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.[1-5] The course is usually acute, but subacute, or chronic inflammation is also possible.[6] 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).[7,8] 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).

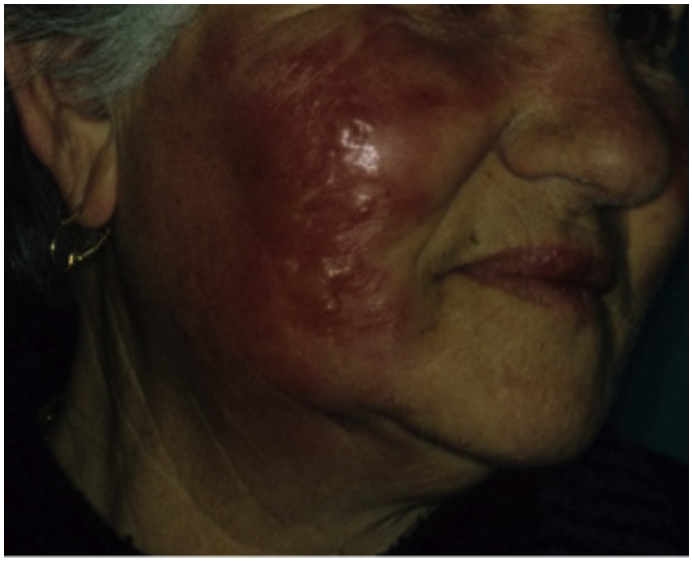

Figure 1. Facial cellulitis with involvement of the superior maxillary region.
The erythematous edematous surface is partially covered with vesicles and small bullae. Margin are ill-defined.

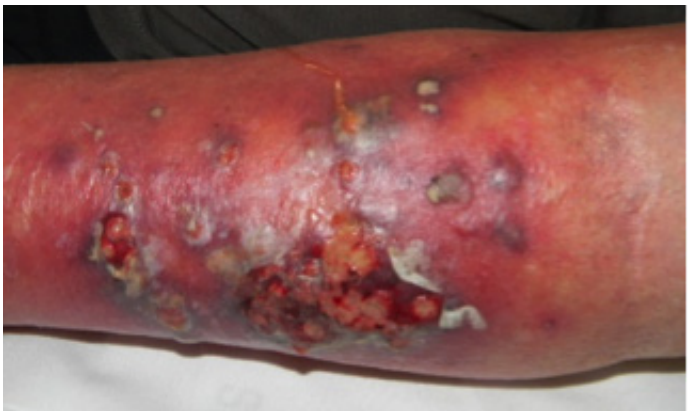

Figure 2. Severe leg cellulitis with vesicles and pustules, discharging haemorrhagic and necrotic material.

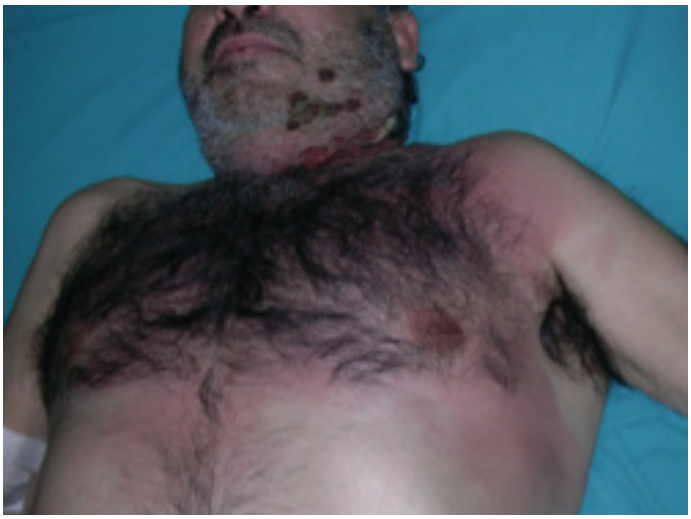

Figure 3. Rapidly progressive neck cellulitis, extending to the trunk, with crusts and slough formation (escara) in the site of primary involvement.

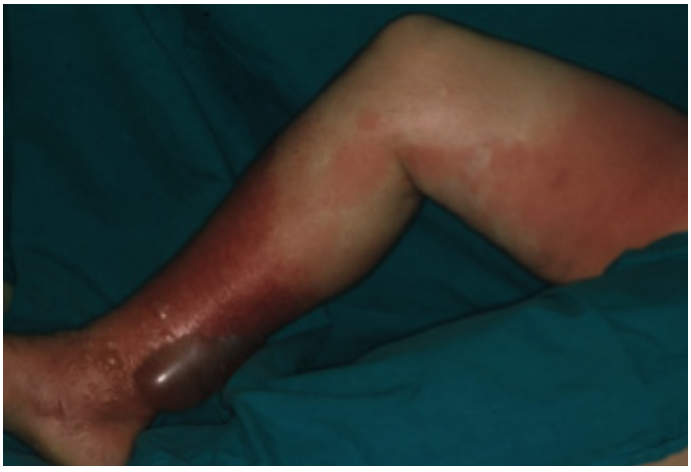

Figure 4. Leg cellulitis with large bullous lesions and visible lymphangitis.

