NEW TRENDS IN CELLULITIS
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ABSTRACT

Cellulitis is a severe infection of the soft tissues, with a variable aetiology from Gram-positive to Gram-negative bacteria and deep fungal infections, whose early recognition is mandatory to avoid potentially life threatening complications. Some pathogens might cause very similar clinical entities, and cellulitis differentiation at presentation towards abscess, necrotising fasciitis, and gangrene, requires expertise. Many mimics are also to be excluded, conditioning the treatment and patient’s prognosis. The dermatologist is in a lead position to avoid misdiagnosis, to evaluate the type of assessment, and address initial treatment. Besides, skin and soft tissue infections are a common reason for emergency room visits and hospital admission, lacking precise clinical definition and managed with empirical antibiotic treatments. History, physical examination and laboratory data can help characterise the severity of the disease, and the probability of complications development, mainly necrotising fasciitis. Several admittance scores have been proposed to address the emergency decisions, and guidelines for treatment proposed. The present review will focus on clinical challenges and actual open questions on cellulitis management.

Keywords: Cellulitis, skin and soft tissue infections, erysipelas, emerging pathogens, cellulitis mimics.

INTRODUCTION

Maintained Criteria for Diagnosis

Cellulitis is a severe inflammation of the dermis and hypodermis sparing the fascial planes due to an infective, generally bacterial cause. The course is usually acute, but subacute, or chronic inflammation is also possible. Presentation is common to any aetiology, characterised by an expanding area of erythema, where all signs of inflammation are expressed: redness, warmth, tenderness, and swelling. Borders are ill-defined in true cellulitis, with a typical dusky hue that might be mistaken for an accidental injury, especially when the superior maxillary region is involved (the ‘bruised cheek’ sign). The surface breaks in some points with vesicles (Figure 1) and/or pustules appearance (Figure 2), which progress to haemorrhagic bullae and necrotic tissue discharge, or adherent crusts and slough formation (escara) (Figure 3). Ascending lymphangitis might be seldom visible, especially on the internal leg surface directing towards mid-thigh (Figure 4).

Figure 1. Facial cellulitis with involvement of the superior maxillary region.
The erythematous edematous surface is partially covered with vesicles and small bullae. Margin are ill-defined.
Regional lymphadenopathy is usually constant, from mild to severe. Systemic symptoms, such as fever with chills, general malaise, usually precede the eruption and accompany the full development of the disease, which can take hours, up to a few days. Patients suffer heavy pain, with higher peripheral sensibility, and frequent paraesthesia. On the contrary, hypoaesthesia is an alarming sign of a deeper nerve involvement, which is a characteristic of necrotising fasciitis (NF) (also known as flesh-eating bacteria syndrome).\(^9\)\(^,\)\(^10\)

The origin of the infection is sometimes difficult to establish, and microbiology tests are positive in approximately a quarter of patients,\(^3\)\(^,\)\(^11\) because inflammation usually prevails on bacterial invasion and proliferation. Even a small amount of fragmented bacterial antigens released, amplified by the cytokines and lymphokines, are responsible for the massive neutrophils chemotaxis and skin infiltration. Moreover, the responsible pathogens are typically able to produce rising titres of several enzymes, such as streptolysin, deoxyribonuclease B, hyaluronidase, neuraminidase, phospholipase, which directly delivered in the deeper compartments induce degradation of the connective tissue core components, and cytoskeleton, thus, facilitating the spreading. In more aggressive forms, the release of bacterial toxins (pyrogenic exotoxin A or B) as well as synergistic effects of different bacterial species, such as \textit{S. aureus} and anaerobes, is to be suspected. Massive lipopolysaccharide release from destroyed Gram-negative bacteria might result in severe vascular injury and keratinocytes necrosis, sometimes indicated by the term haemorrhagic cellulitis.\(^12\)

A distinction in three stages has been proposed:\(^13\) the serous stage is the initial inflammatory process, which may resolve on its own or after appropriate treatment. However, this frequently develops into a suppurative phase, in which pus formation might be detected by palpation, producing the sign of fluctuation. Imaging studies are useful to reveal deep gathered abscess before clinical evidence, especially when dealing with facial and neck compartments.\(^14\)\(^-\)\(^18\) Once the pus is formed, resolution of the condition requires drainage, spontaneously through a fistulisation phase, or by means of surgical procedure.

