

Lymphoedema and cellulitis: A narrative review

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ABSTRACT

The human lymphatic system is an integral part of homeostasis, as it serves to drain excess fluid from the tissues while acting as a roadway for the cells of the immune system. In lymphoedema, these roadways become blocked, preventing the fluid from being drained, resulting in swelling in the area distal to the blockage.

One of the side effects of lymphoedema is the increased prevalence of cellulitis infections in the affected areas due to the disruption of the immune pathways. A review was undertaken with the goal of establishing the methods and timelines of treatment. As a corollary, the literature was examined with an interest in methicillin-resistant *Staphylococcus aureus* (MRSA) infections and whether treatment methods differed for those infections. A total of 34 studies were examined, and showed that beta-lactam antibiotics with activity against penicillinase are used to treat acute cellulitis and phenoxymethyl penicillin is used prophylactically to prevent further infections. However, limited information was available regarding both the duration of treatment, as well as the effectiveness of treatment for MRSA infections in patients with lymphoedema. This review aims to establish areas of potential research and set the groundwork for future studies on cellulitis occurring in conjunction with lymphoedema.

Keywords: Lymphatic, lymphoedema, cellulitis, MRSA.

LYMPHOEDEMA PATHOLOGY

Lymphoedema is a pathology that embodies an excess collection of protein-filled fluid in the tissue of a localised part of the body, usually in one or more limbs, although its effects can manifest in other organs. The over-abundance of fluid stems from an imbalance between the demand for lymphatic flow and the capacity of the lymphatic circulation¹. Lymphoedema differs from other oedemas as the limitation stems from damage to the lymphatic system due to congenital or acquired defects in lymphatic drainage². It has traditionally been seen as incurable and debilitating³. Although treatment methods do exist, it poses long-term physical and psychological difficulties that often accompany a significant change to quality of life and a complex therapeutic treatment regime².

Lymphoedema can be due to an intrinsic, possibly genetic, fault within the lymphatic system (primary lymphoedema), or due to an acquired condition caused by damage or compromise to an individual's existing lymphatic system (secondary lymphoedema)⁴.

For example, a frequent cause of secondary lymphoedema is the surgical removal of lymph nodes and radiation during breast cancer treatment. Both processes damage the lymphatic circulation and lead to lymphoedema^{5,6}.

The mechanical obstruction following surgical procedures, as well as other kinds of lymphatic compromise, can result in outflow resistance and a rise in lymphatic pressure. This increased pressure can also cause lymphatic valve compromise⁴. The lymphatic system functions via a negative pressure system that is aided by valves and muscle pump pressures from surrounding tissue contraction, similar to the veins of the lower leg⁷. Valvular incompetence can lead to lymph backflow towards the skin⁴.

After the swelling develops, the disease tends to stay in a steady state for months to years, with fluctuations and deteriorations in the severity determined by environmental, treatment, and pathological influences. Trauma and infection both lead to increased swelling and an increased severity of the illness⁸. This swelling in the interstitium also leads to the disruption of nutrient distribution in the cells, inhibiting natural wound healing from taking place⁹.

While infection is often a complicating factor in existing lymphoedema, it can also be the cause of onset. While the majority of lymphoedema occurs as a result of cancer treatment, it can also arise due to infection inhibiting lymph drainage⁴. Cellulitis can cause lymph inflammation, and recurrent infection can lead to lymphatic pathology if the lymph tissue is damaged¹⁰. The worsening progression of lymphoedema due to infection also occurs as the release of inflammatory mediators

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causes increased fluid to accumulate in the tissue that results in a subsequent increase in demand on the lymphatic system⁶.

The treatment for lymphoedema is referred to as complete decongestive therapy (CDT). The treatment is defined by two phases: the treatment phase and the maintenance phase. The treatment phase consists of therapeutic exercises, skin and nail care in order to prevent abrasions and infections, limb compression using bandages that are repetitively applied, and manual lymph drainage (MLD): a massage technique used to aid the clearance of lymph through lymphatic vessels³. The maintenance phase consists of compression garments, exercises, and self-manual lymph drainage, used to conserve and clear fluid gained from the treatment phase of CDT¹¹. The treatments function by decreasing overall limb volume and symptoms, and increasing quality of life¹².

