Am J Clin Dermatol 2003; 4 (3): 157-163
1175-0561/03/0003-0157/$30.00/0

Erysipelas
Recognition and Management

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Contents

Abstract

Erysipelas is an acute bacterial infection of the dermis and hypodermis that is associated with clinical inflammation. It is a specific clinical type of cellulitis and, as such, it should be studied as a specific entity. Erysipelas is generally caused by group A streptococci; it is highly probable that streptococcal toxins also play a role, which could, in part, help explain the clinical inflammation.

Erysipelas of the leg is the main clinical type encountered. The face, arm, and upper thigh are the other most common sites for the occurrence of erysipelas. After a sudden onset, areas of erythema and edema characteristically enlarge with well-defined margins. Athlete's foot is the most common portal of entry for the disease. Erysipelas is generally associated with high fever, and adenopathy and lymphangitis are sometimes present.

At the time of diagnosis, it is important to look for clinical markers of severity (local signs and symptoms, general signs and symptoms, co-morbidity, social context) which would necessitate hospitalization.

There are many differential diagnoses, particularly in the case of atypical dermo-hypodermitis. Some bacterial infections may have specific clinical aspects or may lead to a diagnosis of cellulitis. Necrotizing cellulitis or fasciitis are life-threatening diseases and a rapid diagnosis is important. Other noninfectious types of cellulitis have been reported in many diseases, both localized or generalized.

The biology of typical erysipelas is of little value in diagnosis and a laboratory workup is usually not required. There are few local complications associated with erysipelas; abscess can occur in some patients and septicemia is rare. Recurrence is the more distressing complication.

Treatment of patients with erysipelas has been evaluated in a small number of studies. In most of them, erysipelas has been included in therapeutic studies of 'severe cutaneous infections'. This is not justified as in fact erysipelas is usually sensitive to penicillin G. Amoxicillin and macrolides are also effective. However, comparative, cost-analysis studies need to be performed to determine the best therapeutic option. Bed rest with the leg elevated is also important. Anticoagulants are indicated in patients at risk of venous thromboembolism. The portal of entry will also require treatment. Long-term antibacterial therapy is required for patients with recurrence.

Erysipelas is an acute bacterial infection of the dermis and the hypodermis (table I). It is mainly caused by streptococci and, at present, there is no proof that any other bacteria may cause typical erysipelas. The role of streptococcal toxins is probably important in the pathogenesis of this disease. An epidemic flare has been observed in many countries for 20 years, although data are mainly based on hospital series and are, therefore, subject to many biases.[1] In our department, there was a gradual increase with five patients diagnosed in 1978 and 40 in 1990.[2] There are no antibacterial resistance issues and penicillin is always the standard therapy.

Although the clinical diagnosis of erysipelas is easy in the typical form, in some patients, where the infection is deeper, it is more difficult because of the clinical appearance and the possibility of other bacteria being involved. A consensus conference which covered all aspects of erysipelas was held on this subject in France in 2000 and this paper discusses much of the data from the conference.[3]

1. Definition

Erysipelas is defined as a clinical type of cellulitis mainly of the dermis and, to a lesser extent, of the hypodermis. French dermatologists do not use the term 'cellulitis' any more because it is not sufficiently precise in its description of the location and definition of this group of diseases. It does not correspond to an anatomical or histopathological tissue. Moreover, other nonbacterial forms of inflammation of the skin are described within the term cellulitis, such as Wells' cellulitis. French dermatologists now use the term bacterial dermo-hypodermitis. The more dermal location of erysipelas probably accounts for the more defined limits of the erythema and edema. In some patients with dermo-hypodermitis the site is deeper in the hypodermis leading to a more undefined limit, with a pink color. In such patients, a streptococcal origin is frequent but not unique and other bacteria, either alone or synergistically, may be encountered.[3]

Table I. Cutaneous bacterial infections

Depth	Location	Infection
Superficial	Epidermis	Impetigo, ecthyma
	Hair follicle	Folliculitis, carbuncle, anthrax, sycosis
	Nail	Perionyxis, digits
Deep	Dermo-hypodermis	Erysipelas
	Dermo-hypodermis	Other types of dermo-hypodermitis
	Dermo-hypodermis	Necrotizing dermo-hypodermitis
	Fascia	Necrotizing fasciitis

