Original article

Delving into skin and soft tissue infections (SSTI). Part III: focus on cellulitis

ABSTRACT

In this third part of a series of articles (Part I WCET® Journal Volume 36 Number 2 – April/June 2016: PP29-34; Part II WCET® Journal Volume 37 Number 3 – July/September 2017: PP20-24) on skin and soft tissue infections (SSTI), cellulitis syndromes are explored. A case-based approach to the diagnosis and management of cellulitis for clinicians is discussed.

Keywords soft tissue infection, case-based review, cellulitis

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INTRODUCTION

Skin and soft tissue infections (SSTI) represent a spectrum of diseases, from mild superficial infection such as erysipelas and cellulitis to deep fascial infections as seen in necrotising fasciitis. The presentations vary but are common both within primary and acute care settings. The burden of SSTI is vast, with rates rising through the late 1990s–2000s, attributed to increasing age and comorbidities such as obesity[1]. However, there are no significant differences between men and women[2]. A US-based study in 2010 showed SSTI to be two-times more common than UTI and 10 times more common than pneumonia, with rates as high as 48.5 cases per 1000 person years[3]. Similarly, a study examining rates of cellulitis in the US between 1998–2013 demonstrated the rates of acute hospitalisation were nearly double, with costs totalling nearly US$3.74 billion[4]. At the same time, a challenging aspect of cellulitis and other SSTI is diagnosis, with a reliance on clinical history and physical examination. The absence of objective microbiological or laboratory testing allows for non-infectious aetiologies to be mistakenly diagnosed as SSTI. This too is costly to the system, with one study showing up to 30% of patients admitted with lower limb cellulitis were misdiagnosed, with an estimated cost of between US$195–515 million[5].

Endeavours to develop aids in the diagnosis of cellulitis have been undertaken; however, challenges remain around developing 'gold standard' diagnostics and appropriate comparators, given the heterogeneity of alternative diagnoses. A 2019 systematic review found several tools to aid in diagnosis; however, none were adequately validated for lower limb cellulitis[6].

As previously discussed, SSTI often result from minor superficial trauma to the skin barrier[7,8]. Trauma can come in the form of external damage to the skin, chronic venous insufficiency, or inflammation[4,9,10].

CELLULITIS OVERVIEW

Clinical manifestations

Cellulitis is a rapidly progressive SSTI involving the dermis and subcutaneous tissues[11]. Symptoms typically include acute

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onset redness, warmth, oedema and pain, but can occasionally include systemic symptoms such as fevers and rigours. Most commonly, cellulitis is found on the lower extremities, with rates as high as 39.9% of all cellulitis[12]. As mentioned previously, damage to the skin surface through trauma, inflammation or oedema typically precedes infection. Less commonly, cellulitis can occur due to spread of an infection from the bloodstream or a contiguous source (i.e. abscess in the fat tissue expanding outward)[2].

Numerous risk factors exist for the primary/first episode of cellulitis, including homelessness, advanced age, obesity, skin breakdown (ulcers, inflammation, trauma), oedema/lymphoedema, toe web infections (fungal, bacterial) venous insufficiency and previous venectomy among others[13]. At the same time, risk factors for recurrent cellulitis include obesity, tinea pedis, oedema/lymphoedema and venous insufficiency, but also smoking, malignancy and previous cellulitis[1]. Recurrence rates of cellulitis following a primary episode are high but ranges vary depending on the study, with some reporting ~8–20%[12] while others show between 22–49% when risk factors are present[1].

Non-necrotising and non-purulent infections rarely cause mortality[1]. However, the estimated overall mortality rate for cellulitis is reported to be 1.1%, although infection itself may only be the culprit in up to one third of cases[1,14]. The vast majority of infections are caused by *Staphylococcus aureus* and streptococci and, in one study, where microbiologic diagnoses were confirmed, these two pathogenic groups were cultured 97% of the time[13].

Several scoring systems have been developed, including the ERON[15] and the modified Dundee classification, which have been included in the UK CREST guidelines[16]. However, these criteria have not been widely adopted and have been criticised for being overly simplified or not clinically robust in distinguishing severity[11,17].

Interestingly, recent studies have shown the incidence of cellulitis can vary by season. One such study out of Denver showed a trend toward higher rates of admissions for primary cellulitis in warmer months, with July having 66.63% higher odds of infection compared to the colder winter months[18]. At the same time, a study out of southwestern Taiwan showed rates of lower extremity cellulitis increased in the days immediately following a typhoon, suggesting climates prone to floods and excessive precipitation may place occupants at risk of cellulitis with enteric, gram-negative and water-borne organisms due to exposure to contaminated water[19]. One explanation may be soaking of the extremities for prolonged periods, thus impairing natural host defence systems and facilitating a portal of entry through the skin surface[19]. Furthermore, during climate disasters, bites from animals and insects may also contribute to increased rates of infection[18].