With treatment, the severity of the symptoms of lymphoedema can be controlled in the majority of patients¹³. Patients who are unsuccessful with the above treatments can also resort to surgical options such as lipectomy, the surgical removal of fatty tissue, although the long-term success for these treatments is still unclear^{8,14,15}. Techniques to repair the damaged lymphatics themselves are yet unrefined.

Treatment for the reduction of fluid or accumulated tissue associated with lymphoedema will not be examined further in this review.

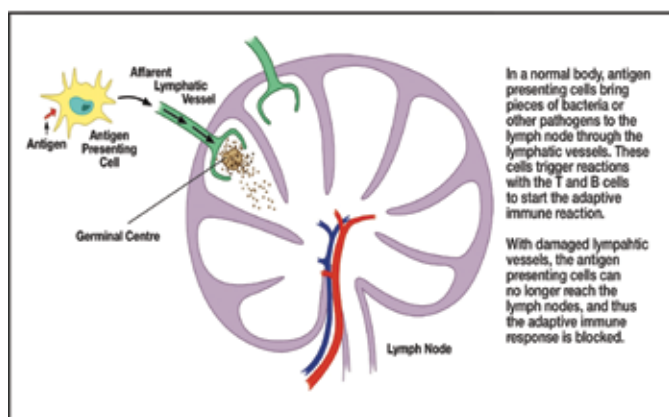


Figure 1: The lymphatic system and its role in the immune system

LYMPHOEDEMA AND INFECTION

Lymphoedema has long been linked with cellulitis, erysipelas (infection of the upper dermis), and lymphangitis and infection is considered one of the major problems associated with the condition^{8,16,17}. An increased risk of cellulitis is linked to skin trauma and tinea pedis, both factors associated with lymphoedema. Other specific predisposing factors for cellulitis are lymphatic obstruction due to surgery for breast and pelvic lymph node dissection¹⁰.

The literature on lymphoedema resulting from breast cancer shows that cellulitis is a common effect following lymphoedema brought on by breast cancer treatment, with differing treatments resulting in

different historical timelines for the commencement of the recurrent infections. Women who had a lumpectomy and radiation therapy were more likely to be diagnosed with cellulitis in the affected area in the first year after their therapy, while more radical treatment methods tended to delay the onset of cellulitis until after the first year⁶. The combination of history of malignancy and ipsilateral dermatitis greatly increased the likelihood of the patient suffering from recurrent cellulitis¹⁸.

The areas predisposed to infection are the ipsilateral arm and breast when lymphoedema follows treatment by radical mastectomy. Infection of the breast tissue occurs more frequently now due to the increased use of breast conservation therapy¹⁹. Increased rates of cellulitis have also been seen following radical hysterectomy and pelvic lymphadenectomy²⁰.

One of the reasons for the increased risk of infection is the increase in size of the skin layers. Hyperkeratosis and papillomatosis, conditions of skin thickening and elevation, are both linked with different stages of lymphoedema²¹. These conditions harbour microbes that produce an odour and increase the risk of infection. The ability to control the surface colonisation of bacteria and fungi is a major treatment goal of lymphoedema⁸, as infection can cause further damage to the lymphatic tissue and commence a cycle leading to recurrent infection and lymphatic damage⁹. Patients with lymphoedema have also been found to be at an increased risk of bacteraemia¹⁹.

The ability to thrive in tissues suffering from lymphoedema, as well as the compromised ability of the lymphatics to remove these bacteria, leads to an accumulation of the pathogens in the tissue. These organisms are often streptococci, but can also be staphylococci. Group A, B or G haemolytic streptococci are organisms commonly associated with lymphoedema cellulitis^{9,22,23}.

Another explanation for the increased incidence of infection in tissues affected by lymphoedema is the lymphatic system's role in the immune system. Mallon and Ryan describe the lymphatic system's role in the immune process and the result when the lymphatic system is compromised:

The lymphatics are the pathway for exit of T lymphocytes and Langerhans cells. The immunologic processes that occur in the skin need the lymphatic system to function. Macrophages and Langerhans cells leaving the skin travel in the lymphatics to lymph nodes where they are recognised and induce an immunologic response. Contact dermatitis cannot develop without the lymphatics, as cellular immunity cannot develop without lymphatics directing antigen from the skin to the lymph node. Patients with lymphoedema are prone to develop secondary infection, as the lymphatics are the normal pathway for clearance of bacteria from the interstitium⁹.