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 *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.[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.[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.[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.[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.[6,11,22] Swab culture of the nasopharynx is advisable to isolate occult aetiologic pathogens.[23]

Radiologic Examination

Radiologic examination is advisable when the leg is involved to exclude subjacent osteomyelitis, and/or gas presence.[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.[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.[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.[14,15,24] Ultrasonography is the first step of imaging a paediatric patient,[27] but in adults the hypodermis infiltration blocks ultrasound transmission,[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.[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.[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%,[30] and might occur in neglected cases, when highly virulent organisms are involved or complications arise, mainly for shock, and multiple organ failure.[31] Possible systemic complications include septicaemia, 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.[15,19,53] Recurrent episodes of cellulitis are a major concern,[32,33] but a population-based cohort study suggest that only 11% of patients develops a recurrence within 1 year.[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,[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,[34] covering the 37.3% of the hospitalised population.[36]

Considering the site of involvement, lower extremities are the most frequently affected in adults,[36-38] while the head and neck district is typically involved in children,[7,27,39] and the umbilical region in neonates.[40] 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.[39]

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.[32,33,41-46] Complications following surgery is a major concern,[3,47,50] especially in chronically immune-suppressed patients, in course of rheumatoid arthritis or lupus erythematosus.[48,51] 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[13] 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,[52-55] as well as tattooing and body piercing.[56,57] Infections can also spread from distant sites following the bloodstream and/or the lymphatic system.[58] Being overweight is an additional risk factor,[1-3,32,47] 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.[32,34,42,45]

Bad prognosis risk factors have not been clearly investigated in controlled studies.[3] 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).[31,59] 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.[60,61] The risk is particularly reported in children with varicella-zoster infections,[62] 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.

Predisposing to cellulitis development	Providing a port of entry: • Wounds, both accidental, voluntary (tattoo, piercing) or surgical • Superficial or localised infections • Eczematous dermatitis
Influencing the severity of the disease	• Infections - Sepsis • Immunodeficiency (HIV) and immune-suppression (systemic treatments, ageing) • Vascular damage (Ischemia; venous insufficiency; lymphatic stasis) • Chronic illness (malignancies, kidney and liver insufficiency) • Obesity • Diabetes • Malnutrition, vitamins deficiency, calamities, and war conditions
Controversial conditions	• Alcohol misuse • Intravenous drugs abuse • Tobacco smoking

respect to patients treated with antibiotics alone. The rationale of the supplemental use of anti-inflammatory therapy refers to the role of the host inflammatory response on the amplification of the infectious tissue damage and cellulitis clinical manifestations development.[63] By contrast compromised host's defence and tissue functional deterioration are complications predisposing conditions frequent in diabetes, kidney and liver insufficiency, malnutrition, vitamin deficiency, as well as in course of malignancies, especially in patients exposed to chemotherapy and radiation regimen. War is an old but ever actual condition in which cellulitis might rapidly develop from wounds, but also from occult nasal infections.[24]

THE PROBLEM OF DEFINITIONS

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.[2,3,64-66] In recent large observational studies, around 3% of emergency medical consultations at a UK district general hospital were due to cellulitis,[2] 27% of the patients were hospitalised in a larger collection of cases from 56 US hospitals,[67] and from a similar Scottish experience, about 70% of the cases could have been managed in the community.[68] Moreover, an extraordinary variation in antibiotic regimens are prescribed worldwide, from 46 in the US[69] to 35 in the Scottish experience,[68] and 25 initial regimens from a computerised provincial charts audit of five Canadian Emergency Departments.[65] 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,[2-4,70] 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 wide-spread 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).[70] 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.[1-5,9,10]

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

- Extension and Site of primary infection,[71] 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,[2,72] 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.

o 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:[73,74] 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.[68] 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.[31,59,69]

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.[66,75,77] A study conducted in an infectious disease service suggests that more than 10% of the urgent referrals for cellulitis had a final alternative diagnosis.[78] Consultation with a dermatologist is recommended,[75] 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 2 and 3).

Table 2. Cellulitis differential diagnosis in the spectrum of the skin and soft tissue infections.

Entity	Definition	Clinical presentation
Abscess	An enclosed collection of necrotic tissue, bacteria and inflammatory cells, surrounded by a reactive capsule and a cell wall from nearby healthy tissues.	An erythematous painful swelling area with fluctuation and trophic alteration. A thick yellowish pus escapes from the abscess naturally by fistulisation or through medical intervention.
Necrotising fasciitis	Rapidly progressive necrosis of subcutaneous fat and fascia, also known as "flesh-eating syndrome". The patient is toxic, with fever, chills, tachycardia, malaise, and altered levels of consciousness. Type I: mixed infection of anaerobes plus facultative species such as *streptococci* or *Enterobacteriaceae*. Type II: infection with group *A streptococci*	An ill-defined red-purple to grey shiny patch, with violaceous bullae, ulcers and areas of shiny watery malodorous fluid discharge, due to fat necrosis. Deep palpation reveals a wood hardness. The presence of hypo- or anaesthesia suggests deeper nerve involvement.
Gangrene	Necrosis of deep soft tissue primarily due to a loss of blood supply, sometimes permitting invasion and proliferation of bacteria, especially those able to survive with little or no oxygen, such as the Clostridium family. It often has an abrupt onset following a deep penetrating wound.	Tender, dark yellow or brown discolouration of the skin, with sera-haematic bullae and patches of necrosis. A mousy smelling is common. Crepitus at palpation support the diagnosis of gas producing bacteria (Gas gangrene).
Erysipeloid	An occupational disease, caused by the *Erysipelotrix rhusiopathiae*, a Gram-positive rod contaminating dead matter of animal or fish origin. Veterinarians, meat packers, fishermen are frequently exposed to minimal trauma while handling the contaminated material.	Clinical features are common to erysipelas and other bacterial cellulitis, but it is usually milder and tends to self-limitation.

