertrigo', from the Latin roots 'inter (between) + terere (to rub)', medically groups different conditions involving the flexural areas of the body, where the opposing surfaces produce friction and promote inflammation and thereby modification of the cutaneous ecosystem, which is habitually colonised by polymicrobial flora, precariously balanced by biologic interference mechanisms.¹⁻³ Interdigital toe folds are frequently affected,⁴ and differentiation from major dermatitis on a clinical basis is sometimes a challenge (Table 1), especially from contact eczema, atopic dermatitis, and inverse psoriasis, which are frequently predisposed to, and are maintained by the intertrigo, triggering a vicious cycle. Presentation is also variable, from mild erythematous-scaling forms, more or less asymptomatic with a chronic trend,

to severe acute exudative, macerating, painful inflammatory forms, causing discrete functional impotence. Gram-negative prevalence over other bacteria, dermatophytes, and *Candida* spp. usually cause a sudden aggravation of the lesions.⁵⁻⁷ This review aims to outline the main clinical aspects of Gram-negative foot intertrigo, causative organisms, promoting factors, and the most common therapeutic actions.

Epidemiology

Current literature on interdigital Gram-negative infections is limited, and an incidence rate cannot be extrapolated from such a small case series,^{4,7-11} but daily practice suggests the disease is more common and probably underestimated, because of empirical diagnosis and treatment. Any race, age, or sex is affected. The sharp prevalence of male gender, with 4:1 ratio⁷ is justified by the more

extensive use of closed shoes for professional and extraprofessional reasons or during the practice of sports.^{1,6-13} A US military survey for Gram-negative bacteria colonisation in healthy asymptomatic personnel showed that toe web spaces were Gram-negative colonised in 35% of cases.¹⁴ The study also documented a relevant community onset of multidrug-resistant (MDR) *Escherichia coli*

colonisation, with Afghanistan-based personnel showing a 5.5-fold higher prevalence in respect to other US military.¹⁴ The high frequency of asymptomatic carriers and diffusion of MDR bacteria in the community are critical points, suggesting a possible increase of the infection cases, unresponsive to common treatment, especially in precarious healthy conditions.

Table 1: Clinical differential features of toe web infections and other frequent inflammatory conditions.

Disease	Clinical presentation	Symptoms
Simple intertrigo	Mild erythema on each side of the skin fold, almost in a mirror image, more evident on convexity than on bottom.	Warming sensation
Gram-positive intertrigo	Well-demarcated bright red erosions, with abundant weeping and crusting, foul odour. No satellite lesions.	Burning sensation
Candida intertrigo	Mild-to-moderate erythema and maceration, with a central fissure, and typical satellite papules and small size white pustules.	Moderate itching
Tinea pedis	Mild erythema, mainly under a scaling macerated surface, more evident in the fold bottom, which might present a superficial erosion.	Mild itching, often asymptomatic
Gram-negative intertrigo	Intense erythema, erosions, and maceration, with profuse oozing or purulent discharge, crusting, typically malodorous. A green discolouration of the lesion borders is highly evocative of <i>P. aeruginosa</i> isolate. Oedema and severe erythema of surrounding tissues in severe forms.	Burning and pain, possible functional disability
Scabies	Mild erythematous scaling lesions, linear or isolated papules.	Itching more severe than expected from visible lesions, night worsening
Inverse psoriasis vulgaris	Smooth erythematous well-demarcated lesions, with compact scaling at the periphery. Plantar hyperkeratosis, and/or typical psoriasis lesions on other skin areas, nail changes.	Variable from warm itching sensation to burning
Contact dermatitis	Erythema, maceration, severe weeping, and crusting. Sometimes visible vesicles at the periphery.	More intense itching; positive patch tests distinguish allergic from simple irritant dermatitis
Atopic dermatitis	Eczematous variable manifestations. Coexisting atopic disease or positive family history.	Intense itching
Dyshidrotic eczema	Clear, deep blisters, more visible on the side of the inter-digital surfaces. Mild erythema and flexural fissures on the fold.	Itching and/or burning