Pathogenesis

Once superficial damage occurs to the skin surface, bacterial contamination with the patient's own skin flora can occur. This explains why staphylococcal and streptococcal species are the most prevalent organisms in cellulitis. Successful infection occurs in three steps – the bacteria must first adhere to the host's cells, then invade the tissue while evading the host's defences, and finally utilise its toxigenic factors[19]. A cytokine and neutrophil response are triggered after bacteria penetrate the skin. This epidermal response results in antimicrobial peptide production and keratinocyte proliferation, both of which induce the characteristic examination findings of cellulitis[2]. The portal of entry is not always evident, particularly as cellulitis can occur with seemingly intact skin in the context of other risk factors. In these instances, microscopic cracks occur in skin; these become irritated or inflamed, thus facilitating bacterial migration inward[20].

Clinical approach / microbiology

Cellulitis can be classified into non-purulent and purulent forms based on the clinical presentation. Non-purulent cellulitis, classically caused by streptococci, presents as a unilateral, poorly demarcated, warm and red area lacking purulent discharge or abscess. Conversely, purulent cellulitis, classically caused by staphylococci, generally develops around wounds, collections or carbuncles. In both, there is surrounding oedema and tenderness to palpation which can expand rapidly as the infection progresses. Other local features can include local necrosis and abscess formation (subsequent to cellulitis process) based on the bacterial species and infection severity.

S. aureus is more frequently associated with purulent cellulitis, although both bacterial species are capable of severe infectious features based on the virulence factors of the infecting strain. Other streptococci that are also implicated in cellulitis include Group B, C and G streptococcus – these are more common in persons with diabetes or vascular disease. As a wound becomes chronic, there is a transition of skin flora to one that is polymicrobial with colonisation by enteric gram-negatives, anaerobes or environmental pathogens. Following a similar pathogenesis, these organisms can cause infection, often in those with untreated wounds, poor circulation, or diabetic foot ulcers[21].

More atypical organisms can be involved in cellulitis, including those seen in animal bite, fresh/salt water, or aquarium exposures. These are often identified with careful history and require broader spectrum therapies which are beyond the scope of this review.

Differential diagnosis

Given the wide spectrum of dermatologic conditions, the largely subjective nature of history and physical examination, and the non-specific symptoms (i.e. tenderness, erythema, oedema) seen in the skin, cellulitis is frequently misdiagnosed[22]. Syndromes that mimic cellulitis include statis dermatitis, lipodermatosclerosis and lymphoedema; these are summarised in Table 1[22]. Stasis dermatitis is the most common mimic of cellulitis, although it tends to be slower onset and more often bilateral. However, stasis dermatitis and other mimics are risk factors for SSTI and, as such, infection should

Table 1. Characteristics of non-infectious mimics of cellulitis

Non-infectious mimic	Key features
Stasis dermatitis	• Pitting oedema (ill-defined, bilateral) concentrated in lower extremities • Erythema • Hyperpigmentation • Serous drainage • Desquamating skin
Lipodermatosclerosis	• Diameter of leg narrowed below calf, "inverted bowling pin" • Acute phase: poor demarcation, inflammation, oedema, severe lower-extremity pain, warmth and erythema • Chronic phase: defined demarcation, induration, unilateral/bilateral symmetry, sclerotic plaques bound to subcutaneous tissue, skin may appear bronze due to haemosiderin deposits, and fibrosis
Lymphoedema	• Localised oedema, induration, erythema and secondary cutaneous changes (i.e. hyperkeratosis)
Contact dermatitis	• Well-defined erythematous patches and plaques • Geometric distribution alongside irritated skin • Lesions located at site of contact or at a distant site • Chronic, un-healing leg ulcers
Papular urticaria	• Multiple urticarial papules near site of bite or large, indurated, erythematous plaques • Intense itching
Erythema nodosum	• Fever • Abdominal pain • Arthralgia • Bilateral, symmetrical, painful nodules located on extensor surfaces (knees and legs) • Oedema of the ankles
Deep vein thrombosis	• Unilateral leg swelling, pain, erythema • Occasional erythema • History of immobility, recent surgery, malignancy or trauma

remain on the differential. Lymphoedema refers to oedema resulting from abnormal lymphatic flow of any cause and presents most commonly as a unilateral non-pitting oedema. There can be associated erythema due to inflammation, but pain and warmth may not be present. Other conditions that can mimic infections include contact dermatitis and papular urticaria, both relating to a dermal sensitivity reaction to an allergen or insect bite[22]. Generally, addressing other factors such as systemic signs, laboratory tests and occasionally biopsy can assist in making a diagnosis in more challenging cases[23].