Table 3. Cellulitis mimickers.

Site of involvement	Clinical conditions	Differential criteria
Extremities	• Deep wounds • Superficial infections, especially candidal intertrigo on hands, bacterial foot intertrigo, and tinea pedis. • Diabetic and gangrenous foot. • Acute gout attack and septic arthritis. • Stasis dermatitis, chronic lymphoedema, venous insufficiency. • Pyoderma gangrenosum.	• Long-standing manifestations, with initial indolent course and sudden worsening. • Presence of minimal bilateral or pre-existing changes, such as pitting oedema, superficial scaling or *xerosis*, hyperpigmentation, varicosities and scars. • Bound-down plaques or inverted champagne bottle appearance. • Comorbidity: Obesity, diabetes, and bad nutritional state.
Cephalic involvement	• Recent surgical procedures on the head and neck. • Herpes infections, especially H. Zoster ophthalmicus. • Chronic sinusitis, otitis, and per-orbital inflammation, dental abscesses. • Urticaria angioedema. • Contact dermatitis. • Carcinoma erysipeloides.	• Manifestations are usually milder, simulating a very initial inflammation. • Allergic manifestations tend to be itching rather than painful. • History of previous infections, allergy, and malignancy is often evocative. • Systemic upset and fever are usually absent in all these conditions.
Any or multiple sites	• Insect bites • Major surgical procedures • Sweet Syndrome • Well's cellulitis	• History of recent change in lifestyle, outdoor excursions or travel. • Malignancies, and/or immune suppression are to be considered. • More generalised lesions with fever and malaise are suspect for a systemic inflammatory disease.

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 *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 *Erysipelothrix rhusiopathiae*.[83]

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.[75] 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'.[84-86] 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.[87] Carcinoma erysipeloides is sometimes confused with cellulitis at presentation, especially when metastasis involves the sphenoid and posterior wall of the orbit.[88-90] 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.[91-94] 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.[95-97] Wells' eosinophilic cellulitis is another great simulator, which progresses slowly with erythematous oedematous lesions with sharp borders, a green hue and central clearing.[98-100] 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,[1-5] but Gram-negative and polymicrobial infections[12,102] as well as widespread resistance to antimicrobial agents, especially methicillin-resistant *S. aureus* (MRSA)[103-110] 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*[107] and *Haemophilus influenzae* are responsible of very severe cases.[7,8,112,113] Gram-negative *Neisseria meningitidis*, *Klebsiella pneumonia*, *Yersinia enterocolitis*, *Pseudomonas aeruginosa*, *Pastorella multicida* are increasingly reported,[114,116] together with mixture of Gram-positive and Gram-negative bacteria, aerobes and anaerobes, especially after surgical procedures and dental pathologies.[37] 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.[117-119] 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.[120-128] Histoplasmosis and mucormycosis might manifest with cellulitis in those countries where the infections are prevalent.[129,130]

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.[1-5,100-104,131] Military trainees and athletes are other apparently healthy categories in which increasing MRSA infections have been reported.[132-136]

Considering microbiologic variability and clinical difficulties, it is not surprising that 'gold standard' treatment for cellulitis has not been achieved,[1-5] 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,[3] while coverage for MRSA should be considered in peculiar settings.[5] 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.[73] 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.[72,137,138] Cephalosporins are often used alone or in association, especially intramuscular ceftriaxone.[139,140] Other penicillase-resistant betalactams include dicloxacillin, nafticillin, 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.[2,3,141] Concomitant therapy with ciprofloxacin and metronidazole is prescribed for polimicrobial infections.[98]

Very resistant infections are firstly treated with vancomycin, or teicoplanin, although susceptibility is decreasing for both drugs.[142,143] New antibiotics includes linezolide[144-146] quinupristin-dalfopristin[147,148] daptomycin,[153-155] ertapenem.[156] 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.[139,148,157,159] Old (ceftrixone, teicoplanin) and new drugs (quinupristin-dalfopristin, daptomycin, ertapenem) are under evaluation.[158]

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,[160] and other experiences using corticosteroids and other anti-inflammatories to improve response.[72,161,164] Concern relies on progression to NF, sepsis and metabolic aggravation, whose signs and symptoms might be masked by anti-inflammatory and analgesics.[164] Hyperbaric oxygen therapy has been proposed in severe cases as adjuvant measure.[165-167] 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.[5,168,169]

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

1. Gunderson CG. Cellulitis: definition, etiology, and clinical features. Am J Med. 2011;124(12):1113-22.

2. CREST (Clinical Resource Efficiency Support Team) Guidelines On The Management Of Cellulitis In Adults. CREST. 2005;1–31.

3. Kilburn SA et al. Interventions for cellulitis and erysipelas. Cochrane Database Syst Rev. 2010;(6):CD004299.

4. Morris AD. Cellulitis and erysipelas. Clin Evid (Online). 2008;pii:1708.

5. Swartz MN. Clinical practice. Cellulitis. N Engl J Med. 2004;350(9):904-12.

6. Hook EW 3rd. Acute cellulitis. Arch Dermatol. 1987;127:460-1.

7. Watt RW et al. Systemic Haemophilus influenzae and facial cellulitis in infants. Br Med J (Clin Res Ed). 1981;282(6261):399.

