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16.1 Introduction

Infection in lower limb oedema is a common entity. While an often unnoticed cutaneous barrier disruption in an oedematous limb is the initiation point of entry for pathogens causing infections, uncontrolled infections can result in limb loss and morbidity. In this chapter, we briefly summarize the recent insights into the microbiological aspects of infection, the diagnostic strategies, choices of antibiotics for early management and treatment and preventive approaches in form of non-pharmacological measures. Finally, we also discuss the challenges in management of such infections from the perspectives of developing countries.

16.2 Mechanisms of Infection in Lower Limb Oedema

In all tissues, passive fluid exchange between capillary microcirculation and the interstitial fluid is governed by Starling's principle of fluid exchange [1]. The 4 Starling forces namely Capillary hydrostatic pressure (P_c), Interstitial hydrostatic pressure (P_i), Capillary oncotic pressure (Π_c) and Interstitial oncotic pressure (Π_i) maintain a perfect balance in fluid exchange thus protecting against oedema formation. Any oedema, whatever might be the aetiology, is caused due to overwhelming capillary filtration in comparison to lymphatic drainage over a sufficient period of time. The physiological mechanism has been shown in Fig. 16.1.

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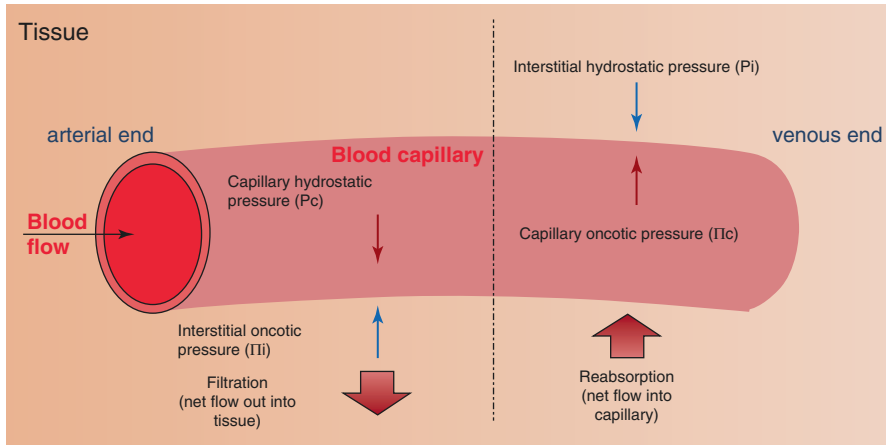


Fig. 16.1 Physiology of fluid exchange across capillary walls

The most commonly encountered types of leg oedema are venous oedema and lymphoedema [2]. While venous oedema due to venous insufficiency consists of low viscosity interstitial fluid which is poor in proteins ultimately leading to increased capillary filtration beyond the capacity of lymphatic drainage, lymphoedema on the other hand consists of protein-rich interstitial fluid [2]. This protein-rich or depleted stagnant fluid along with a state of local immune deficiency provides an excellent media for growth of microorganisms [3]. Additionally, lymphoedema in infected areas also impedes the action of antibiotics or action of phagocytes for the effective clearing of the pathogens [4].

The skin constitutes the first anatomical barrier that mechanically prevents entry of any microbes. There are several epidermal, dermal and subcutaneous protective factors in intact healthy skin. Among the prominent epidermal factors are also included the tightly linked corneocytes with a high rate of bacterial shedding and modulation of local immunity by the skin commensals [5]. Any breach in the skin due to underlying oedema can lead to dire consequences. These areas of broken skin are often the 'entry lesions' serving as potential sources of infection. Per se lower limb oedema does not itself cause infection but it probably facilitates its development by impairing local defence mechanisms.