Classification on the base of area involvement is useful, as common localised forms tend to be less severe than very diffuse forms.
A well-known diffuse and life-threatening condition for the imminent asphyxia risk is Ludwig's angina.\textsuperscript{19,20} Additional signs and symptoms may vary depending on the site of involvement. Facial cellulitis frequently occurs on the orbit, where an accurate assessment reveals impaired painful ocular movements, ptosis and proptosis of the eyelid, raised intraocular pressure, reduced or complete loss of trigeminal nerve sensation.\textsuperscript{21} In the oropharyngeal area, other alert signs suggestive of spread into cervical spaces are: altered levels of consciousness, speech alteration, difficulty breathing, dysphagia, and intense lockjaw.\textsuperscript{13}

**Laboratory Findings**

Laboratory findings usually support the infective origin, demonstrating a slight leukocytosis with neutrophilia, and augmentation of inflammatory indexes. A sudden decrease in blood count might precede a shock reaction to lipopolysaccharide release in Gram-negative infections. Exudates cultures by needle aspiration or swab are not routinely performed in logical, cost-effective management.\textsuperscript{1-5} Identification of pathogen and testing sensitivity to antibiotics is mandatory to adjust the treatment in those patients who fail to respond to treatment within 48 hours, and the further delay of performing culture at that moment might negatively affect the patient’s prognosis. Blood culture is of limited use because it is positive in a minority of cases and the isolates are usually the same as in the skin lesions.\textsuperscript{6,11,22} Swab culture of the nasopharynx is advisable to isolate occult aetiologic pathogens.\textsuperscript{23}

**Radiologic Examination**

Radiologic examination is advisable when the leg is involved to exclude subjacent osteomyelitis, and/or gas presence.\textsuperscript{16} In facial cellulitis, radiology might be useful to rule out dental pathologies, thickening of prevertebral soft tissue, displacement of the airways, or an eventual gas presence. A computed tomography (CT) scan and magnetic resonance imaging (MRI) scan provide assessment of the extent of the involvement, topographical limits, detection of abscesses, and presence of air within tissues.\textsuperscript{14-17,24-26} CT combines fast image acquisition with precise anatomical information, representing the most reliable technique for the evaluation of deep and multi-compartment lesions, detecting progression towards fasciitis, mediastinal and intracranial complications, as well as vascular complications with the contrast agent administration.\textsuperscript{15,17} MRI is time-consuming, and the main advantage over CT is the multiplanar capability, useful to better investigate the retropharyngeal space, the epidural space, infections reaching the skull base, pre and paravertebral spaces, but also complements CT in the evaluation of osteomyelitis.\textsuperscript{14,15,24} Ultrasonography is the first step of imaging a paediatric patient,\textsuperscript{27} but in adults the hypodermis infiltration blocks ultrasound aspiration,\textsuperscript{25} as well as the field-of-view limitation and poor anatomical information confines its use to superficial lesions, detecting the subcutaneous accumulation of pus and guiding aspiration or drainage.\textsuperscript{15,16,27} Invasive assessment, such as biopsy, is only seldom performed but the main histological features are: superficial and deep dermal oedema, diffuse heavy neutrophils infiltration, and vascular and lymphatic dilatation.\textsuperscript{28,29} Large numbers of bacteria are usually present and identifiable with special stains. Necrosis of epidermal keratinocytes, and red cell extravasation are variable features, while in later stages, lymphocytes and histiocytes might prevail, eventually with granulation tissue formation.