8. Charnock DR et al. Bruised cheek syndrome: Haemophilus influenzae, type B, cellulitis. Otolaryngol Head Neck Surg. 1990;103(5(Pt 1)):829-30.

9. Bouvet A. Cellulitis and necrotizing fasciitis: microbiology and pathogenesis. Ann Dermatol Venereol. 2001;128(3 Pt 2):382-9.

10. Roujeau JC. Necrotizing fasciitis. Clinical criteria and risk factors. Ann Dermatol Venereol. 2001;128(3 Pt 2):376-81.

11. Leppard BJ et al. The value of bacteriology and serology in the diagnosis of cellulitis and erysipelas. Br J Dermatol. 1985;112:559-67.

12. Musher DM. Cutaneous and soft tissue manifestations of sepsis due to Gram negative enteric bacilli. Rev Infect Dis. 1980;2:854-66.

13. de-Vicente-Rodríguez JC. Maxillofacial cellulitis. Med Oral Patol Oral Cir Bucal. 2004;9(Suppl):133-38;126-33.

14. Theranzadeh J et al. Magnetic resonance in osteomyelitis. Crit Rev Diagn Imaging 1992; 33: 495-543.

15. Maroldi R et al. Emergency imaging assessment of deep neck space infections. Semin Ultrasound CT MR. 2012;33(5):432-42.

16. Jaovisidha S et al. Emergency ultrasonography in patients with clinically suspected soft tissue infection of the legs. Singapore Med J. 2012;53(4):277-82.

17. Rahmouni A, Chosidow O. Differentiation of necrotizing infectious fasciitis from nonnecrotizing infectious fasciitis with MR imaging. Radiology. 2012;262(2):732-3.

18. Nisha VA et al. The role of colour Doppler ultrasonography in the diagnosis of fascial space infections - a cross sectional study. J Clin Diagn Res. 2013;7(5):962-7.

19. Chou YK et al. An upper airway obstruction emergency: Ludwig angina. Pediatr Emerg Care. 2007;23:892–6.

20. Srirompotong S et al. Ludwig's angina: a clinical review. Eur Arch Otorhinolaryngol. 2003;260:401–3.

21. Armstrong PA et al. An eye for trouble: orbital cellulitis. Emerg Med J. 2006;23:e66.

22 Perl B et al. Cost-effectiveness of blood cultures for adult patients with cellulitis. Clin Infect Dis. 1999;29:1483–8.

23. Boden JH et al. Methicillin-resistant ascending facial and orbital cellulitis in an operation Iraqi Freedom troop population. Ophthal Plast Reconstr Surg. 2007;23(5):397-9.

24. Weber AL et al. Inflammatory lesions of the neck, including fascial spaces – evaluation by computed tomography and magnetic resonance imaging.

25. Malghem J et al. Necrotizing fasciitis: contribution and limitations of diagnostic imaging. Joint Bone Spine 2013;80:146-54.

26. Schmid MR et al. Differentiation of necrotizing fasciitis and cellulitis using MR imaging. AJR Am J Roentgenol. 1998;170:615-20.

27. Chao HC et al. Sonographic evaluation of cellulitis in children. J Ultrasound Med. 2000;19:743-9.

28. Bailey E et al. Cellulitis: diagnosis and management. Dermatol Ther. 2011;24(2):229-39.

29. Braun-Falco O et al. Histopathology of the so-called cellulitis. Hautarzt. 1972;23(2):71–5.

30. Spellberg B et al. Antimicrobial agents for complicated skin and skin-structure infections: justification of noninferiority margins in the absence of placebo-controlled trials. Clin Infect Dis. 2009;49:383-91.

31. Carratala J et al. Factors associated with complications and mortality in adult patients hospitalized for infectious cellulitis. Eur J Clin Microbiol Infect Dis. 2003;22(3):151-7.

32. Jorup-Rönström C et al. Recurrent erysipelas: predisposing factors and costs of prophylaxis. Infection. 1987;15(2):105-6.

33. Pavlotsky F et al. Recurrent erysipelas: Risk factors. J Dtsch Dermatol Ges. 2004;2(2):89–95.

34. Ellis Simonsen SM et al. Cellulitis incidence in a defined population. Epidemiol Infect. 2006;134(2):293-9.

35. Lamagni TL et al. Epidemiology of severe Streptococcus pyogenes disease in Europe. J Clin Microbiol. 2008;46(7):2359-67.

36. Lipsky BA et al. Skin, soft tissue, bone, and joint infections in hospitalized patients: epidemiology and microbiological, clinical, and economic outcomes. Infect Control Hosp Epidemiol. 2007;28(11):1290-8.

37. Bernard P et al. Causes of erysipelas and cellulites in adults. Arch Dermatol. 1989;125:779-82.

38. Hadzovic-Cengic M et al. Cellulitis--epidemiological and clinical characteristics. Med Arh. 2012;66(3 Suppl 1):51-3.

39. Bosley ARJ et al. Systemic Haemophilus influenzae and facial cellulitis in infants. Br Med J. 1981;282:22.

40. Owa JA et al. Peri-umbilical cellulitis in Nigerian neonates. Cent Afr J Med. 1992;38(1):40-4.

41. Björnsdóttir S et al. Risk factors for acute cellulitis of the lower limb: a prospective case-control study. Clin Infect Dis. 2005;41(10):1416-22.