16.3 Types of Infections and Microbiological Aspects

Along with the progression of oedema, changes in the overlying skin appear due to alterations in perfusion of the skin and in the levels of nutrients. The changes initially manifest as dry, flaky skin with a loss in elasticity. Hyperkeratosis and papilloma soon follow which later lead to blistering and 'weeping legs' [6]. Disruption of the cutaneous barrier results in acute bacterial cellulitis predominantly having a unilateral presentation. Cellulitis is an inflammatory condition of the skin and

subcutaneous tissue, characterized by erythema, swelling, warmth and pain as hallmark presentations [7]. The aetiological agents are most often Gram-positive cocci namely *Streptococcus pyogenes* and *Staphylococcus aureus*, followed by non-group A β -haemolytic streptococci and Gram-negative bacilli. Among the Gram-negative bacilli, members of *Enterobacteriaceae* family along with *Pseudomonas* species often colonize infected areas thus causing delayed healing. In association with anaerobes, these organisms like *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter*, are often present in wounds, especially associated with diabetes [8]. In cases of exposure to animal bites, rare organisms like *Pasteurella* and *Capnocytophaga* could be the probable cause, while infections following exposure of broken skin to brackish or fresh water are often associated with *Vibrio* species and *Aeromonas* species, respectively [5, 9]. Cellulitis is a known medical emergency, the severity of which differs from mild to severe infections with life-threatening consequences. Although dermatophytes do not cause cellulitis, they lead to scaling and fissure formation and by disruption of the skin provide a niche for bacteria facilitating their entry into the body. Tinea pedis often promotes the initiation of infection in an oedematous limb [10].

Erysipelas, a subtype of cellulitis with erythema is characterized by well-demarcated sharp palpable edges along with fever. Once thought to be only of streptococcal aetiology, there is growing evidence now that there is extensive overlap between these two entities. Consequently, these two conditions are preferably grouped together as skin and soft tissue infections (SSTIs) [5].

Cellulitis can progress as rapidly spreading erythema and severe sepsis along with excruciating pain, the condition known as necrotizing fasciitis [1]. This presentation commonly proceeds faster in the elderly and immunosuppressed patients with compromised skin elasticity and nutritional factors. Besides Group A streptococci which is often associated with the development of necrotizing fasciitis, a mixed group of organisms comprising Gram-negative bacilli and anaerobes are also involved [9]. Realizing the urgency to diagnose necrotizing fasciitis immediately in order to prevent devastating effects, one should be prompt in identifying the condition early. Some of the clinical features that hint towards the condition in comparison to simple cellulitis have been summarized in Table 16.1 [11]. Besides, a laboratory risk indicator for necrotizing fasciitis (LRINEC) is based on estimation of C-reactive protein (CRP), white blood cell counts (WBC), haemoglobin, sodium, creatinine and glucose. Magnetic resonance imaging (MRI) along with LRINEC have often been used to distinguish cellulitis from necrotizing fasciitis. However, clinical suspicion and prompt medication or surgical exploration is superior [5].

Table 16.1 Clinical features suggesting early suspicion of necrotizing fasciitis

| Features | Findings |
|------------------|---|
| Symptoms | High fever, altered sensorium, lethargy, disproportionate pain |
| Signs | Hypotension, tachycardia, pallor |
| Limb examination | Watery discharge, crepitus, aggravated oedema, hypoesthesia of underlying skin, areas of normal skin surrounded by infection. |

16.4 Risk Factors for Infection in Lower Limb Oedema

A systematic review on the risk factors, complications and predictors of complications of lower limb cellulitis in Africa over more than 30 years revealed that obesity was the only general risk factor [10]. Among the local risk factors, a break in the continuity of the skin barrier, chronic wounds, use of depigmentation drugs in addition to lower limb oedema or lymphedema were reported. Complications in infections were associated with nicotine addiction, chronic non-steroidal anti-inflammatory drugs (NSAIDs) use, delay in initiation of antibiotic therapy and increased erythrocyte sedimentation rate (ESR). Skin depigmentation products contain potent corticosteroids, prolonged use of which cause fragile skin with huge propensity to break. This in turn promotes penetration and colonization with pathogenic organisms. Over-the-counter use of inappropriate antibiotics especially in developing countries is also one of the most challenging issue for early diagnosis and treatment of infections [11]. Comorbid conditions like diabetes mellitus, peripheral arterial diseases, venous insufficiency and chronic tinea pedis increase the risk of developing cellulitis. Fungal infections in the toe webs, i.e. toe web dermatophytosis is also a common risk factor. In another study in 647 patients with lower limb infection, 77% had barrier defects the commonest being fungal infections [12]. It has been usually seen that a quarter of lymphoedema patients develop at least one episode of cellulitis or skin-related infections.