**Mortality**

Mortality of untreated patients has been recorded in 11%,\textsuperscript{30} and might occur in neglected cases, when highly virulent organisms are involved or complications arise, mainly for shock, and multiple organ failure.\textsuperscript{31} Possible systemic complications include sepsis, pneumonia, toxic syndrome, and for the head and neck compartments, also descending mediastinitis, upper airway obstruction, thrombosis of the cavernous sinus, cerebral abscess, and meningitis.\textsuperscript{15,19,53} Recurrent episodes of cellulitis are a major concern,\textsuperscript{32,33} but a population-based cohort study suggest that only 11% of patients develops a recurrence within 1 year.\textsuperscript{34} Long-term sequelae consist of scars, persistent lymphoedema, venous ulcers, and neurological alterations.

**CONSIDERATION ON EPIDEMIOLOGY AND PREDISPOSING FACTORS**

Cellulitis affects individuals of any ethnicity rather than producing epidemics, occurring in apparent healthy patients,\textsuperscript{1-6,35} facts indirectly attesting the role of predisposing individual conditions in the
development of the disease. The precise incidence of the disease is uncertain, but some American studies rated 24.6 cases per 1,000 person/year might be affected with cellulitis, covering the 37.3% of the hospitalised population.

Considering the site of involvement, lower extremities are the most frequently affected in adults, while the head and neck district is typically involved in children, and the umbilical region in neonates. Children are affected at a very young age: 7-10 months, and a history of infections is often reported in the weeks before, especially otitis media.

Research data on risk factors can be divided into two groups: factors predisposing to the development of cellulitis, and conditions influencing the severity of the disease (Table 1). In an attempt to give priority criteria, a port of entry is the first thing to search, as confirmed by published cohort and case-control studies. Complications following surgery is a major concern, especially in chronically immune-suppressed patients, in course of rheumatoid arthritis or lupus erythematosus. Concerning leg cellulitis, injuries by foreign body, puncture wound, venous insufficiency, lymphoedema, venous or pressure ulcers, bacterial intertrigo and tinea pedis, are the most frequent conditions. Occurrence in course of dental pathology is one of the most relevant causes of facial cellulitis, followed by major procedures on the head and neck, especially after traumatic, vascular, or neoplastic intervention. Previous varicella-zoster infections might provide portal of entry, as well as tattooing and body piercing. Infections can also spread from distant sites following the bloodstream and/or the lymphatic system. Being overweight is an additional risk factor, while the role of alcohol misuse, intravenous drug abuse, or smoking remain anecdotal, these are not confirmed in large series. Case-control and cohort studies have examined main recurrence associated factors, which again included venous insufficiency, local injury, obesity, lymphoedema, tinea pedis, and smoking.

Bad prognosis risk factors have not been clearly investigated in controlled studies. Observational retrospective studies suggest the role of chronic illness and bad nutritional status as risk factors for complications and mortality in skin and soft tissue infections (SSTIs). Immunodeficiency should always be suspected, either as a primary cause (HIV) or as a consequence of systemic treatment, such as corticosteroids, and cytostatics. The potentially harmful role of oral non-steroidal anti-inflammatory drugs (NSAID) is controversial as some studies suggest an increased risk of complications, inducing a relief of nonspecific symptoms, which are alarm signals of the progression from cellulitis to NF. The risk is particularly reported in children with varicella-zoster infections, for an impairment of neutrophil blood cell function induced by NSAIDs. On the contrary, another study assesses the beneficial effects of combining the antibiotic treatment with anti-inflammatory drugs, shortening the time to recover, and hospital dismissal, and accounting for an increased number of complete resolution in

Table 1. Predisposing factors.