42. Cox NH. Oedema as a risk factor for multiple episodes of cellulitis/erysipelas of the lower leg: a series with community follow-up. Br J Dermatol. 2006;155(5):947-50.

43. Mokni M et al. Risk factors for erysipelas of the leg in Tunisia: a multicenter case-control study. Dermatology. 2006;212(2):108-12.

44. Dupuy A et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. BMJ. 1999;318(7198):1591-4.

45. Roujeau JC et al. Chronic dermatomycoses of the foot as risk factors for acute bacterial cellulitis of the leg: a case-control study. Dermatology. 2004;209(4):301-7.

46. Miron D et al. Infections following nail puncture wound of the foot: case reports and review of the literature. Isr J Med Sci. 1993;29(4):194-7.

47. Weakley DR. Orbital cellulitis complicating strabismus surgery: a case report and review of the literature. Ann Ophthalmol. 1991;23(12):454-7.

48. Escalante A et al. Risk factors for early wound complications after orthopedic surgery for rheumatoid arthritis. J Rheumatol. 1995;22(10):1844–51.

49. Thomas TA et al. An analysis of limb threatening lower extremity wound complications after 1090 consecutive coronary artery bypass procedures. Vasc Med. 1999;4(2):83–8.

50. Critchley G et al. Complications of varicose vein surgery. Ann R Coll Surg Engl. 1997;79(2):105–10.

51. Page KR et al. Postoperative pneumococcal cellulitis in systemic lupus erythematosus. Scand J Infect Dis. 2003;35(2):141-3.

52. Atzori L et al. Facial cellulitis associated with Pseudomonas aeruginosa complicating ophthalmic herpes zoster. Dermatol Online J. 2004;10(2):20.

53. Dajer-Fadel WL et al. Descending necrotizing mediastinitis and thoracic cellulitis due to varicella. Asian Cardiovasc Thorac Ann. 2012;20(1):83-5.

54. Schwerk N et al. Cellulitis with compartment syndrome as a complication of varicella zoster infection. Klin Padiatr. 2008;220(4):268-70.

55. Girouin D et al. Extensive cellulitis during chicken-pox. Six cases. Sem Hop. 1978;54(21-24):738-42.

56. Metts J. Common complications of body piercing. West J Med. 2002;176(2):85-6.

57. McLean M et al. Life-threatening cellulitis after traditional Samoan tattooing. Aust N Z J Public Health. 2011;35(1):27-9.

58. Nelson JD et al. A hypothesis on the pathogenesis of Haemophilus influenzae buccal cellulitis. J Pediatr. 1976;88:709-10.

59. Salgado Ordóñez F et al. Epidemiological characteristics and mortality risk factors in patients admitted in hospitals with soft tissue infections. A multicentric STIMG (Soft Tissue Infections Malacitan Group) study results]. An Med Interna. 2006;23(7):310-6.

60. Aronoff DM et al. Assessing the relationship between the use of nonsteroidal antiinflammatory drugs and necrotizing fasciitis caused by group A streptococcus. Medicine (Baltimore). 2003;82(4):225-35.

61. Chosidow O et al. Nonsteroidal anti-inflammatory drugs in cellulitis: a cautionary note. Arch Dermatol. 1991;127(12):1845-6.

62. Mikaeloff et al. Nonsteroidal anti-inflammatory drug use and the risk of severe skin and soft tissue complications in patients with varicella or zoster disease. Br J Clin Pharmacol. 2008;65(2):203-9.

63. Dall L et al. Rapid resolution of cellulitis in patients managed with combination antibiotic and anti-inflammatory therapy. Cutis. 2005;75(3):177-80.

64. Koerner R et al. Changes in the classification and management of skin and soft tissue infections. J Antimicrob Chemot. 2011;66:232-4.

65. Dong SL et al. ED management of cellulitis: a review of five urban centers. Am J Emerg Med. 2001;19:535-40.

66. Rajan S. Skin and soft-tissue infections: classifying and treating a spectrum. Cleve Clin J Med. 2012;79(1):57-66.

67. Lipsky BA et al. A prospective, multicenter, observational study of complicated skin and soft tissue infections in hospitalized patients: clinical characteristics, medical treatment, and outcomes. BMC Infect Dis. 2012;12:227.

68. Marwick C et al. Severity assessment of skin and soft tissue infections: cohort study of management and outcomes for hospitalized patients. J Antimicrob Chemoter. 2011;66:387-97.

69. Edelsberg J et al. Clinical and economic consequences of failure of initial antibiotic therapy for hospitalized patients with complicated skin and skin-structure infections. Infect Control Hosp Epidemiol. 2008;29:160-9.

70. Celestin R et al. Erysipelas: a common potentially dangerous infection. Acta Dermatovenerol Alp Panonica Adriat. 2007;16:123-7.

71. Ki V et al. Bacterial skin and soft tissue infections in adults: a review of their epidemiology, pathogenesis, diagnosis, treatment and site of care. Can J Infect Dis Med Microbiol. 2008;19(2):173-84.

72. Eron LJ et al. Managing skin and soft tissue infections: expert panel recommendations on key decision points. J Antimicrob Chemother. 2003;52(Suppl1):i3–17.

73. Jorup-Ronstrom C et al. The course, costs and complications of oral versus intravenous penicillin therapy of erysipelas. Infection. 1984;12:390-4.

74. Paterson R et al. Prediction of in-hospital mortality and length of stay using an early warning scoring system: clinical audit. Clin Med. 2006;6:281-4.