As both the process of forming a cellular immune response (the afferent pathway), as well as the process for implementing that response (the efferent pathway) are both compromised when there is significant lymphatic damage²⁴, the body's ability to control normal bacterial flora is deterred. The lymphatics are needed in order for the

Langerhans cells to present gathered antigens to the lymph nodes that then establish the immune response, as well as for the T lymphocytes to circulate and recollect from the skin^{24,25}.

Along with a decline in the body's response to bacterial and fungal pathogens, there is evidence that the body's ability to defend against tumour cells is also disrupted. Lymphoedematous limbs have been found to contain basal and squamous cell carcinomas, as well as lymphangiosarcomas. An increased prevalence of malignant tumours would be expected in a system that suffered from chronic lymphoedema due to the immune-compromising properties the condition can cause²⁴.

Cellulitis in patients with lymphoedema is treated with beta-lactam antibiotics with activity against penicillinase¹⁹, but the treatment must be given promptly or else the infection will not be significantly deterred by the drug treatment and the infection will follow a disease pattern similar to recurrences of herpes simplex²⁶. Cellulitis can also be more serious in lymphoedematous limbs due to the compromised ability of the tissue to heal itself due the poor distribution of nutrients in the affected tissues⁹. An outbreak of cellulitis would also necessitate a stop to certain oedema control therapies, like MLD and compression, in order to stop the spread of the infection as well as facilitate healing¹¹. This stop to treatment has a compounding effect of allowing more fluid to accumulate and increasing the problem that allowed the infection to arise in the first place.

All episodes of cellulitis should be treated. If patients experience three or more episodes of cellulitis in a year, it is suggested that they begin an extended period of antibiotic therapy¹¹, which is penicillin unless a staphylococcal infection is suspected. In such cases penicillinase-resistant penicillins are used. The organism responsible for the infection is not usually cultured or identified⁹.

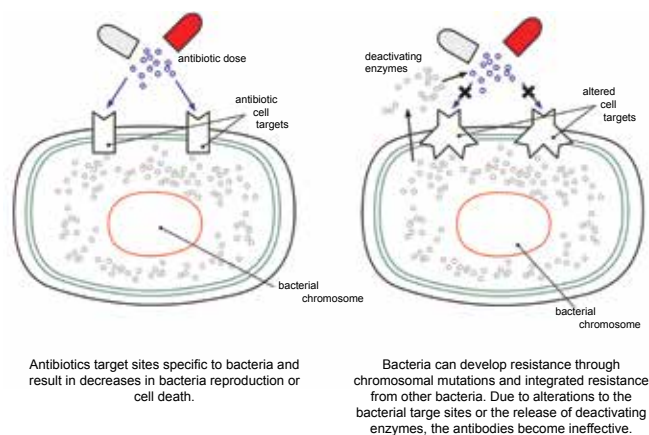


Figure 2: Antibiotics target sites specific to bacterial cells and cause decreased bacterial reproduction or cell death (left). Chromosomal mutations and integrated components of other bacteria can cause the alteration of bacterial target sites and the release of deactivating enzymes causing antibiotic resistance (right)

If the patient suffers from bouts of recurrent cellulitis, prophylactic antibiotics are used to prevent further infections and resultant damage to the tissues⁹. Along with good skin care, hygiene, oedema control and prompt treatment of any abrasions, 500 mg of phenoxymethyl penicillin given daily indefinitely has been found effective in preventing recurrences of cellulitis and helping to compensate for local immunocompromise²⁶.

While there is much published on the link between infection and lymphoedema, there is little detail about the treatment period and resources needed to fight the infection. Due to the immunocompromise found in patients with lymphoedema, the infections become more serious and more common, but there is little information about the percentage of infections that require hospitalisation for their treatment, or the duration of time it takes to resolve the infection once treatment is started. Patients with cellulitis typically begin to improve within 24 to 72 hours, where therapy is given for 5 to 10 days¹⁰. Parenteral therapy with antibiotics is usually given for one or two weeks in other patients with cellulitis who are immune-deficient²⁷. Is a similar treatment schedule expected for patients with lymphoedema?

