# Chapter 25
# Infection

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## General Overview

Infections and inflammation of the skin and soft tissues of the lower and upper limbs are more common than those of other cutaneous regions because of exposure to the environment. The hands and feet have direct contact with surrounding matter, which is covered in micro-organisms and chemical substances. Readily acquired damage to the epidermis, such as abrasions, cuts, pricks, and closed injuries, create portals of entry for environmental bacteria.[1,2] The skin surface, and appendices such as sweat, sebaceous glands, and hair follicles, are inhabited by commensal bacteria, mostly *Staphylococcus epidermidis* and coagulase-negative strains. *Staphylococcus aureus* and corynebacteria are also present. In addition, the feet and calves may be colonized by pathogenic microbes originating from the perineal region, such as *Enterococcus*, *Enterobacter*, *Acinetobacter*, *Proteus*, *Escherichia coli*, and *Pseudomonas*. These microbes float down from the perineum on desquamated epidermal scales.

The commensal microbes are not pathogenic as long as they remain in their physiological niche. Once they have penetrated the epidermis the local host defense response is initiated. This response depends on the mass of penetrating microbes. A mass of $10^5$ of bacteria per gram of tissue is the threshold value. Interestingly, the skin-colonizing bacterial strains are sensitive to most antibiotics.

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## Primary and Secondary Infections

### *Primary Infections*

These include lymphangitis, erysipelas, necrotizing fasciitis, and other rare conditions. The predisposing conditions are lymph stasis in the form of latent or overt lymphedema and chronic venous insufficiency.

Lymphangitis is characterized by the occurrence of an inflammatory streak (red, warm, and painful), the topography of which is that of the superficial lymphatic vessels. It is accompanied by fever. There is a non-inflammatory spreading lesion.

Erysipelas is a non necrotizing bacterial subdermal inflammation usually associated with streptococcal infection.[3-5] Group A beta-hemolytic *Streptococcus* (*S. pyogenes*) is the usual etiological agent. It may sometimes be a complication of chronic lymphedema.[6] Erysipelas is often of sudden onset, marked by frank systemic signs – fever >38° C, chills – and general malaise. Local signs develop within a few hours; a red, warm, painful, inflammatory spreading lesion with centrifugal extension develops within a few days. Inflammatory, satellite adenopathy and lymphangitis are associated with erysipelas.

Necrotizing dermal–subdermal bacterial infection, or necrotizing fasciitis, is characterized by necrosis of the fascia and myositis, resulting in a presentation of infectious gangrene. Diffuse, indurated edema extends beyond the margins of the erythematous and sometimes slightly inflammatory spreading lesion. Deep necrosis may be manifest in the initial stage solely as a cyanotic, grayish-blue, poorly demarcated swelling with a geographical map-like presentation. Fever is a usual finding, but it can be mild or absent. A septic syndrome (with hemodynamic signs, hypoxia, and thrombocytopenia) subsequently develops. This should prompt emergency hospitalization of the patient.

Other acute forms of dermal–subdermal bacterial infection are caused by *Erysipelotrix rhusiopathiae* (Rouget's swine erysipelas), *Haemophilus influenzae*, *Pasteurella multocida*, and *Borrelia burgdorferi*.

### *Secondary Infections: Dermato-Lymphangio-Adenitis*

#### Chronic Dermatolymphangioadenitis

Each case of lymphedema is predisposed to infections and chronic dermatolymphangioadenitis (DLA).[7] This is due to impairment of bacterial elimination via lymphatics. Lymphedema is complicated by infection of the skin and deep tissues in approximately 40% of cases, irrespective of what is the primary etiological factor for the development of this condition. In the upper extremities after mastectomy and local irradiation, infection of the swollen limb, expressed as acute and later as chronic inflammation, ranges between 20% and 40%.[4] The recurrence rate of acute attacks of DLA is higher in subjects with a long duration of edema. It is followed by a rapid

increase in limb volume. In the lower extremities, infection with inflammation is estimated to affect 50% of patients.[8] It is most common in the post-inflammatory type of lymphedema, followed by the post-traumatic and post-surgical types. Lower limbs are particularly exposed to the environmental microbial flora. Bacterial, fungal, and viral infection are more common there than in other skin regions. In advanced stages of lower limb lymphedema, systemic septic accidents requiring hospitalization and intensive antibiotic therapy are common, especially in tropical countries.