75. Keller EC et al. Distinguishing cellulitis from its mimics. Cleve Clin J Med. 2012;79(8):547-52.

76. Lio PA. The many faces of cellulitis. Arch Dis Child Educ Pract Ed. 2009;94:50-4.

77. Calandra GB et al. Evaluation of new anti-infective drugs for the treatment of selected infections of the skin and skin structure. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis. 1992;15(Suppl1):S148–54.

78. Hepburn MJ et al. Alternative diagnoses that often mimic cellulitis. Am Fam Physician. 2003;67(12):2471.

79. File T et al. Group A streptococcus necrotizing fasciitis. Com Ther. 2000;26:73-81.

80. Bakker DJ. Clostridial myonecrosis (gas gangrene). Undersea Hyperb Med. 2012;39(3):731-7.

81. Flores-Díaz M et al. Role of Clostridium perfringens phospholipase C in the pathogenesis of gas gangrene. Toxicon. 2003;42(8):979-86.

82. Crock GW et al. Gas gangrene infection of the eyes and orbits. Br J Ophthalmol. 1985;69:143–8.

83. Brooke CJ et al. Erysipelotrix rhusiopathie: bacteriology, epidemiology and clinical manifestations of an occupational pathogen. J Med Microbiol. 1999;48:789-99.

84. Farage MA et al. Clinical implications of aging skin: cutaneous disorders in the elderly. Am J Clin Dermatol. 2009;10:73-86.

85. Barron GS et al. Dermatologic complications of chronic venous disease: medical management and beyond. Ann Vasc Surg. 2007;21:652-62.

86. Miteva M et al. Lipodermatosclerosis. Dermatol Ther. 2010;23:375-88.

87. Goodyear PW et al. Periorbital swelling: the important distinction between allergy and infection. Emerg Med J. 2004;21(2):240-2.

88. Ng CS. Carcinoma erysipeloides from prostate cancer presenting as cellulitis. Cutis. 2000;65(4):215-6.

89. Finkel LJ et al. Inflammatory breast

carcinoma (carcinoma erysipeloides): an easily overlooked diagnosis. Br J Dermatol. 1993;129(3):324-6.

90. Homler HJ et al. Lymphangitic cutaneous metastases from lung cancer mimicking cellulitis. Carcinoma erysipeloides. West J Med. 1986;144(5):610-2.

91. Withrow RA et al. Cellulitis unresponsive to antibiotics. Sweet's syndrome. J Fam Pract. 2011;60(3):149-51

92. Khatri ML et al. Sweet's syndrome associated with myelodysplastic syndrome presenting as periorbital cellulitis. Int J Dermatol. 2007;46(5):496-9.

93. Oshitari K et al. Sweet syndrome presenting as orbital cellulitis. Nihon Ganka Gakkai Zasshi. 2004;108(3):162-5.

94. Crum NF et al. Sweet's syndrome masquerading as facial cellulitis. Cutis. 2003;71(6):469-72.

95. Lindberg-Larsen R et al. Traumatic pyoderma gangrenosum of the face: pathergy development after bike accident. Dermatology. 2009;218(3):272-4.

96. Hobman JW et al. Bilateral pyoderma gangrenosum complicating minimal access cranial suspension face lift. Aesthet Surg J. 2006;26(4):440-2.

97. Lachapelle JM et al. Superficial granulomatous pyoderma gangrenosum of the face, successfully treated by ciclosporine: a long-term follow-up. Dermatology. 2001;202(2):155-7.

98. Consigny S et al. Histological and clinical forms of the eosinophilic cellulitis. Ann Dermatol Venereol. 2001;128(3 Pt 1):213-6.

99. Sinno H et al. Diagnosis and management of eosinophilic cellulitis (Wells' syndrome): A case series and literature review. Can J Plast Surg. 2012;20(2):91-7.

100. Ferreli C et al. Eosinophilic cellulitis (Well's syndrome): a new case description. J Eur Acad Dermatol Venereol. 1999;13(1):41-5.

101. Stevens DL et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005;41:1373-406.

102. Sharma S et al. Skin and soft tissue infection. Indian J Pediatr. 2001;68(Suppl 3):S46-50.

103. Schwaber MJ et al. The effect of antimicrobial resistance on patient outcomes: importance of proper evaluation of appropriate therapy. Critical Care. 2009;13:106-7.

104. Eady EA et al. Staphylococcal resistance revisited: community-acquired methicillin resistant Staphylococcus aureus--an emerging problem for the management of skin and soft tissue infections. Curr Opin Infect Dis. 2003;16(2):103-24.

105. Naimi TS et al. Comparison of community- and health care-associated methicillin resistant Staphylococcus aureus infection. JAMA. 2003;290:2976–84.

106. Herold BC et al. Community-acquired methicillin-resistant Staphylococcus aureus in children with no identified predisposing risk. JAMA. 1998;279:593–8.

107. Witte W. Community-acquired methicillin-resistant Staphylococcus aureus: what do we need to know? Clin Microbiol Infect. 2009;15(Suppl 7):17–25.

108. Antri K et al. High prevalence of community and hospital acquired infections of methicillinresistant Staphylococcus aureus containing Panton-Valentine leukocidin gene in Algiers. Pathol Biol. 2010;58:e15–20.

109. Kohlenberg A et al. Regional trends in multidrug-resistant infections in German intensive care units: a real-time model for epidemiological monitoring and analysis. J Hosp Infect. 2009;73:239–45.