CELLULITIS AND THE ROLE OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

The literature about lymphoedema and cellulitis caused by streptococcal and methicillin-sensitive staphylococcal bacteria is present but lacking in detail, while there is almost no mention of how patients with lymphoedema respond to strains of methicillin-resistant *Staphylococcus aureus* (MRSA).

While the most common cellulitis pathogens are from beta-haemolytic streptococci, *S. aureus* can also cause cellulitis. If the patient has purulent cellulitis and does not have a drainable abscess, the cellulitis is treated with the assumption that MRSA is the pathogen responsible for the infection¹⁰.

MRSA bacteria arose in the 1960s and are now emerging as resistant to all current antibiotic classes^{28,29}. The infections arose primarily in health care settings and spread mainly to patients already in hospital or long-term care settings. However, the bacterial strain is now present in some communities and is becoming a part of the normal flora of human beings in some populations^{30,31}.

Vancomycin is the first-line treatment for MRSA, with fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin, and minocycline being used if vancomycin is not tolerated³². However, there is concern about some strains of MRSA developing increased resistance to vancomycin as well^{29,32}, thus progressing the already ample risk posed by this bacterial strain.

In order to control the nosocomial-spread of MRSA, contact precautions are undertaken in hospital settings to slow the spread of the infection. Gowns, gloves and hand antisepsis use by care staff, and the use of topical antimicrobials on carriers have had varying degrees of success at controlling infections³³.

SUMMARY AND RECOMMENDATIONS

Due to its increasing rate in the community, as well as its rise in antibiotic resistance, MRSA has become a serious health care concern. However, there has been very little published on the possible impact an MRSA infection would have on a lymphoedema patient. Increased rates of MRSA are seen in intensive care settings and in patients with surgical wounds³⁴, which is of concern given that many lymphoedema patients are breast and pelvic cancer survivors. Also, considering the litany of health problems that lymphatic dysfunction can cause, increased hospitalisation could lead lymphoedema patients to increased exposure to the bacteria.

If MRSA continues to become more commonly found as normal flora in the community, lymphoedema patients will be at even greater risk of infection. Even in patients taking phenoxymethyl penicillin as prophylactic treatment, there would be little protection from cellulitis brought on by an MRSA infection due to its resistance to beta-lactam treatments. Considering that antibiotics given after the development of cellulitis have little effect on recovery, prophylactic methods against MRSA for lymphoedema patients may be even more important.

More research into the rate of MRSA infection in patients with lymphoedema is needed, along with comparison between severity and length of infection between lymphoedema patients and patients with healthy immune systems. The necessitation of increased contact precautions with lymphoedema patients in hospital may be necessary. If there is an increased risk of an MRSA infection for a lymphoedema patient, due to a stay in hospital or an increased prevalence of MRSA infections in their community, it is possible that the prophylactic use of antibiotics should be changed from phenoxymethyl penicillin to a drug like TMP, which is more effective at targeting methicillin-resistant strains of bacteria.