Development of cellulitis and lymphoedema is a vicious cycle each complementing one another for further damage. This vicious cycle is often multifactorial and unrelated to the primary aetiology of the infection. Early detection of the microbiological agent responsible for infection helps in deciding appropriate antibiotic therapy [4]. However, diagnosing cellulitis in lower limb oedema in early stages of infection is of low value by the commonly employed microbiological methods. While intact skin swabs are of no value, advanced ulcers and erosions often reveal colonization of wounds rather than the actual pathogen. In initial phases of cellulitis, blood cultures are of limited value as there is no overt bacteraemia unless the infection spreads as necrotizing fasciitis. It has been seen that blood cultures are positive in only 10% of the cases while swab culture is positive in only 30% of the cases [13]. Another study revealed that 31% of patients with cellulitis who were hospitalized were misdiagnosed [14].

16.5 Non-pharmacological Preventive Care for Protection Against Infection

Intensive self-care alone may significantly decrease the progression to infection. Majority of the studies on effectiveness of various antibiotic regimens have finally concluded that good foot care aids in decreasing infections in lower limb oedema [3]. Preventive approaches should encompass skincare, exudate management, care of wounds at initial stages and compression therapy. In this regard, the International

Table 16.2 Non-pharmacological measures for infection prevention in lower limb oedema

| Skin changes | Non-pharmacological measures |
|--|---|
| Early stages of oedema that reduce on limb elevation Presence of varicose veins | Class 1 or 2 compression garments Skincare Emollients Simple exercises |
| Dermatitis with skin discoloration and occasional skin breaks | As above Limb elevation and short walks |
| Wounds with ulcerations and exudates | All above Full leg compression garments |
| Skin thickening with pigmentation and associated changes in limb shape | Full leg compression bandaging followed by class 2 or 3 compression garments Manual drainage by simple massage Skincare Emollients Limb elevation exercises |
| Dry, flaky hardened and fragile skin with skin folds due to prolonged oedema | All above |

Lymphedema framework emphasizes the importance of lifelong treatment in cases of lower limb oedema with special importance of compression therapy and patient's own foot care education and enthusiasm [6]. The various non-pharmacological measures based on skin changes have been summarized in Table 16.2.

16.5.1 Skin Care

Care for one's skin is the pivot in the prevention of infection in all patients with chronic lower limb oedema irrespective of aetiology. Patients should pay attention to skin integrity and inspect daily for any areas of irritation or inflammation, drying, cracks, blistering or increased localized temperature [3]. Skincare consists of three main key components, i.e. cleansing, drying and moisturizing. Frequent washing of the limb, at least thrice weekly, is important for the removal of all the likely sources of infection like the dead cells of the skin, the assembly of emollients and the colonizing microorganisms. Normal soap can make the skin dry and disrupt the acidic mantle of the skin. To prevent this, a pH-neutral cleanser or emollient can be used instead of soap [15]. If a wound is present, it needs proper caring and regular dressing. Make sure all of the limb is cleaned, not just the skin around the wound. Wound cleansing is important to maintain a healthy wound bed to optimize the chance of wound closure. Skin folds and web spaces should be specially cared for and ensured for complete dryness after cleaning as these are often the sites for fungal infections. Emollients should be applied along with the direction of the hair growth to prevent skin desquamation. Nail care is equally important to avoid scratches and infections from nails.

16.5.2 Manual Oedema Mobilization

Besides skincare, additional steps like belly breathing, light lymphatic massages, exercises involving elevation of limbs and compression garments should be considered. These help in improving lymphatic flow and clearance of fluid from tissues, improving venous return, reducing limb volumes and weight and increasing the range of movements. Infected areas should not be massaged as it helps in spread of infection [16].

Manual lymphatic drainage (MLD) is a type of specialized massage aimed at encouraging the flow of lymph around the body [17]. It can be useful to ease congestion and reduce limb volume in the intensive/decongestion phase of treatment. It helps to move extra lymph fluid from the tissues of the affected area so it can drain normally. It is usually used in conjunction with compression bandaging or hosiery to improve the efficacy of these treatments. Based on the initial skin changes, the following protective measures should be adopted at the earliest in order to prevent widespread infections [18, 19].