110. Marchese A et al. Molecular analysis and susceptibility patterns of meticillin-resistant Staphylococcus aureus (MRSA) strains circulating in the community in the Ligurian area, a northern region of Italy: emergence of USA300 and EMRSA-15 clones. Int J Antimicrob Agents. 2009;34:424–8.

111. Gubbay JB et al. Cellulitis in childhood invasive pneumococcal disease: a population-based study. J Paediatr Child Health. 2006;42:354-8.

112. Lin WJ et al. Cellulitis resulting from infection by Haemophilus influenzae type b: report of two cases. Acta Paediatr Taiwan. 2004;45:100-3.

113. Branca G et al. Haemophilus influenza cellulitis. A review and case report. N Y State Dent J. 2003;69:34-6.

114. Cartolano GL et al. Fatal acute cellulitis due to Neisseria meningitidis. J Clin Microbiol. 2003;41:3996-7.

115. Hook EW 3rd et al. Microbiologic evaluation of cutaneous cellulitis in adults. Arch Intern Med. 1986;146:295-7.

116. Lewis R. Soft tissue infections. World J Surg. 1998;22:146-51.

117. Baumgartner JC et al. Occurrence of Candida albicans in infections of endodontic origin. J Endod. 2000;26:695-8.

118. Matusow RJ. Acute pulpal-alevolar cellulitis syndrome. III endodontic therapeutic factors and the resolution of a candida albicans infection. Oral Surg Oral Med Oral Pathol. 1981;52:630-4.

119. Kwak OS et al. A rare case of facial Candida albicans cellulitis in an uncontrolled diabetic patient. Mycoses. 2009;52:379-81.

120. Shachor-Meyouhas Y et al. Primary cutaneous Nocardia brasiliensis cellulitis in immunocompetent child. Harefuah. 2012;151(8):476-8, 497, 496.

121. Asgeirsson H et al. Nocardiosis in immunocompromised host presenting as cellulitis. Laeknabladid. 2010;96(6):423-5.

122. Durán E et al. Primary nocardiosis by Nocardia brasiliensis in Spain. Enferm Infecc Microbiol Clin. 2010;28(8):571-2.

123. Sabater S et al. Nocardia brasiliensis cellulitis in an injection drug user. Enferm Infecc Microbiol Clin. 2009;27(9):551-2.

124. Ni W et al. Disseminated cryptococcosis initially presenting as cellulitis in a patient suffering from nephrotic syndrome. BMC Nephrol. 2013;14:20.

125. Chaya R et al. Disseminated Cryptococcosis presenting as cellulitis in a renal transplant recipient. J Infect Dev Ctries. 2013;7(1):60-3.

126. Fallah H et al. Cryptococcosis presenting as upper limb cellulitis and ulceration: a case series. Australas J Dermatol. 2011;52(4):288-91.

127. Diaz-Sarrió C et al. Systemic cryptococcosis presenting as extensive cellulitis in a patient with rheumatoid arthritis. Actas Dermosifiliogr. 2010;101(3):274-5.

128. Zorman JV et al. Primary cutaneous cryptococcosis in a renal transplant recipient: case report. Mycoses. 2010;53(6):535-7.

129. Ribeiro LC et al. Mucormycosis in Mato Grosso, Brazil: a case reports, caused by Rhizopus microsporus var. oligosporus and Rhizopus microspores, var. rhizopodiformis. Mycopathologia. 2012;173:187-92.

130. Chang P et al. Skin lesions in histoplasmosis. Clin Dermatol. 2012;30:592-8.

131. Tascini C et al. Cellulitis caused by a methicillin-sensitive Staphylococcus aureus isolate harboring Panton-Valentine toxin in an American soldier returning from Iraq. Int J Dermatol. 2011;50(2):206-7.

132. Wells RD et al. Comparison of initial antibiotic choice and treatment of cellulitis in the pre- and post-community-acquired methicillin-resistant Staphylococcus aureus eras. Am J Emerg Med. 2009;27(4):436-9.

133. Ellis MW et al. Natural history of community-acquired methicillin-resistant Staphylococcus aureus colonization and infection in soldiers. Clin Infect Dis. 2004;39(7):971-9.

134. Cohen PR. Cutaneous community-acquired methicillin-resistant Staphylococcus aureus infection in participants of athletic activities. South Med J. 2005;98(6):596-602.

135. Cohen PR. The skin in the gym: a comprehensive review of the cutaneous manifestations of community-acquired methicillin-resistant Staphylococcus aureus infection in athletes. Clin Dermatol. 2008;26(1):16-26.

136. Begier EM et al. A high-morbidity outbreak of methicillin-resistant Staphylococcus aureus among players on a college football team, facilitated by cosmetic body shaving and turf burns. Clin Infect Dis. 2004;39(10):1446-53.

137. Leman P et al. Flucloxacillin alone or combined with benzylpenicillin to treat lower limb cellulitis: a randomised controlled trial. Emerg Med J. 2005;22(5):342-6.

138. Tan R et al. The design, characteristics and predictors of mortality in the North of England Cellulitis Treatment Assessment (NECTA). Int J Clin Pract. 2007;61(11):1889-93.

139. Seaton RA et al. Outpatient parenteral antibiotic therapy: Principles and practice. Eur J Intern Med. 2013;24(7):617-23.