<table>
<thead>
<tr>
<th>Predisposing to cellulitis development</th>
<th>Providing a port of entry:</th>
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<tr>
<td>• Wounds, both accidental, voluntary (tattoo, piercing) or surgical</td>
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<td>• Superficial or localised infections</td>
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<td>• Eczematous dermatitis</td>
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<th>Influencing the severity of the disease</th>
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<tr>
<td>• Infections - Sepsis</td>
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<tr>
<td>• Immunodeficiency (HIV) and immune-suppression (systemic treatments, ageing)</td>
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<td>• Vascular damage (Ischemia; venous insufficiency; lymphatic stasis)</td>
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<td>• Chronic illness (malignancies, kidney and liver insufficiency)</td>
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<td>• Obesity</td>
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<td>• Diabetes</td>
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<td>• Malnutrition, vitamins deficiency, calamities, and war conditions</td>
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<th>Controversial conditions</th>
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<td>• Alcohol misuse</td>
<td></td>
</tr>
<tr>
<td>• Intravenous drugs abuse</td>
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<td>• Tobacco smoking</td>
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Cellulitis is part of a major spectrum of diseases, clustered under the common category of SSTIs, as the same pathogens are often the cause. The unpredictable course of such infections at presentation has led to ‘unproven clinical practice’, which relies on hospital admission to close clinical monitoring, and empirical broad spectrum intravenous antibiotic treatment. In recent large observational studies, around 3% of emergency medical consultations at a UK district general hospital were due to cellulitis, and from a similar Scottish experience, about 70% of the cases could have been managed in the community. Moreover, an extraordinary variation in antibiotic regimens are prescribed worldwide, from 46 in the US to 35 in the Scottish experience, and 25 initial regimens from a computerised provincial charts audit of five Canadian Emergency Departments. Although there is clinical concern for rapid development of life-threatening conditions, careful history and clinical examination at presentation are usually sufficient to distinguish between severe and complicated conditions that require emergency admittance and uncomplicated patients who could be successfully treated as outpatients. Therefore, criteria definition update and constant clinical training improvement is to be promoted, both in primary and tertiary cares.

Current trends are to consider erysipelas (from the Greek ἐρυσίπελας—red skin) as a milder form of cellulitis rather than a distinct entity, although the term is widely accepted and well describes the peculiar presentation of this very superficial dermis infection, which consists of a bright red swelling patch, sharply demarcated from the adjacent unaffected skin. Italian literature named ‘step sign’ this typical raised border, of non-pitting oedema absent in frank cellulitis, where the soft tissue inflammation is deeper and widespread from the very beginning. The erysipelas histology hallmark involvement is confined to the superficial dermis and lymphatic, which depends on a characteristic pyogenes tropism towards lymphatics, especially the Group A Beta-haemolytic streptococcus (GAS). Nevertheless, the lymphatic involvement is also severe in all forms of cellulitis, and inflammation arising superficially might extend deeply within hours. From an anatomical point of view, dermis and subcutaneous tissues are intercommunicating spaces, the main first anatomical barrier being deep septa and fascial planes, confining the inflammation for a certain period of time, and differentiating cellulitis from NF and gangrene.

Clinical attempts to stratify SSTIs cases and provide early identification of high-risks patients include:

- Extension and Site of primary infection, distinguishing among head and hand involvement from inferior limb localisation, and a body area involvement >9% following the rule of nines. The face involvement has a higher risk of complications due to the abundance of sensitive anatomical structure.

- Eron’s Clinical Classification, adopted from the CREST guidelines, considers four classes of patients with different prognosis and management:
  - Class I: no signs of systemic toxicity, no uncontrolled comorbidities. The patient can usually be managed with oral antimicrobials on an outpatient basis.
  - Class II: history of comorbidity which may complicate or delay resolution of the infection (such as peripheral vascular disease or obesity). The patient is suitable for short-term (up to 48 hours) hospitalisation and discharge on outpatient parenteral antimicrobial therapy (OPAT), where this service is available.
  - Class III: significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension or unstable comorbidities that may
interfere with a response to therapy or limb-threatening infection due to vascular compromise.

- Class IV: patients with sepsis syndrome or severe life-threatening conditions.

Clinical severity charts adopted to predict in-hospital mortality and length of stay, such as the standardised early warning score (SEWS), based on the assessment of several parameters: respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate, and level of consciousness. A score of ≥4 requires urgent medical assistance.