AETIOLOGY AND PATHOGENESIS

Gram-negative bacteria are ubiquitous, sometimes present as part of the normal human flora, but potentially very aggressive,^{5,6} and the fine mechanisms turning from bacterial colonisation to active proliferation, invasion, and tissue damage (infection phase) are complex and variable. Toe web spaces provide a hospital niche for several microorganisms, with warm and moistening air entrapment. The most common isolates that have been reported include: *Pseudomonas*, *Moraxella*, *Alcaligenes*, *Acinetobacter*, *Proteus*, and *Erwinia* species.^{7,10-15} Pathogens determinant of virulence are crucial for subsequent tissue infection, but host defence impairment for local, as well as general predisposing conditions, is necessary to lose the natural ability to counteract infections. In intertrigo process, first, integumental alteration depends on mechanical chafing, as the skin-on-skin rubbing causes an initial corneal damage favouring bacterial or fungal invasion.¹⁶ Clothes, especially tight-fitting shoes, but also climate variables, such as increased temperature and relative humidity, as well as pH modification, cause over-hydration of the stratum corneum and favour surface concentration of Gram-negative bacteria.^{17,18} Primary or secondary hyperhidrosis and poor hygiene further collaborate to produce a fertile breeding ground for several microorganisms.

A previously unrecognised interdigital dermatophyte infection (tinea pedis) might be a crucial promoting factor of Gram-negative bacterial proliferation because fungal release of natural antibiotic substances can affect the composition of the residing flora and determine antibiotic-resistant strain selection.^{7,16,19} In other cases, Gram-negative intertrigo appears independently, the peculiar microclimate favouring survival of germs with minimal nutritional requirements. *Pseudomonas aeruginosa* is a typical opportunistic organism that is unable to overcome normal cutaneous defences on its own, but rapidly takes advantage of inefficient or compromised barriers, and by its broad enzyme heritage, easily adapts to unfavourable environments, as well as resisting most common antibiotics.^{6,10,18-24} Polymicrobial contamination is common, especially by faecal germs such as *E. coli*, which pass the genetic poly-resistance information through the plasmids.^{4-6,12} A careful screening for predisposing factors is necessary to prevent further infection and relapses. Obesity and diabetes are very frequently associated with intertrigo,^{1-3,7,23}

but healthy individuals might also be affected throughout life, especially athletes or people attending to swimming pools, gyms, public showers/dressing rooms, and thermal baths.^{7,11,20}

Promoting factors are also topical medications with antifungal, mixed antibiotic, and cortisone creams which are commonly used for other conditions, such as tinea pedis or contact dermatitis.^{7,16} These treatments are rarely based on diagnostic support, are auto prescribed, and often inadequate or too prolonged. Besides, a confirmed allergic contact dermatitis might be a frequent condition, which was reported in 20% of patients in our published experience.⁷ Sensitisation further reduces the choice of medications, cosmetic products, clothes, and shoes. Some of our patients underwent aggravation after a footbath with potassium salts, and patch tests revealed potassium dichromate sensitisation, alone or combined with cobalt chloride, balsam of Peru, leather, rubber, and fragrance sensitisations.⁷ Other than recreational activities, occupational activities might be a determinant, such as the use of safety shoes or working in wet, warm conditions.^{7,8,13,19}

CLINICAL MANIFESTATIONS AND EVOLUTION

Gram-negative intertrigo is characterised by dark red oedema and erythema, varying from mild to very severe forms. Initial, mild manifestations (Figure 1) are clinically undistinguishable from tinea pedis, *Candida* and/or Gram-positive infection, in which quite dry and scaling, well-defined areas of erythema are common features. When the infection worsens, more unique characteristics occur, with severe and diffuse oozing erosions (Figure 2), involving both feet and extending to the back surfaces, with marked oedema and undermined borders. The abundant yellow-green exudate has a pungent malodorous smell. A typical green discolouration is very suspicious for *P. aeruginosa* colonisation (Figure 2). Patients complain of a burning pain, rather than itching, and walking impairments are frequent.⁷ Differential diagnosis criteria from other infections and common skin diseases affecting the toe web resumed, as seen in Table 1. Patients with severe bacterial intertrigo, especially if overweight or diabetic, are at high risk of local complications, such as osteomyelitis (Figure 3) and/or cellulitis development.²⁵ Systemic dissemination, endocarditis, and sepsis are extremely rare complications, but are potentially life-threatening.²²



Figure 1: A mild erythematous scaling form of intertrigo, involving the third and fourth interdigital fold. From this clinical presentation it is impossible to further diagnose the type of microorganism, as dermatophyte, yeasts, as well as Gram-positive bacteria might cause it.



Figure 2: A more severe, exudative form, in which the responsibility of Gram-negative bacteria is quite certain.

The inflammatory process involves both feet, every interdigital space, and the digito-plantar sulcus, also extending to the back of the foot. Note the marked maceration and a green discoloration of the epithelial undermined borders in another patient (left bottom inset), and the diffusion of the infection to both feet, with functional impairment.