140. Gainer RB 2nd. Ceftriaxone in treatment of serious infections. Skin and soft tissue infections. Hosp Pract (Off Ed). 1991;26(Suppl 5):24-30.

141. Daniel R. Azithromycin, erythromycin and cloxacillin in the treatment of infections of skin and associated soft tissues. European Azithromycin Study Group. J Int Med Research. 1991;19(6):433–45.

142. Allen GP et al. Determination of the mutant selection window for clindamycin, doxycycline, linezolid, moxifloxacin and trimethoprim/sulfamethoxazole against community-associated meticillin-resistant Staphylococcus aureus (MRSA). Int J Antimicrob Agents. 2010;35(1):45–9.

143. Sakoulas G et al. Increasing antibiotic resistance among methicillin-resistant Staphylococcus aureus strains. Clin Infect Dis. 2008;46(Suppl5):S360–7.

144. Wang G et al. Increased vancomycin MICs for Staphylococcus aureus clinical isolates from a university hospital during a 5-year period. J Clin Microbiol. 2006;44:3883–6.

145. Edelstein HE et al. Intravenous or intramuscular teicoplanin once daily for skin and soft-tissue infections. DICP. 1991;25(9):914-8.

146. de Lalla F et al. Teicoplanin in the treatment of infections by staphylococci, Clostridium difficile and other gram-positive bacteria. J Antimicrob Chemother. 1989;23(1):131-42.

147. Van Laethem Y et al. Teicoplanin compared with vancomycin in methicillin-resistant Staphylococcus aureus infections: preliminary results. J Antimicrob Chemother. 1988;21(Suppl A):81-7.

148. Weigelt J et al. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother. 2005;49(6):2260-6.

149. Marchese A et al. Evolution of antibiotic resistance in gram-positive pathogens. J Chemother. 2000;12(6):459-62.

150. Testore GP et al. Linezolid as rescue drug: a clinical case of soft tissue infection caused by a Staphylococcus aureus strain resistant in vivo to teicoplanin. J Chemother. 2006;18(4):430-2.

151. Allington DR et al. Quinupristin/dalfopristin: a therapeutic review. Clin Ther. 2001;23(1):24-44.

152. Rehm SJ et al. Successful administration of quinupristin/dalfopristin in the outpatient setting. J Antimicrob Chemother. 2001;47(5):639-45.

153. Pertel PE et al. The efficacy and safety of daptomycin vs. vancomycin for the treatment of cellulitis and erysipelas. Int J Clin Pract. 2009;63(3):368-75.

154. Davis SL et al. Daptomycin versus vancomycin for complicated skin and skin structure infections: clinical and economic outcomes. Pharmacotherapy. 2007;27(12):1611-8.

155. White B et al. Complicated skin and soft tissue infections: literature review of evidence for and experience with daptomycin. Infect Drug Resist. 2011;4:115-27.

156. Goldstein EJ et al. General microbiology and in vitro susceptibility of anaerobes isolated from complicated skin and skin-structure infections in patients enrolled in a comparative trial of ertapenem versus piperacillin-tazobactam. Clin Infect Dis. 2002;35(Suppl 1):S119-25.

157. Nathwani D. Developments in outpatient parenteral antimicrobial therapy (OPAT) for Gram-positive infections in Europe, and the potential impact of daptomycin. J Antimicrob Chemother. 2009;64(3):447-53.

158. Chapman AL et al. Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement. J Antimicrob Chemother. 2012;67(5):1053-62.

159. Lamont E et al. Development of teicoplanin dosage guidelines for patients treated within an outpatient parenteral antibiotic therapy (OPAT) programme. J Antimicrob Chemother. 2009;64(1):181-7.

160. Hepburn MJ et al. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Arch Intern Med. 2004;164(15):1669-74.

161. Bergkvist PI et al. Antibiotic and prednisolone therapy of erysipelas: a randomized, double blind, placebo-controlled study. Scand J Infect Dis. 1997;29(4):377-82.

162. Pushker N et al. Role of oral corticosteroids in orbital cellulitis. Am J Ophthalmol. 2013;156(1):178-83.

163. Badger C et al. Antibiotics / anti-inflammatories for reducing acute inflammatory episodes in lymphoedema of the limbs. Cochrane Database Syst Rev. 2004;(2):CD003143.

164. Aronoff DM et al. Assessing the relationship between the use of nonsteroidal antiinflammatory drugs and necrotizing fasciitis caused by group A streptococcus. Medicine (Baltimore). 2003;82(4):225-35.

165. Douso ML. Hyperbaric oxygen therapy as adjunctive treatment for postoperative cellulitis involving intrapelvic mesh. J Minim Invasive Gynecol. 2009;16(2):222-3.

166. de Vaumas C et al. Non pharmacological treatment of severe cutaneous infections: hyperbaric oxygen therapy, dressings and local treatments. Ann Fr Anesth Reanim. 2006;25(9):986-9.

167. Wang J et al. Hyperbaric oxygen as adjunctive therapy in Vibrio vulnificus septicemia and cellulitis. Undersea Hyperb Med. 2004;31(1):179-81.

168. Thomas KS et al. Penicillin to prevent recurrent leg cellulitis. N Engl J Med. 2013;368(18):1695-703.

169. UK Dermatology Clinical Trials Network's PATCH Trial Team, Thomas K et al. Prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg: results of the UK Dermatology Clinical Trials Network's PATCH II trial. Br J Dermatol. 2012;166(1):169-78.