16.5.3 Compression Therapy

It is used to deliver external pressure to the limb so that on contraction of the calf-muscle pump, blood and lymph within the limb are squeezed from the tissue back into the circulation via the lymphatics [20]. It can be applied using bandaging, hosiery or wraps and should be applied in a graduated way, with pressure that is greatest at the ankle gradually decreasing towards the knee, with further reduction to the thigh if compression is applied to the full length of the leg. This graduation allows the venous blood to be pushed back up from the leg towards the heart [21]. Recently a single-centre, randomized, non-blinded trial, involving cases with chronic oedema of the leg and recurrent cellulitis in a 1:1 ratio compared leg the effects of compression therapy plus education (compression group) and education alone (control group) on cellulitis prevention. The study revealed that compression therapy resulted in a lower incidence of recurrence of cellulitis than conservative treatment [22].

16.5.4 Wound Care

Patient's skin condition and the effectiveness of the skincare regimen which is being followed should be monitored and assessed at regular intervals. Failure to do so might give rise to complications like leakage of lymph fluid through the skin in form of lymphorrhoea and recurrent cellulitis. Once cellulitis steps in and is diagnosed, prompt management is of utmost importance to prevent devastating complications. Such type of skin is more prone to infections and mechanical damage thus causing immense pain. In such painful situations, compression therapy should be temporarily discontinued. Once pain becomes less and bearable, therapy should be resumed

to control oedema and prevent any further complications. The choices for treatment of cellulitis with oral antibiotics in mild cases and with intravenous antibiotics in severe cases have been discussed in later part of the chapter. Once cellulitis develops, risk of recurrent episodes of infections increases which can amount to repeated admissions in the hospital and its consequences associated with increasing economic burden for the patient [23, 24]. As repeated episodes of infections is a common entity accounting for nearly 2–3% of all hospital admissions [25]. It is a priority for the patient and the caregivers to break this vicious cycle of recurrent episodes of infection by adopting proper measures for skincare and being prompt for any breach in the continuity of the skin.

16.5.5 Lymphorrhoea

Lymphorrhoea is commonly perceived as ‘wet leaky legs’. This entity is often mismanaged in the community due to lack of awareness on the causes responsible for the condition. In simple terms, cleaning up the leaking fluid is of immediate and utmost importance rather than trying to treat the underlying cause first. A better management approach is using compression therapy. If left untreated, the loss of fluid can be severe enough to debilitate the patient and he/she might be forced to use plastic bags and soaking incontinence pads to absorb the leaking fluid. Therefore, compression therapy is perhaps the only way to resolve this condition. Compression therapy in form of short-stretch compression bandaging can be used. Lymphorrhoea usually gets controlled once oedema reduces with compression therapy [26].

16.6 Management Protocol for Infection in Lower Limb Oedema

Management of infection in the vulnerable population is definitely laborious and time consuming. Therefore, it is very important to educate, counsel and encourage patients themselves for their own care as there has been evidence that this ultimately improves their outcomes [27]. The management protocol for infection prevention and treatment has been summarized in Fig. 16.2 a, b [28].

16.7 Antibiotic Therapy

Antibiotics should not be routinely used to treat the lower limb swelling until there is evidence of infection. Appropriate antibiotic therapy is essential for effective control of infections at early stages. Role of both empirical and target directed therapy should be kept in mind while prescribing antibiotics for infections. While there is no controversy on indications of antibiotics for acute episodes of cellulitis in lower limb oedema, opinions vary on the use of prophylactic low-dose antibiotics for prevention of recurrence [9]. However, recurrence in cellulitis is common and is most