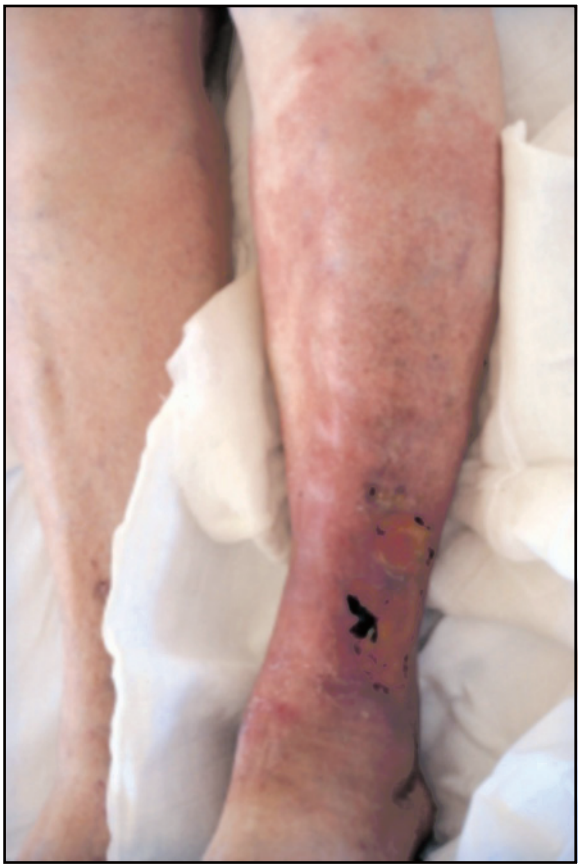

Fig. 1. Erysipelas of the leg.

2. Pathology

In the acute phase, a dense dermal inflammatory infiltrate of neutrophils is observed, which is less intense in the hypodermis. It may be associated with pustules, abscesses or focal necrosis. The dermal, fibrin-rich edema is important and it may contribute to subepidermal bullae. Dilated lymphatics are filled with neutrophils and macrophages. Neutrophils are also observed in the venule walls and thrombosis may occur.

3. Physiopathology

Erysipelas is a bacterial infection and most researchers consider streptococci to be the primary cause.[4] Three species of streptococci are found: *Streptococcus pyogenes* (A) in 58–67%; *S. agalactiae* (B) in 3–9%; and *S. dysgalactiae* sp. *equisimilis* (C and G) in 14–25% of the patients. In some patients with erysipelas, other bacteria are found that may or may not be associated with streptococci, such as *Staphylococcus aureus* in 10–17%, and *Pseudomonas aeruginosa* and enterobacteria in 5–50%. These

findings have raised questions about the role of these bacteria in the pathogenesis of erysipelas and some have been described as causing 'pseudo-erysipelas'.[5]

Indirect arguments exist to favor the unique role of streptococci in erysipelas. The number of streptococcal bacteria is small in erysipelas and methods using streptococcal antigens have greatly increased the percentage of streptococcal positive erysipelas cases.[2,6] Bacterial colonization of the skin is frequent and this explains the presence of staphylococci and *Pseudomonas* sp. in intertriginous areas. Staphylococcal-positive blood culture has not been found in erysipelas. Finally, penicillin G to which staphylococci are usually resistant is regularly used with success in erysipelas and in the treatment of recurrences.

Streptococci have many protective and virulence factors, and this may explain the clinical symptoms of erysipelas. Protein M and the capsule delay phagocytosis and facilitate tissue invasion. Protein M and teichoic acids enhance cellular adhesion. No clonality of protein M has been observed in erysipelas. The diffusion of enzymes and exotoxins (e.g. streptolysins, erythrogen toxin, DNAase, NADase, streptokinase, proteinase, amylase, and esterases) greatly contribute to local inflammation. In erysipelas, SpeB and SpeC exotoxins are the most frequently encountered and SpeA (responsible for toxic shock syndrome) is rarely observed.[7] These streptococcal superantigens also contribute to inflammation and cell death.