The recent Scottish retrospective study pointed out the doubtful prognostic significance of co-morbidity in otherwise healthy patients (SEWS<4), and suggests that Class I and II of the CREST guidelines can be merged, indicating less severe cases, safely managed as outpatients. On the contrary, sepsis is a puzzling condition, worsening the patient’s prognosis although the vital signs are not alarming (SEWS<4), and without comorbidity. Other international experiences confirm that sepsis is the major risk factor for mortality.

**DIFFERENTIAL DIAGNOSIS**

As specific criteria for the diagnosis of cellulitis are lacking, physician’s experience is critical to point out cellulitis from the many mimics. A study conducted in an infectious disease service suggests that more than 10% of the urgent referrals for cellulitis had a final alternative diagnosis. Consultation with a dermatologist is recommended, for their visual ability in recognising different conditions, evaluating the weight of each, favouring pre-existing conditions and determining if a biopsy is necessary. A first distinction should be made among clinical conditions representing possible complications of cellulitis, usually clustered in the same SSTIs spectrum, and the many imitators of cellulitis, whose assessment and treatment might differ greatly from antibiotics.

<table>
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<th>Table 2. Cellulitis differential diagnosis in the spectrum of the skin and soft tissue infections.</th>
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<td><strong>Entity</strong></td>
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<tr>
<td>Abscess</td>
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<tr>
<td>Necrotising fasciitis</td>
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<tr>
<td>Gangrene</td>
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<tr>
<td>Erysipeloid</td>
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A: Cellulitis Differential Diagnosis in the Spectrum of SSTIs

Considering erysipelas as a mild form of cellulitis, the main common entity that should differentiate from cellulitis is the abscess, which is defined as an enclosed collection of necrotic tissue, bacteria, and inflammatory cells (pus). Nevertheless, abscess formation and fistulisation is a frequent evolution of cellulitis, especially when not adequately treated (suppurative stage). Skin necrosis may complicate conventional cellulitis, extending through the subcutaneous fat and fascial planes or may occur with distinctive clinical features, configuring the NF. The distinction is not purely anatomical, as NF represents a more severe and extensive infection that poorly responds to wide spectrum antibiotics and requires aggressive surgical treatment (fasciotomy). Cellulitis evolution towards NF might progress at a very alarming rate, usually announced by a change in skin colour from red-purple or bluish to grey, with occurrence of violaceous bullae, and areas of shiny watery malodorous fluid discharge, due to fat necrosis, while consistency becomes hard as wood on deep palpation.\(^9,10,79\) The term gangrene is also frequently used in association with cellulitis, especially in the form of gas gangrene which is synonymous with anaerobic cellulitis. Gangrene occurs primarily due to loss of blood supply, rapidly evolving to necrosis of soft tissue, muscles, and eventually bones. The infective form is usually due to a deep penetrating wound, allowing invasion and proliferation of those bacteria able to survive with little or no oxygen, such as the \textit{Clostridium} family. These ubiquitous Gram-positive bacilli found in soil and bowel flora generate gas, whose presence is advised by soft tissue crepitating at palpation.\(^80-82\)

There is another peculiar disease in the spectrum of cellulitis, called erysipeloid, from the causative Gram-positive rod \textit{Erysipelothrix rhusiopathiae}.\(^83\)

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### Table 3. Cellulitis mimickers.