DIAGNOSIS

Microbiologic tests usually rapidly confirm the abundant presence of Gram-negative rods, but culture is essential to isolate strains and to test antimicrobial susceptibility. *P. aeruginosa*, alone or in association with other Gram-negative bacteria, is the main causative agent, especially of acute gravescent forms. *E. coli*, *Proteus mirabilis*, and *Morganella morganii* are among the other most frequent isolates. In 20% of the cases,

Gram-positive bacteria are isolated together with the Gram-negative, as well as *Candida* minor species, such as *C. parapsilosis* and *C. guilliermondii*, which might be resistant to fluconazole. These complex polymicrobial interactions make intertrigo management a constant challenge. A Wood's light examination might rapidly help to confirm *Pseudomonas* (green fluorescence) before laboratory results, as well as *Corynebacterium minutissimum* (coral-red fluorescence) infections, although erythrasma very rarely affects toe webs.



Figure 3: A severe Gram-negative toe web intertrigo, complicated with osteomyelitis in a diabetic patient.

A matter of concern is the antibiotic resistance occurrence during treatment.^{22,26} A sudden worsening of the symptoms during the healing phase might also occur for the dermatophytes or yeasts reappearance and proliferation, which were temporarily relegated in the deepest recesses of the stratum corneum by the bacterial antifungal substances release.^{11,13,14,16} From our decennial prospective survey,⁷ the mycological examination of skin scraps at the end of treatment showed unequivocally that a fungal infection had reappeared, after recovery from a bacterial infection.

Histology is not usually performed because intertrigo has no characteristic features, but it might be necessary to rule out major underlying pathologies, especially psoriasis. Patch tests might disclose an allergic dermatitis, especially sensitisation to potassium, chloral cobalt, shoe rubber, and dye, but also topical emollients, antibiotics, antiseptics, and conservatives. This condition heavily affects daily life and further topical treatment choice. Routine blood chemical tests are usually performed to exclude comorbidity, and the study of humoral and cellular immunity might be advisable in patients with severe clinical forms, resistant to treatment or with frequent recurrences.

TREATMENT

No guidelines have been diffused on this topic,³ but conventional therapy should be initiated after having taken adequate samples for bacterial cultures, as for systemic infections. Culture lab results can take up to 72 hours, and treatment should

not be delayed; the initial antibiotic choice might be modified later, based on antibiotic sensitivity. Among the most active antibiotics there are third-generation cephalosporin and quinolones, together with the aminoglycosides.^{7,9} Antimicrobial testing should be repeated if a sudden worsening occurs, or to finally assess recovery at the end of treatment.

Topical treatment should be performed after accurate cleansing and debridement of the lesions because macerated skin might impede correct drug penetration.²⁷ In our experience, amikacin 5% gel and hot compresses with 2-5% solutions of acetic acid, for 15 days, were well tolerated and effective.⁷ Measures to minimise moisture and friction should be suggested during the healing phase to prevent relapses. Patient education includes careful drying after washing, wearing light absorbent non-constricting socks and shoes, and avoiding nylon and other synthetic fibres. New bio textiles have been used in atopic patients, and might be of interest for intertrigo prevention.²⁸ Absorptive powders, talc or corn starch-based, and barrier creams are controversial, potentially causing occlusion and further irritation.²⁹ Another very controversial issue is the addition of corticosteroids, which might be indicated when an underlying condition, such as psoriasis or atopic and contact eczema, has favoured the infection. The use of hydrocortisone 1% cream or powder is very popular^{1,30} to reduce inflammation.

In all severe ingravescient forms, systemic therapy should be considered, and oral ciprofloxacin (500 mg bid) for 10 days is usually effective,⁷

although, in some cases, parenteral therapy is necessary (intramuscular ceftriaxone or ceftazidime 1-3 g/d or cefotaxime 2 g/d).⁹ When yeasts or dermatophytes are isolated, supplementation with specific antifungal drugs is necessary.¹⁹ This strict monitoring of the microbial flora, rather than waiting for a period of time after the antibiotic treatment, is crucial to avoid the high frequency of relapses and chronicity.

CONCLUSIONS

In all symptomatic toe web infections, the presence of Gram-negative germs, such as *P. aeruginosa*,

should be investigated to avoid the risk of treatment failures and more severe local or systemic complications. The frequency of relapses depends on the complexity of the polymicrobial interactions, with possible subsequent infection by different microorganisms, eventually selected by the treatment given. Thus, repeated antimicrobials and mycological tests are recommended, as well as correction of local promoting factors and/or pathologic conditions to obtain satisfactory therapeutic results. Patient education about types of clothing, minimising moisture and friction, and drying toe web spaces after showering is the main key to avoiding chronicity and recurrences.

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