**Acute DLA**

Severe systemic symptoms during attacks of DLA resemble those of septicemia. The clinical characteristics are local tenderness and erythema of the skin, sometimes red streaks along the distribution of the superficial lymphatics, and enlarged inguinal lymph nodes. Systemic symptoms include malaise, fever, and chills. In its subacute or latent form, only skin involvement is observed. Each episode of DLA is commonly followed by worsening of limb swelling. Patients with acute episodes of DLA reveal bacteremia in a high percentage of cases.[8] Blood bacterial isolates were found in 21% of acute cases and 26% of subacute cases. The diversity of blood and tissue bacterial isolates in these patients points to a breakdown of the skin immune barrier in lymphedema and subsequently indiscriminate bacterial colonization of deep tissues and spread to blood circulation. Fatal cases have been observed.

## *Differential Diagnosis of Lymphangitis, Erysipelas and Dermato-Lymphangio-Adenitis*

There is a lot of misunderstanding concerning the differences among these three conditions, which has implications for treatment decisions:

(a) Lymphangitis is a primary, local, non-systemic, non-spreading change in the skin and subcutaneous tissue caused by the patient's own skin flora, with a mild clinical course. It may lead to the development of lymphedema.
(b) Erysipelas is a primary, acute, local, spreading condition in the skin with systemic reaction. It is caused by streptococci. It may be contagious. It either develops in lymphedematous tissues or is the primary factor for lymphedema development.
(c) Dermato-lymphangioadenitis is a secondary condition complicating lymphedema of the soft tissues in the limb, caused by colonizing staphylococci, but not streptococci (which cause erysipelas). It is non-contagious and has a tendency to recur. In the United States, DLA is commonly referred to as cellulitis, which is the accepted non-European term for soft tissue bacterial infection. Cellulitis must not be confused with "cellulite," a cosmetic term that describes the presence of fatty deposits that cause a dimpled or uneven appearance, typically of thighs and/or buttocks.