The differentiation between erysipelas and cellulitis is often challenging, but often not clinically relevant. Erysipelas, by definition, involves the superficial epidermis, whereas cellulitis involves the dermis and subcutaneous tissues[24]. Cellulitis and erysipelas both have similar clinical presentations; however, cellulitis usually presents as a flat, erythematous patch. Erysipelas, however, may be raised and tends to be more well demarcated than cellulitis, with clear margins between infected and uninfected skin[25]. Additionally, erysipelas is more classically described in the face[25]. In light skinned individuals, lesions also differ in colour, with cellulitis being more pink and erysipelas being described classically as 'salmon-red'. Clinically, both erysipelas and cellulitis are treated with similar agents and for similar duration[24].

A final important differential consideration are necrotising SSTI, including necrotising fasciitis. While erythematous skin changes are common to both, necrotising fasciitis tends to be exquisitely painful, beyond what the clinician would expect of the skin changes present. In contrast to cellulitis, there are often systemic symptoms, including fever, hypotension, tachycardia or altered level of consciousness, but these findings may be late in the disease process[26]. Additionally, there may be blisters, bullae, skin discolouration, crepitus (presence of gas under the skin), pain, and rapid extension of erythema within hours[26].

Therapy

The degree of clinical severity determines the type of treatment that is needed for cellulitis; a guideline detailing treatment approaches can be found elsewhere[24]. Cases of cellulitis that lack systemic signs of infection (i.e. fever, tachycardia) can be treated with an oral antimicrobial agent that is active against streptococci alone (mild cases). Moderate–severe cases may require intravenous antimicrobials initially, with a subsequent step down to oral antibiotics after a period of improvement. For severe infections, empiric coverage against methicillin-resistant *S. aureus* (MRSA) may be considered based on the location of infection, risk factors, and local MRSA prevalence. In purulent cellulitis, incision and drainage may be indicated alongside antimicrobial therapies.

Although classical descriptions exist to differentiate streptococcal and staphylococcal cellulitis, the distinctions are not generally clear and, as such, agents with activity against both are often used. For treatment, penicillins with staphylococcal activity or cephalosporins are frequently used, with the latter also used in cases of penicillin allergy – for severe reactions other classes will be considered. Clinical improvements often lag antimicrobial therapy by 24–48 hours and at times erythema can extend[27]. In these cases, it is often appropriate to continue with therapy and reassess at 72 hours, when the body's inflammatory response begins to subside. In the absence of improvement at 72 hours, the diagnosis or choice of therapy may need to be reassessed.

Prevention

As described above, recurrence is a common and costly in cellulitis, with each additional episode causing more

inflammatory damage to the lymphatic system, thus perpetuating the problem[28]. Non-pharmacological prevention options include regular moisturisation, prevention of toe-space infections (tinea pedis), weight loss, regular exercise, and lower leg compression therapy (e.g. compression stockings[29]). While there is no evidence for topical solutions to prevent cellulitis, topical antibiotic ointments have been shown to reduce infection in acute lacerations and wounds[28,30]. After initiating the non-pharmacological options above, if recurrent cellulitis remains an issue, low dose suppressive penicillin has been shown to be effective in preventing recurrent cellulitis[27].

CASE STUDIES

Case 1

Ms Lee is a 35-year-old otherwise healthy woman who presents with a 2-day history of fever, redness, pain and swelling around her left ear. There was no recent trauma or injury. There is no previous history of dermatologic ailments in the head or neck, including eczema. Physical examination reveals a fever of 38.5˚C, heart rate of 90 beats per minute, and blood pressure of 95/60 (normal). Examination of the left ear itself reveals a normal tympanic membrane with no drainage or lesions. There is marked erythema and induration around the left ear with tender pre-auricular nodes. Note is made of an 'ear pit' or preauricular sinus proximal to the tragus of the left ear (Figure 1).