<table>
<thead>
<tr>
<th>Site of involvement</th>
<th>Clinical conditions</th>
<th>Differential criteria</th>
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</thead>
<tbody>
<tr>
<td>Extremities</td>
<td>• Deep wounds</td>
<td>• Long-standing manifestations, with initial indolent course and sudden worsening.</td>
</tr>
<tr>
<td></td>
<td>• Superficial infections, especially candidal intertrigo on hands, bacterial foot intertrigo, and tinea pedis.</td>
<td>• Presence of minimal bilateral or pre-existing changes, such as pitting oedema, superficial scaling or \textit{xerosis}, hyperpigmentation, varicosities and scars.</td>
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<tr>
<td></td>
<td>• Diabetic and gangrenous foot.</td>
<td>• Bound-down plaques or inverted champagne bottle appearance.</td>
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<tr>
<td></td>
<td>• Acute gout attack and septic arthritis.</td>
<td>• Comorbidity: Obesity, diabetes, and bad nutritional state.</td>
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<tr>
<td></td>
<td>• Stasis dermatitis, chronic lymphoedema, venous insufficiency.</td>
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<td></td>
<td>• Pyoderma gangrenosum.</td>
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<tr>
<td></td>
<td>• Abscess formation and fistulisation is a frequent evolution of cellulitis, especially when not adequately treated (suppurative stage).</td>
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<tr>
<td>Cephalic involvement</td>
<td>• Recent surgical procedures on the head and neck.</td>
<td>• Skin necrosis may complicate conventional cellulitis, extending through the subcutaneous fat and fascial planes or may occur with distinctive clinical features, configuring the NF.</td>
</tr>
<tr>
<td></td>
<td>• Herpes infections, especially H. Zoster ophthalmicus.</td>
<td>The distinction is not purely anatomical, as NF represents a more severe and extensive infection that poorly responds to wide spectrum antibiotics and requires aggressive surgical treatment (fasciotomy).</td>
</tr>
<tr>
<td></td>
<td>• Chronic sinusitis, otitis, and per-orbital inflammation, dental abscesses.</td>
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<tr>
<td></td>
<td>• Urticaria angioedema.</td>
<td>Cellulitis evolution towards NF might progress at a very alarming rate, usually announced by a change in skin colour from red-purple or bluish to grey, with occurrence of violaceous bullae, and areas of shiny watery malodorous fluid discharge, due to fat necrosis, while consistency becomes hard as wood on deep palpation.(^9,10,79) The term gangrene is also frequently used in association with cellulitis, especially in the form of gas gangrene which is synonymous with anaerobic cellulitis. Gangrene occurs primarily due to loss of blood supply, rapidly evolving to necrosis of soft tissue, muscles, and eventually bones. The infective form is usually due to a deep penetrating wound, allowing invasion and proliferation of those bacteria able to survive with little or no oxygen, such as the \textit{Clostridium} family. These ubiquitous Gram-positive bacilli found in soil and bowel flora generate gas, whose presence is advised by soft tissue crepitating at palpation.(^80-82)</td>
</tr>
<tr>
<td></td>
<td>• Contact dermatitis.</td>
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<tr>
<td></td>
<td>• Carcinoma erysipeloides.</td>
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| Any or multiple sites | • Insect bites | • History of recent change in lifestyle, outdoor excursions or travel. |
|                      | • Major surgical procedures | • Malignancies, and/or immune suppression are to be considered. |
|                      | • Sweet Syndrome | • More generalised lesions with fever and malaise are suspect for a systemic inflammatory disease. |
|                      | • Well’s cellulitis | |

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It is an unusual pathology, due to the exposure to contaminated materials derived from animals or fish, configuring an occupational disease in veterinarians, meat packers, and fisherman. Clinical features are common to other bacterial cellulitis, and a biopsy at the advancing edge of the lesion, extending through the entire dermis thickness, might be performed to assess the diagnosis, stating the usually milder, self-limited course.