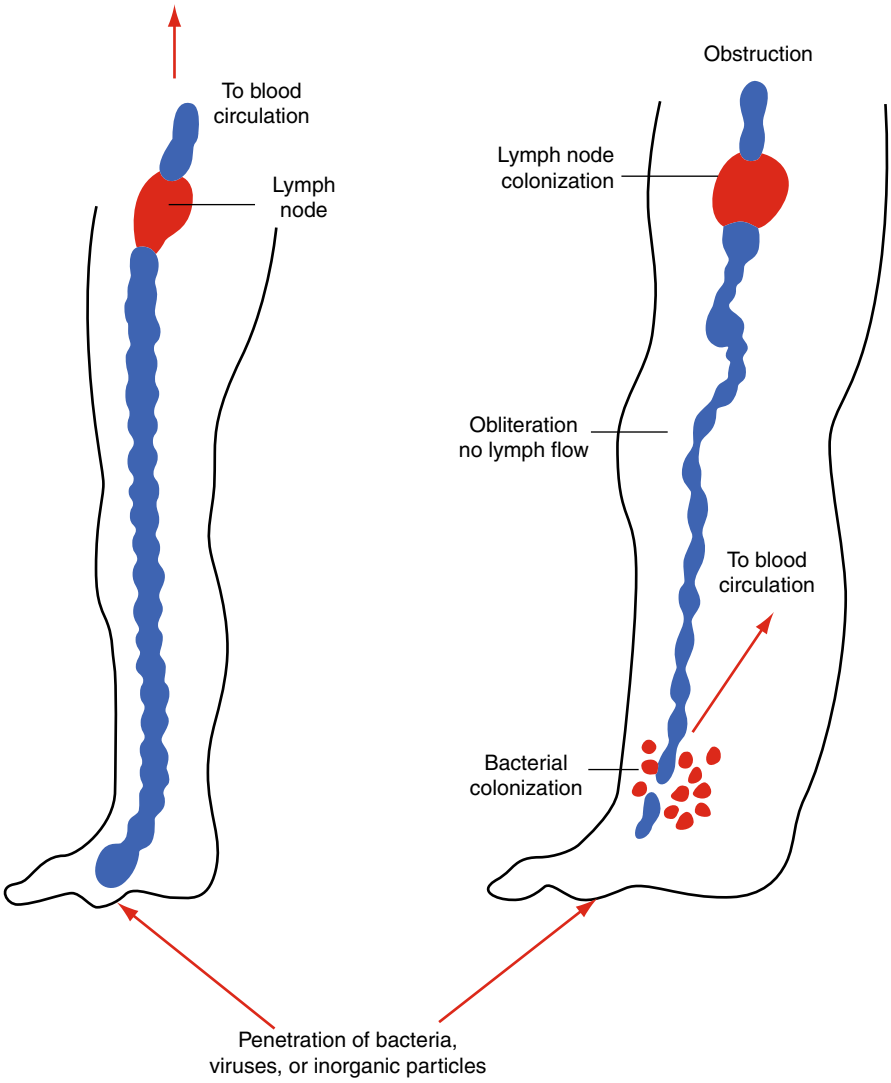


**Fig. 25.1** Schematic presentation of the pathways of the spread of skin bacteria in deep tissues and penetration to blood circulation in lower limb lymphedema

## *Pathogenesis of Tissue Infection and Inflammation in Lymphedema*

Under normal conditions, microbes that penetrate the glabrous skin of the palm or sole are transported away from the tissue via lymphatics and eliminated in the regional lymph nodes (Fig. 25.1). These are the strains that reside permanently on the skin and are acquired from the environment. The bacterial load is low and there is no clinically detectable reaction. In lymphedema, lymphatic transport is mildly to

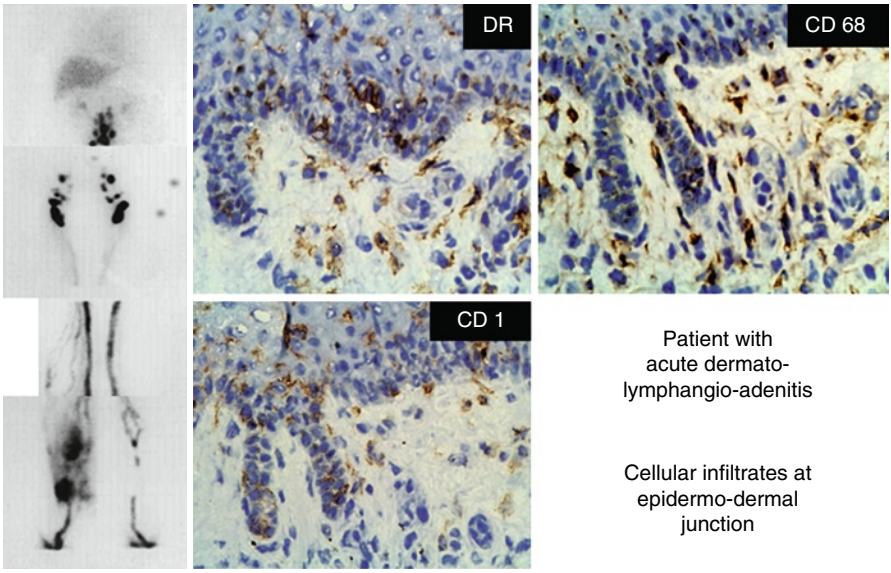


**Fig. 25.2** A lymphoscintigram and skin histology in a patient with acute recurrent attack of DLA in the right lower limb. Lymphoscintigraphy depicts focal accumulation of isotope in the calf with dilatation of lymphatics below the knee. On histology, cellular infiltrates of DR-positive, brown-stained activated migrating immune cells, CD68-positive cells (macrophages) and CD1-positive cells (Langerhans' cells). Under normal conditions CD1 cells normally reside only in the epidermis. In DLA they are also seen in dermis being attracted, presumably, by bacterial antigens

severely restricted. The penetrating microbes colonize tissues, proliferate, and evoke a local inflammatory reaction with recruitment of host immune cells. Frequently, bacteria begin to proliferate rapidly and inflammation of all of the soft tissues of the limb develops, as well as systemic septic symptoms with bacteremia (Fig. 25.1). On histology, infiltration of the dermis and epidermis by mononuclear cells and granulocytes, macrophages, and Langerhans' cells is seen (Fig. 25.2).

## Bacteriology of Lower Limb Skin

### *Bacterial Flora of Normal Foot and Calf Skin*

Swabs taken from the surface of the foot and calf skin reveal the presence of microbes in 100% (Table 25.1). The dominant species are cocci (60%). Among them, *S. epidermidis* and other coagulase-negative strains account for 90% of all isolates. The other, less frequent strains are *E. coli*, *Citrobacter*, *Corynebacterium*, *Acinetobacter*, *Proteus*, and *Bacillus cereus*. These strains originate from the patient's perineum and anal skin.