Table II. Markers of severity of erysipelas which may lead to hospitalization

General signs and symptoms
Elevated fever with confusion
Drowsiness or disorientation
Tachypnea
Tachycardia
Oliguria
Hypotension
Blemish
Local signs
Intense local pain
Major edema
Hemorrhagic bullae
Focal necrosis
Hypoesthesia
Livedo reticularis
Crepitation
Other factors
Co-morbidity: diabetes mellitus, obesity
Social context: homeless

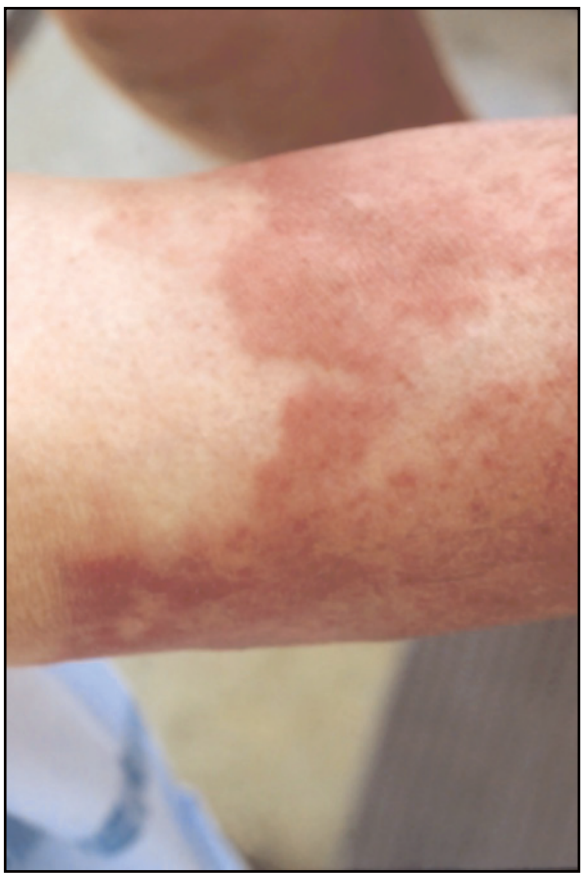

Fig. 2. Demarcation of erysipelas.

4. Clinical Diagnosis

The leg of the patient is involved in erysipelas 90% of the time. Other sites of erysipelas are the arm (5%), the face (2.5%), and places such as the thigh, particularly in patients having a hip surgery.[8] Erysipelas is characterized by its sudden onset. Fever is usually apparent some hours before the skin signs and symptoms appear, and it is usually higher than in patients with cellulitis and fasciitis.[9] However, fever is not present in 15% of patients.[10] An erythema gradually extends on the leg, and is associated with edema and pain. The plaque is well demarcated and extends by 2–10cm each day; however, no central involution is observed (figure 1 and figure 2) The portal of entry is mainly through athlete's foot; a controlled study showed it was more frequent in patients with erysipelas than in a sex- and age-matched control population.[11] Other portals of entry include leg ulcers, venous stasis dermatitis and superficial wounds.

General symptoms associated with an enlarging erythema are usually diagnostic. A regional lymphadenopathy is sometimes observed, as well as lymphangitis. At the time of diagnosis,

it is important to look for clinical markers of severity, which may lead to the decision to hospitalize (table II). They may be present at the onset or may appear later.

The rapid, favorable response to antibacterials also supports a diagnosis of erysipelas. Within 24–72 hours, there is no more fever, pain is reduced as are the skin signs, such as the borders decreasing in size and in thickness. If this is not the case, investigation for a complication or a marker of severity must be performed.

The risk factors for erysipelas are numerous. Local conditions (athlete's foot, leg ulcer) as well as associated diseases (lymphedema, diabetes mellitus, and alcoholism) or social conditions (a vagrant lifestyle) have been advocated. Only one case-control study[11] has been conducted on erysipelas. It showed that lymphedema (odds ratio [OR] 71.2, 95% CI 5.6–908) and the portal of entry (OR 23.8, 95% CI 10.7–52.5) were the main factors in a multivariate analysis. Leg edema, venous incompetence and obesity were also associated (OR 2.5, 2.9 and 2, respectively).