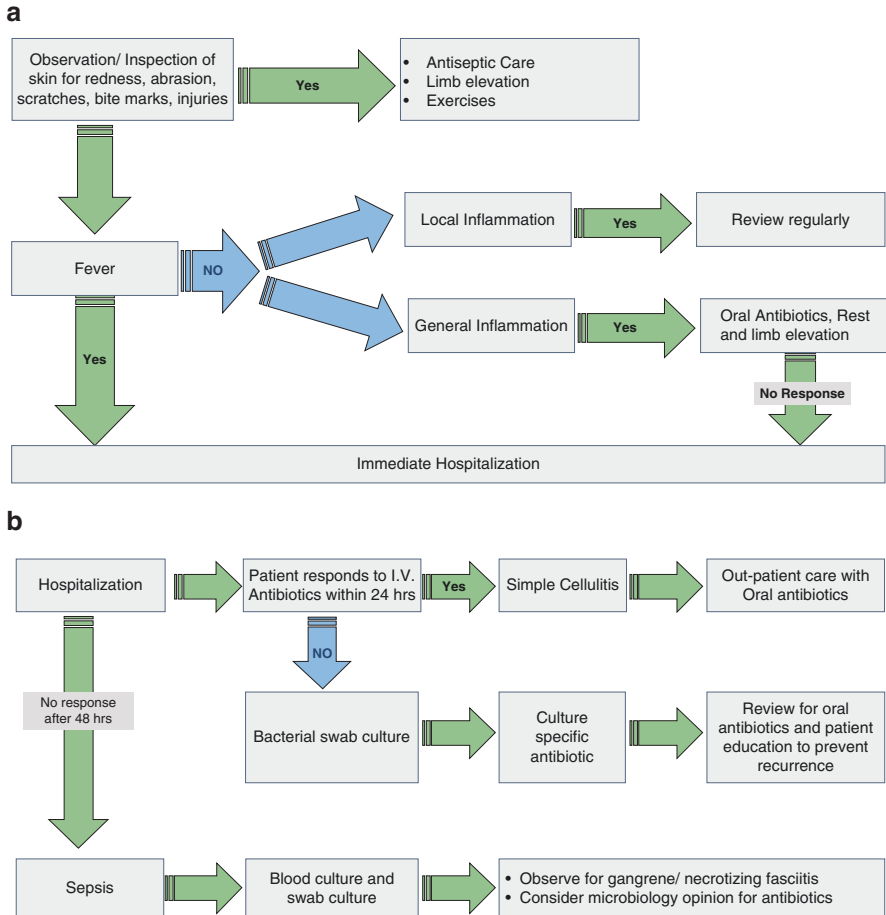


Fig. 16.2 Protocol for management of infection (a) prior to hospitalization and (b) after hospitalization

commonly caused by the *Streptococcus pyogenes*. Approximately 30% of admissions of cellulitis cases are for recurrent ones [29]. The recurrence rates progressively increase with time after the first episode of cellulitis [5]. Therefore, standard guidelines and randomized control trials provide guidance for appropriate antimicrobial therapy and prophylaxis. Of note, is the PATCH study conducted from June 2006 to January 2010, prior to which there were only a handful of studies inconclusive for prophylactic use of antibiotics in cases of lower limb oedema.

Majority of the studies have revealed the predominance of *Streptococcus pyogenes* and *Staphylococcus aureus* in these infections. Among other causes, *Streptococcus pneumoniae*, *Haemophilus influenzae*, Gram-negative bacilli and anaerobes are also responsible [30]. Therefore, the choice of antibiotic for prophylaxis should be based on the recent microbiological aetiology of the infection. Choice of the same antibiotic for both treatment and prophylaxis should be avoided.

The major recommendations from few of the listed trials and guidelines have been mentioned followed by the preferred choice of antibiotics in Tables 16.3 and 16.4, respectively [7, 30, 31].

While most of the international bodies from developed countries advocate the above choice of antibiotics, situations in developing countries are worrisome, which are often marked by the burden of multi-drug resistant pathogens. In this aspect, the Indian Council of Medical Research [11] has developed treatment guidelines on common syndrome approach in recognition with the problem of antimicrobial resistance. As per these guidelines following are the choice of antibiotics usually employed in regions of probability of infections with drug-resistant pathogens [11] as mentioned in Table 16.5.