**Table 25.1** Prevalence of bacterial isolates from specimens obtained from lower limb tissues, lymph, and lymph nodes of 54 European patients with secondary lymphedema. The values from 30 healthy volunteers are given in parentheses

| Specimen | Number of specimens | | Percentage of positive culture |
|---|---|---|---|
| | Total | Positive | |
| Toe-web swab | 52 | 52 | 100 (100) |
| Calf skin swab | 52 | 52 | 100 (100) |
| Calf surgical incision swab | 41 | 4 | 10 (7) |
| Leg lymph | 20 | 12 | 60* (7) |
| Inguinal lymph node | 20 | 6 | 33* (0) |

*$p < 0.05$

**Table 25.2** Numerical prevalence of bacterial strains in tissues and fluid specimens from lymphedematous legs of 54 European patients

| | Toeweb swab | Calf skin swab | Surgical wound swab | Lymph | Lymph node |
|---|---|---|---|---|---|
| Number of specimens | 52 | 52 | 41 | 20 | 20 |
| *Enterococcus* | | | | | |
| *E. durans* | | 2 | | | |
| *E. faecium* | 2 | 2 | | | |
| *Citrobacter* | 3 | 2 | | | |
| Coryneforms | | | | | |
| Group 2 | 2 | | | | |
| ANF | 3 | 11 | | | |
| Pseudo | 1 | | | | |
| Minutissimus | 1 | | | | |
| Group F | 1 | | | | |
| Xerosus | 3 | | | | |
| *Klebsiella* | | | | | |
| *K. oxytoca* | 1 | | | | |
| *K. pneumoniae* | 1 | 1 | 1 | | |
| *Acinetobacter* | 5 | 6 | | | |
| *Escherichia coli* | 2 | | | | |
| *Proprionibacterium* | 1 | | | | |
| *Neisseria flava* | 1 | 1 | | | |
| *Bacillus subtilis* | 2 | 4 | | | |

## *Bacterial Flora of Normal Leg Lymph*

*Staphylococcus epidermidis* was detected in 12% of samples collected in volunteers in studies of lymphatic lipid transport.

## *Bacterial Flora of Lymphedematous Leg Lymph*

Cocci were isolated in 60% of samples from European populations, with *S. epidermidis* and occasionally *S. aureus* predominating (Tables 25.2, 25.3). In the Indian

**Table 25.3** Numerical prevalence of microorganisms isolated from specimens obtained from lymphedematous legs of 54 European patients

| | Toeweb swab | Calf skin swab | Surgical wound swab | Lymph | Lymph node |
|---|---|---|---|---|---|
| Number of specimens | 52 | 52 | 41 | 20 | 20 |
| *Micrococcus* | | | | | |
| species | 31 | 28 | | | |
| *M. luteus* | 6 | 11 | | 2 | 2 |
| *Staphylococcus* | | | | | |
| *S. aureus* | 4 | 9 | | | |
| *S. capitis* | 2 | 4 | | 2 | |
| *S. cohni* | 11 | 7 | | | |
| *S. epidermidis* | 24 | 15 | | | |
| *S. hemolyticus* | 4 | 6 | 2 | | 4 |
| *S. hominis* | 20 | 18 | | 6 | |
| *S. lentus* | 2 | 1 | | | |
| *S. simulans* | 1 | | 1 | | |
| *S. sciuri* | 3 | | | 2 | |
| *S. saprophyticus* | 6 | 4 | | | |
| *S. warneri* | 6 | 2 | | | |
| *S. xylosus* | 6 | 3 | | | |
| *Streptococcus* | | | | | |
| *S. milleri* | | 2 | | | |
| *S. mitis* | | 1 | | | |
| *S. faecium* | 3 | 2 | | | |

population, with high-risk exposure to environmental infections, the values were higher and reached 70% of isolates, mostly cocci, in lymph and lymph nodes.[9]

### *Sensitivity of Isolates to Antibiotics*

The skin, subcutaneous tissue, lymph, and lymph node isolates, from both patients with lymphedema and normal subjects, were sensitive to most antibiotics (Tables 25.4, 25.5).[10] Surprisingly, microbes showed the least sensitivity to penicillin, although this antibiotic proved to be very effective in the prevention of DLA attacks in a long-term administration protocol.[11,12] The high level sensitivity of most strains suggests their environmental, but not hospital, origin.