B: Cellulitis Mimickers

In distinguishing cellulitis from other clinical conditions one should consider the site of involvement and extension, as lower extremities and the head/neck region recognise different alternate diagnosis, while more rare entities, which include several inflammatory non-infective diseases, usually diffuse, occurring in any site of the body. Some concepts applied to all conditions: cellulitis is rarely bilateral, is rapidly progressive, with smooth, indistinctive borders, accompanied by systemic symptoms. Trauma, insect bites, surgical procedures, allergies, and contact dermatitis are common at any age, while diabetic and gangrenous foot, gout, septic arthritis, and stasis dermatitis are elderly conditions. Patients with insect bites or allergies usually complain of intense itching rather than pain, and careful anamnesis usually helps to find a recent change in lifestyle, such as outdoor excursions or travel, hobbies, previous cutaneous allergies, or recent medications. The most common reported mimickers of leg cellulitis in adults are stasis dermatitis and chronic lymphoedema, both presenting ill-defined areas of erythema and not-pitting induration, with sudden worsening and serous drainage. Patient history usually reveals a long-standing process, and although one leg is usually more affected during flares, careful observation usually depicts bilateral involvement, superficial scaling areas, pigmentation alterations, varicosities, and scars from previous ulcerative lesions, with bound-down plaques appearance. Patients are often obese, diabetic, or have a history of major trauma or surgery, such as radical lymphadenectomy for melanoma, or breast cancer when the arm is affected. Advanced skin changes, due to vascular and lymphatic compromise, cause lipodermatosclerosis, whose sudden worsening, with painful evidence of ill-defined warm erythematous-oedematous plaques is difficult to differentiate from cellulitis, which in turn might also complicate the disease at any moment. Leg observation usually reveals dark pigmentation, hyperkeratosis with wart-like buttons, and underlying sclerosing panniculitis, giving the features of an ‘inverted champagne bottle’ or ‘inverted bowling pin.’ Herpes zoster is usually recognisable for its single dermatome disposition. Chronic sinusitis, otitis and per-orbital inflammation, especially in young patients, can cause mild-to-moderate swelling of the cheek, nose, and eyelid which can be difficult to distinguish from initial signs of cellulitis. Carcinoma erysipeloides is sometimes confused with cellulitis at presentation, especially when metastasis involves the sphenoid and posterior wall of the orbit. Breast cancer is usually the primary tumour, followed by prostate, lung, and the gastrointestinal tract. Absence of fever, and a slower, more indolent course than cellulitis are distinctive features of carcinoma erysipeloides.

Diffuse not-infective cellulitis mimickers include Sweet’s syndrome (acute febrile neutrophilic dermatosis), in its acute presentation, with painful tender erythematous pseudo-vesicular plaques, accompanied by fever, general malaise, and neutrophilic leucocytosis. Pyoderma gangrenosum might also simulate cellulitis, with acute often isolated lesions starting in the subcutaneous fat, with rapid necrotic evolution or superficial diffuse lesions, on erythematous-oedematous enlarging plaques. Wells’ eosinophilic cellulitis is another great simulator, which progresses slowly with erythematous oedematous lesions with sharp borders, a green hue and central clearing. All these immune-mediated entities are corticosteroid-sensitive, and broad spectrum antibiotics will not modify progression.

EMERGING PATHOGENS AND IMPLICATION FOR TREATMENT

The vast majority of cellulitis recognised the same causative agents, responding to common wide spectrum antibiotics, but Gram-negative and polymicrobial infections as well as widespread resistance to antimicrobial agents, especially methicillin-resistant S. aureus (MRSA) have generated an increasing defensive attitude towards hospitalisation and overtreatment.
Major causative pathogens are *Staphylococcus aureus* and *Streptococcus pyogenes* (especially Group A beta-haemolytic *S. Pyogenes* (GAS)). Sporadic cases due to other Gram-positive are reported: group G, B, C, and D Streptococci. In children *S. Pneumonia* and *Haemophilus influenzae* are responsible of very severe cases. Gram-negative *Neisseria meningitidis*, *Klebsiella pneumonia*, *Yersinia enterocolitis*, *Pseudomonas aeruginosa*, *Pastorella multica* are increasingly reported, together with mixture of Gram-positive and Gram-negative bacteria, aerobes and anaerobes, especially after surgical procedures and dental pathologies.