REFERENCES

- Rockson SG. Lymphedema. *Am J Med* 2001; 110(4):288–95.
- Rockson SG. Current concepts and future directions in the diagnosis and management of lymphatic vascular disease. *Vasc Med* 2010; 15(3):223–31.
- Williams A, Vadgama A, Franks P & Mortimer PS. A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema. *Eur J Cancer Care* 2002; 11(4):254–61.
- Mortimer PS. The pathophysiology of lymphedema. *Cancer* 2000; 83(S12B):2798–802.
- Petrek JA, Senie RT, Peters M & Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer* 2001; 92(6):1368–77.
- Simon MS & Cody RL. Cellulitis after axillary lymph node dissection for carcinoma of the breast. *Am J Med* 1992; 93(5):543–8.
- Skobe M & Detmar M (Eds). Structure, function, and molecular control of the skin lymphatic system. *J Invest Dermatol Symp Proc* 2000.
- Mortimer PS. Managing lymphedema. *Clin Dermatol* 1995; 13(5):499–506.
- Mallon EC & Ryan TJ. Lymphedema and wound healing. *Clin Dermatol* 1994; 12(1):89–93.
- Baddour LM. Cellulitis and erysipelas. In: UpToDate, Kaplan S & Sexton D (Eds). Waltham, MA: UpToDate, 2012.
- Mohler ER & Mondry TE. Prevention and treatment of lymphedema. In: UpToDate, Gralow JR (Ed). Waltham, MA: UpToDate, 2012.
- Warren AG, Brorson H, Borud LJ & Slavin SA. Lymphedema: A Comprehensive Review. *Ann Plast Surg* 2007; 59(4):464–72.
- Britton RC & Nelson PA. Causes and treatment of postmastectomy lymphedema of the arm: Report of 114 cases. *JAMA* 1962; 180(2):95–102.
- Eryilmaz T, Kaya B, Ozmen S & Kandal S. Suction-assisted lipectomy for treatment of lower-extremity lymphedema. *Aesthetic Plast Surg* 2009; 33(4):671–3.
- Sando WC & Nahai F. Suction lipectomy in the management of limb lymphedema. *Clin Plast Surg* 1989; 16(2):369–73.
- Overgaard ZKJ. Risk factors of arm lymphedema in breast cancer patients. *Acta Oncologica* 2000; 39(3):389–92.
- Szuba A & Rockson SG. Lymphedema: classification, diagnosis and therapy. *Vasc Med* 1998; 3(2):145–56.
- McNamara DR, Tleyjeh IM, Berbari EF *et al.* A predictive model of recurrent lower extremity cellulitis in a population-based cohort. *Arch Intern Med* 2007; 167(7):709–15.
- Swartz MN. Cellulitis. *N Engl J Med* 2004; 350(9):904–12.
- Dankert J & Bouma J. Recurrent acute leg cellulitis after hysterectomy with pelvic lymphadenectomy. *BJOG* 1987; 94(8):788–90.
- Evans AL, Brice G, Sotirova V *et al.* Mapping of Primary Congenital Lymphedema to the 5q35.3 Region. *Am J Med Genet* 1999; 64(2):547–55.
- Baddour LM & Bisno AL. Non-group a beta-hemolytic streptococcal cellulitis. Association with venous and lymphatic compromise. *Am J Med* 1985; 79(2):155–9.
- Binnick AN, Klein RB & Baughman RD. Recurrent erysipelas caused by group b streptococcus organisms. *Arch Dermatol* 1980; 116(7):798–9.
- Ryan TJ & Mallon EC. Lymphatics and the processing of antigen. *Clin Dermatol* 1995; 13(5):485–92.
- Ryan TJ, Mortimer PS & Jones RL. Lymphatics of the Skin. *Int J Dermatol* 1986; 25(7):411–9.
- Mortimer PS. Therapy Approaches for Lymphedema. *Angiology* 1997; 48(1):87–91.
- Lowy FD. Treatment of skin and soft tissue infections due to methicillin-resistant *Staphylococcus aureus* in adults. In: UpToDate, Sexton D (Ed). Waltham, MA: UpToDate, 2012.
- Chambers HF. Community-associated MRSA—resistance and virulence converge. *N Engl J Med* 2005; 352(14):1485–7.
- Enright MC, Robinson DA, Randle G, Feil EJ, Grundmann H & Spratt BG. The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA). *Proc Natl Acad Sci* 2002; 99(11):7687–92.
- Baba T, Takeuchi F, Kuroda M *et al.* Genome and virulence determinants of high virulence community-acquired MRSA. *Lancet* 2002; 359(9320):1819–27.
- Gemmell CG, Edwards DI, Fraiese AP *et al.* Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK. *J Antimicrob Chemother* 2006; 57(4):589–608.
- Lowy FD. *Staphylococcus aureus* Infections. *N Engl J Med* 1998; 339(8):520–32.
- Struelens MJ. The epidemiology of antimicrobial resistance in hospital-acquired infections: problems and possible solutions. *BMJ*. 1998; 317(7159):652–4.
- Coello R, Glynn J, Gaspar C, Picazo J & Fereres J. Risk factors for developing clinical infection with methicillin-resistant *Staphylococcus aureus* (MRSA) amongst hospital patients initially only colonized with MRSA. *J Hosp Infect* 1997; 37(1):39–46.