Table 16.3 Recommendations for antibiotic prophylaxis in cellulitis

| Name of the trial/body | Major inferences/guidelines |
|------------------------|---|
| CREST | Recommended antibiotic prophylaxis for 1–2 years in patients with predisposing conditions who have had at least 2 episodes of cellulitis. |
| PATCH | Following first episode or recurrent cellulitis of lower limb, prophylactic low dose penicillin is effective and cost effective in preventing subsequent attacks. |
| NICE | Provided the choice of antibiotics for treatment and prophylaxis. |

Table 16.4 Choice of antibiotics based on international guidelines

| Indications | Antibiotics |
|-------------------------|--|
| Treatment of cellulitis | Flucloxacillin oral 500 mg 4 times daily for 7 days If not oral Flucloxacillin IV 2 gm 4 times daily, review after 48 h If allergic to penicillin Clarithromycin/Erythromycin oral 500 mg 4 times daily for 7 days |
| Prophylaxis | Phenoxymethyl penicillin 250 mg twice daily If allergic to penicillin Clarithromycin/Erythromycin oral 250 mg twice daily |

Table 16.5 Choice of antibiotics in infections with drug-resistant pathogens

| Indications | Antibiotics |
|-------------------------|--|
| Treatment of cellulitis | Cefazolin/cephalexin/amoxicillin-clavulanate +/- clindamycin for 7 days Doses: Cefazolin 1–2 g IV/8 hrly Cephalexin 750 mg BD, 500 mg TID Amoxicillin-clavulanate 1gm BD oral, 1.2 gm IV TDS Clindamycin 600–900 mg IV/8 hrly |
| Necrotizing fasciitis | Piperacillin-tazobactam +/- clindamycin for 14 days Ciprofloxacin + doxycycline for 14 days if <i>Aeromonas/Vibrio</i> spp. suspected Doses: Piperacillin-tazobactam (4.5 gm IV/ 6 hrly) + clindamycin (600 mg IV TDS) Ciprofloxacin 750 mg IV BD Doxycycline: 200 mg IV stat followed by 100 mg 1-0-1 |

16.8 State of the Art in Developing Countries

Developing countries like India are often challenged with the dual problem of unhygienic living conditions often promoting infections and the burden of multidrug-resistant organisms causing infection. Adding to this is the epidemiologic transition in the burden of non-communicable diseases from infectious diseases in most of the developing countries [19]. On one hand, among the major causes of limb oedema, the incidence of filariasis in India is on the decline. On the other hand, India has become the epicentre of many of the comorbid conditions like diabetes, hypertension and associated chronic kidney and liver diseases. Consequently, the challenges of addressing the management and effective control of lower limb oedema have also increased. Poor living conditions, lack of basic amenities, increased levels of malnourishment and undernourishment, inadequate health care facilities and above all lack of awareness and patient education have made infections in vulnerable patients a common entity.

Several cultural practices like walking barefoot, intake of raw salt with meals also compromise personal care. It should be emphasized that in this regard certain traditional practices definitely have a positive impact towards prevention of infection in these cases. While walking barefoot definitely predisposes to infection and provides an easy entry point for invasion by microorganisms, it should be acknowledged that on the contrary it facilitates better control of the foot position on striking the ground, improves balance, proprioception and muscle strength and develops better foot mechanics [32]. Similarly, integrative approaches involving dermatology therapy coupled with Indian medicine and a set of yoga exercises often addresses the issue of infection and lower limb oedema simultaneously in a much better way [33]. Whatever might be the situation, successful control of infection in any case of lower limb oedema can be done with an appropriate combination of self-care by the patient based on his/her training, education and a dedicated professional team.

16.9 Challenges and Future Directions

Despite considerable progress in our understanding and management of infection in lower limb oedema, several gaps in knowledge exist that require special attention and more scientific evidence. Our understanding of pathophysiology of infections in these cases with respect to skin microbiome alterations should be revealed for better care. While there have been studies revealing that skin commensals can affect the composition of the local microbiome and alter local immunity [34], further studies should clarify the relationships between the microbiome and infections. While microbiological diagnosis of infections is still challenging owing to lack of adequate resources and opinions on the methodologies in practice, exact causes of recurrent infections are not yet established. There has been no universal agreement on effective antibiotic regimens, the preferred antibiotics and the optimal duration of treatment in cases of cellulitis. Studies evaluating the effects of several of the

newer regimens on treatment costs and hospitalizations should also be prioritized. The exact role of compression therapy is still debatable. However, there is enough evidence that successful control of infections in lower limb oedema requires a multidisciplinary team of expert physiotherapists, dieticians, specialized nurses, occupational therapists and psychologists to tackle these challenges.

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