## Prophylaxis of Recurrent DLA

### *Chronic DLA*

Dermato-lymphangio-adenitis is of bacterial etiology and has a tendency toward recurrence. Chronic bacterial propxhylaxis is therefore necessary. It should be of

**Table 25.4** Sensitivity to antibiotics of bacterial isolates from skin surface, surgical skin incision, lymph and lymph nodes in 54 European patients with lymphedema of lower limbs and 30 normal controls (in %)

| | Gram-negative *cocci*, *bacilli*, *coryneforms* | | | |
|---|---|---|---|---|
| | Lymphedema | | Normals | |
| | +++ | + | +++ | + |
| Penicillin | 67[a] | 0 | 27 | 5 |
| Cefotaxime | 100 | 0 | 80 | 25 |
| Kanamycin | 67 | 0 | 100 | 0 |
| Tobramycin | 83 | 0 | 100 | 0 |
| Amikacin | 67 | 0 | 100 | 0 |
| Gentamycin | 86 | 14 | 100 | 0 |
| Tetracyclin | 71 | 0 | 80 | 0 |
| Quinolones | 83 | 17 | 100 | 0 |
| Cotrimoxazole | 67 | 0 | 80 | 0 |

[a]Percentage of isolates

**Table 25.5** Sensitivity to antibiotics of bacterial isolates from skin surface, surgical skin incisions, lymph and lymph nodes of 54 European patients with secondary lymphedema of lower limbs and 30 normal controls

| | *Cocci* | | | |
|---|---|---|---|---|
| | Lymphedema | | Normals | |
| | +++ | + | +++ | + |
| Penicillin | 24[a] | 0 | 28 | 2 |
| Oxacillin | 72 | 0 | 73 | 0 |
| Meticillin | 80 | 0 | 80 | 0 |
| Kanamycin | 68 | 6 | 44 | 8 |
| Tobramycin | 74 | 5 | 75 | 15 |
| Gentamycin | 79 | 3 | 85 | 4 |
| Tetracyclin | 49 | 0 | 61 | 2 |
| Minocyclin | 96 | 4 | 100 | 0 |
| Erythromycin | 49 | 4 | 59 | 8 |
| Lincomycin | 60 | 14 | 69 | 6 |
| Pristinamycin | 92 | 1 | 100 | 0 |
| Fosfomycin | 57 | 6 | 45 | 8 |
| Nitrofurantoin | 85 | 6 | 54 | 25 |
| Quinolons | 72 | 18 | 62 | 12 |
| Rifampicin | 91 | 6 | 91 | 9 |
| Fusidic acid | 81 | 11 | 77 | 18 |
| Yancomycin | 92 | 0 | 88 | 2 |
| Teicomycin | 92 | 0 | 79 | 0 |
| Clotrimoxazole | 78 | 4 | 80 | 0 |

[a]Percentage of isolates

long duration, or even permanent, since the effect of acute treatment is only temporary. It requires the use of penicillin: intramuscular benzathine penicillin 1.2–2.4 million units every 2–3 weeks, or oral penicillin V 2–4 million units in 2–3 doses a day.[10-12] The intramuscular route with local anesthetic ensures better compliance and has proven effective. The alternative, although less effective, is oral 2 g amoxicillin with clavulanic acid for 3 days every 2–3 weeks. Longer breaks between antibiotic administration had a tendency to increase the DLA recurrence rate. In the case of ß-lactam allergy, it is advisable to prescribe a macrolide, such as, for example, roxithromycin.

We investigated the clinical course of lymphedema with respect to the prevalence of DLA in patients receiving injections of long-acting penicillin (benzathine penicillin). Recurrent episodes of DLA over 1 year of follow-up decreased from 100% to 9% in the PCN-treated group ($p<0.002$).[11] There was increased prevalence of cocci and gram-positive bacilli, with a concomitant decrease in Gram-negative bacilli on the foot and calf skin surface. Simultaneously, decreased prevalence of Gram-positive cocci and Gram-negative bacilli isolates was seen in the deep tissues of the limb and in lymph. No resistance to penicillin and other tested antibiotics developed in isolates from the skin surface, deep tissues or lymph.

### *Treatment of Acute DLA Attacks*

All wide-spectrum antibiotics are effective in controlling acute DLA. We recommend oral 2 g amoxicillin with clavulanic acid for 3–5 days. It should be followed by administration of benzanthine penicillin in a regimen analogous to that for chronic DLA.

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