On further questioning, Ms Lee reveals that her mother had a similar sinus which became infected in her 30s and required surgical removal. Ms Lee is initiated on cefazolin 2g IV every 8 hours for 72 hours via home parenteral pump after which she has a 40% improvement. She is stepped down to cephalexin 500mg PO four times daily for 4 days to complete a total 7-day course. She is also referred to the otolaryngology service for consideration of surgical removal of the sinus once her symptoms are resolved.

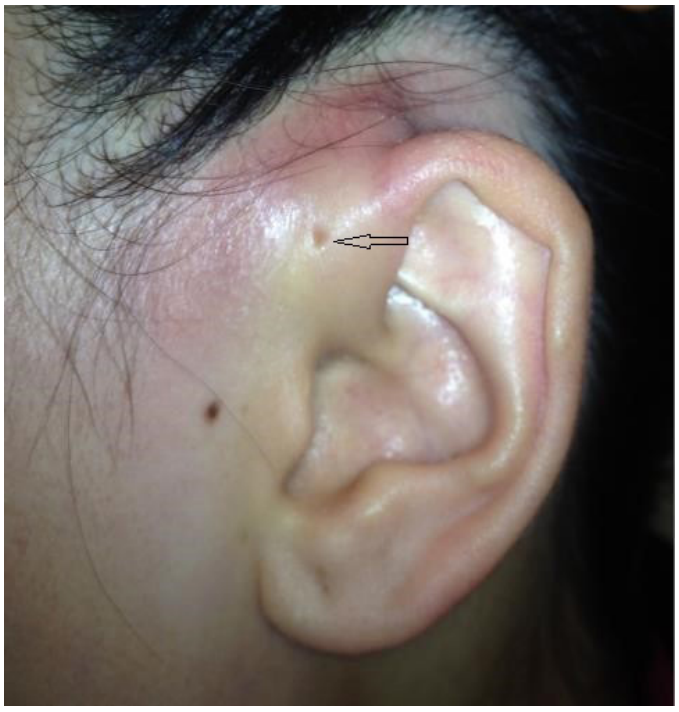

Figure 1. Case study 1.

In case 1, we see an atypical presentation of cellulitis of the outer ear, with the likely risk factor being the anatomical variant described. Therapy targeting staphylococci and streptococci yield clinical improvement. To prevent recurrence, surgical consultation and intervention may be required.

Case 2

Mr Brown is a 56-year-old businessman with no past medical history and no obesity. He presents to the emergency department with a 48-hour history of swollen, erythematous and painful left lower leg after a month-long trip to Turkey. He has just returned home after an >8-hour flight. Pain began prior to the flight but has worsened in recent days. In the emergency department he is mildly tachycardic (HR105), normotensive and afebrile. Other haemodynamic markers are within normal limits. His blood work demonstrates a white blood cell count of 16,000 with elevated CRP. Other laboratorial parameters are within normal limits. A doppler ultrasound of the left leg rules out deep vein thrombosis.

There is no preceding trauma or injury, and no apparent risk factors for cellulitis. The ED physician makes a diagnosis of cellulitis based on the patients presenting clinical history of a swollen, painful erythematous lower leg and exclusion of DVT. He is started on cefazolin 2g IV every 8 hours and discharged home via home parenteral pump. He is followed up in clinic and after 5 days of parenteral therapy has not improved. Treatment is broadened with anti-MRSA therapy in the form of Doxycycline and 3 days later improvement is minimal. Additional history obtained elucidates frequent swimming in pools and fresh/saltwater lakes while abroad. The decision is made to discontinue parenteral therapy at the patient's request. He is started on highly bioavailable oral ciprofloxacin for empiric gram-negative coverage in addition to the gram-positive/MRSA coverage provided by doxycycline. Five days later, the redness, erythema and swelling have reduced 80%. He completes a 7-day course of this combined therapy.

Case 2, on the other hand, introduces two unique considerations. The first is the need to rule out possible differentials, in this case deep vein thrombosis, given the history of long-haul flight. The second consideration are organisms beyond staphylococci and streptococci. As discussed, improvement with typical therapies should be seen within 72 hours. When this has not occurred, re-examining the history and differential is often important. Here, a history of multiple water exposures has been uncovered, leading the clinician to consider therapies targeting gram-negative and environmental pathogens. The ultimate improvement once on anti-gram-negative therapy confirms the diagnosis.

CONCLUSION

Cellulitis and SSTI are an increasing burden to the healthcare system world-wide, owing to the rise in age and comorbidities. Diagnosis and management present major challenges given the absence of gold standard, inter-clinician variability, and the large number of mimics. However, emerging evidence around prevention provides an unique opportunity to prevent morbidity and avoid additional healthcare costs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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