An endodontic origin is evoked in facial *Candida albicans* cellulitis, as well as deep contamination of other body sites through incisions, drainage, and percutaneous endoscopic procedures, especially in diabetic patients. Among the rarest causes of cellulitis, *Nocardia* species and *Cryptococcus neoformans*, should be considered, both as consequence of a disseminated form or when an accidental port of entry have caused a primary skin infection. Histoplasmosis and mucormycosis might manifest with cellulitis in those countries where the infections are prevalent.

Inadequate treatment, for example in course of fungal cellulitis and selection of methicillin-resistant strains should be suspected in patients with a history of previous general antibiotic regimen, chronically immune-suppressed patients, among intravenous drug users, prisoners, male homosexuals, and HIV infected patients.

Military trainees and athletes are other apparently healthy categories in which increasing MRSA infections have been reported.

Considering microbiologic variability and clinical difficulties, it is not surprising that 'gold standard' treatment for cellulitis has not been achieved, and final choice remains empirical, based on expert consensus rather than evidence. European guidelines recommended penicillin as the initial standard treatment for simple community-acquired erysipelas and cellulitis, while coverage for MRSA should be considered in peculiar settings.

CREST guidelines recommend oral antibiotics for Class I severity infections and intravenous antibiotics for any other classes, with an initial 24-36 hours in-hospital monitoring and the opportunity to continue the therapy as outpatients, in Class II and III patients. A randomised trial comparing oral to intravenous therapy showed no outcome differences in patients without complications. Besides, the majority of studies are conducted in emergency settings, and suggest wide coverage of *Streptococcus* strains and *Staphylococcus aureus*, usually with combination of intravenous benzyl penicillin and flucloxacillin. Cephalosporins are often used alone or in association, especially intramuscular ceftriaxone. Other penicillase-resistant betalactams include dicloxacillin, nafcillin, betalactam/clavulanic acid, piperacillin/tazobactam.

For penicillin-allergic patients macrolides are recommended, mainly oral erythromycin or clindamycin, although there are no comparative data and oral azithromycin might be as well efficacious. Concomitant therapy with ciprofloxacin and metronidazole is prescribed for polimicrobial infections.

Very resistant infections are firstly treated with vancomycin, or teicoplanin, although susceptibility is decreasing for both drugs. New antibiotics includes linezolide quinupristin-dalfopristin, daptomycin, ertapenem. Initial short course of intravenous antibiotics in hospital settings and prosecution with several infusion devices and dosage adjustment as outpatient parenteral antibiotic therapy (OPAT) is an actual trend to reduce bad pressure and costs. Old (ceftrixone, teicoplanin) and new drugs (quinupristin-dalfopristin, daptomycin, ertapenem) are under evaluation.

Persistent inflammation rather than infection might be responsible for residual symptoms, mainly fever and pain, and slow skin healing, as suggested from a study showing the same results from 5-10 days treatments, and other experiences using corticosteroids and other anti-inflammatories to improve response. Concern relies on progression to NF, sepsis and metabolic aggravation, whose signs and symptoms might be masked by anti-inflammatory and analgesics. Hyperbaric oxygen therapy has been proposed in severe cases as adjuvant measure. Treatment of predisposing condition is otherwise mandatory, from metabolic compensations to chronic infections and nutritional state control.

Prophylaxis therapy in patients with more than two cellulitis episodes has not be validated, but daily oral penicillin is suggested.
CONCLUSION

Cellulitis is an emergency condition that must be handled early in any medical setting, from primary to tertiary cares. Any age can be affected, suddenly in otherwise healthy patients, although several local and general predisposing conditions might favour the occurrence. Acute complications are fortunately rare, but life-threatening. Long-term complications are recurrences and persistent lymphoedema, which further favour aggravation. Specific types of cellulitis might be tailored to microbiological findings based on cultures and drug sensitivities. Most patients recover completely after timely antibiotics, but guideline recommendations and severity evaluation are cumbersome, so that hospitalisation and overtreatment is a current issue. Clinical training is the clue to correct assessment and management of such challenging conditions.

REFERENCES

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