

## Gram Negative Toe Web Infection – A Not So Rare but Neglected Syndrome

In 1977 Leyden & Kligman (1) introduced the concept of dermatophytosis complex and Gram negative toe web infection. They stated that “ in our view, interdigital athlete’s foot usually begins with invasion of the horny layer by dermatophytes. Because of hot weather, sweating, exercise, or tight shoes, enough moisture accumulates to stimulate an overgrowth of bacteria. Large numbers of normally resident aerobic diphtheroids cause the common wet, macerated type of athlete’s foot, while an overgrowth of Gram negative organisms, such as *Pseudomonas* and *Proteus*, is responsible for the more serious cases“. Gram negative infection of the foot was therefore seen as a secondary consequence of dermatophyte infection of the toe web spaces. The authors pointed out that resolving the bacterial infection through treatment might lead to return of the dermatophyte infection and the potential for a cycle of infection. The clinical appearances described then, and subsequently, were those of soggy and eroded interdigital skin and there was frequently a greenish tinge to the border of the cracked area indicating the presence of *Pseudomonas* in the wound. Patients usually describe soreness or pain, which can be severe and disabling, rather than itching in such lesions. Subsequent work associated the emergence of Gram negative toe web infection with wearing heavy footwear such as that used in heavy industry and mining or in occupations, such as the nuclear fuels industry, where protective footwear would be used (2). A further study of British coal miners showed that this Gram negative infection was also seen in miners working under wet conditions – the so-called wet mines (3) where pooling of water was an ever-present hazard at the coal face. Gram negative foot infection is one of a number of different syndromes involving cracking and erosion of the toe web spaces that include other fungal infections, such as those caused by *Candida*, *Fusarium* and *Neoscytalidium* along with those caused by Gram positive bacteria e.g., coryneforms in erythrasma of the toe web. Diagnosing the cause is an important step in identifying the correct treatment.

Apart from the presence of a previous skin injury at the site, including infection due to dermatophytosis, the other constantly reported accompaniment of Gram negative foot infection is excessive humidity which appears to be necessary for the infection to develop. More recent studies using molecular techniques to identify the skin microbiome have shown that the toe webs of otherwise healthy subjects harbour a specific and diverse, as well as variable, flora including, in otherwise healthy individuals, Proteobacteria including Gram negatives such as *Pseudomonas* (4). What triggers these to change from a normal commensal to a pathogenic role is not clear. It has been shown recently that some of the foot microbiota, particularly those affecting the toe web spaces (5), may include coagulase negative Staphylococcal species that are prolific producers of bacteriocins or bacteria biocides with activity against other skin pathogens including bacteria and

fungi. Changes in their population number and distribution are likely to have profound effects on other microbes normally resident in this area.

In this issue a team of French dermatologists has documented their experience of Gram negative foot infections across a range of different hospitals (6). They recorded that half of their 62 patients experienced more than one episode of Gram negative toe-web infection. *Pseudomonas aeruginosa* was the most prominent bacterium identified, but that many showed mixed populations of microbes, including *Staphylococcus aureus*. They recorded predisposing factors that included eczema and psoriasis, suspected tinea pedis and exposure to humidity or hyperhidrosis and vascular disorders. Five percent of those studied were diabetic, an interesting observation given the growing association between foot Gram negative bacteria and diabetic foot ulceration or diabetic foot studied using mixed techniques of culture plus 16S ribosomal RNA (16SrRNA) genetic analysis (7). The French study included patients with a severe spectrum of disease and over 75% had more than one episode of Gram negative infection, often following failure of initial outpatient management.

The publication of this study is important as it re-emphasises the need for more information on the diagnosis and management of this condition, Gram negative toe web infection, which is by no means uncommon. This echoes an early systematic review of the condition published in 2018 (8) which pointed out the relative paucity of reports and the need for randomized controlled trials designed to provide evidence-based therapies. The severity of some of the cases described in this latest publication serves to underscore this need.

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