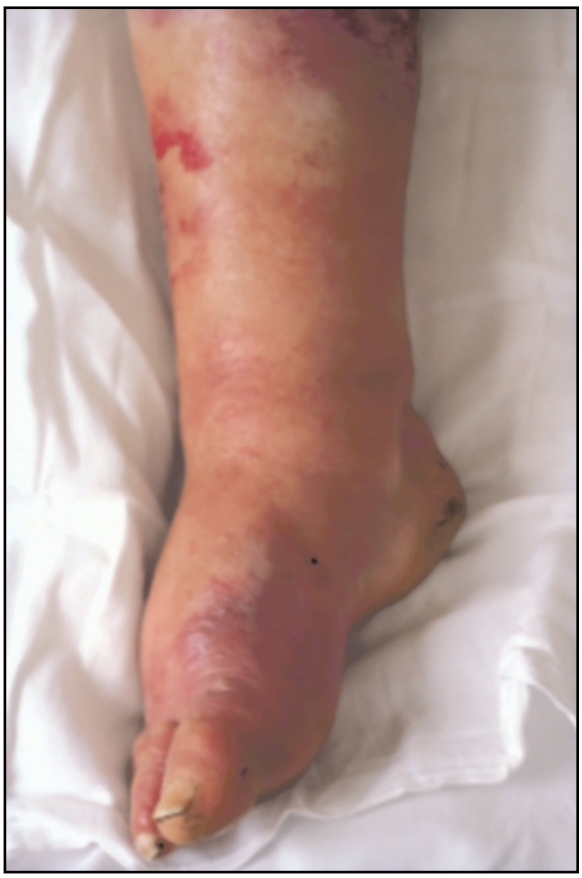

Fig. 3. Dermo-hypodermitis.

Table III. Differential diagnosis of erysipelas: infectious diseases (reproduced from Vaillant,[5] with permission)

Bacterial infections (clinical entities)
Erysipelothrix (*Erysipelothrix rhusiopathiae*): inoculation, specific occupation
Haemophilus influenzae: 'cellulitis', face, children
Yersinia 'cellulitis'
Staphylococcus spp.: face
Lymphangiitis
Pasteurella multocida: cat bite or scratch
Osteomyelitis
Bursitis
Nonbacterial
Herpes zoster
Cryptococcosis
In immunocompromised patients
Dermo-hypodermitis due to staphylococci, *Pseudomonas* sp., *Campylobacter jejuni*, *Acinetobacter calcoaceticus*, *Bacteroides fragilis*, *Escherichia coli*, *Streptococcus pneumoniae*, *Propionibacterium acnes*
Deeper infections
Nonstreptococcal acute dermo-hypodermitis (with or without necrosis)
Necrotizing fasciitis
Myositis (Gram-negative bacteria, streptococci)

Other diagnoses should be considered in patients with atypical dermo-hypodermitis or when the disease does not resolve after 48–72 hours of treatment (figure 3). Many diseases may be considered (table III and table IV), some being more specific to the face or leg.[5]

The more severe diagnosis is necrotizing dermo-hypodermitis or fasciitis. Both may be life threatening and require surgical treatment. Some clinical signs are good indicators of these diagnoses but none is specific to the disease. A scale has been published but it has not been evaluated.[12]

A necrotizing erysipelas has been described in patients who had arterial insufficiency.[13] In such patients, erysipelas decompensates the arterial disease and necrosis occurs. It is mainly observed in the elderly and often in patients with diabetes.

5. Biology

In the classical form of erysipelas no biological examinations are required for diagnosis. Any examination would show the results of a bacterial infectious disease with neutrophilia and elevated C reactive protein levels. Specific laboratory investigations for streptococci have various levels of sensitivity (table V). Bacteriology from the portal of entry is mandatory but it is positive in less than 40% of patients. The results of serology take too long

to be useful; however, blood cultures are indicated in patients with chills and high fever, or toxic signs.

6. Complications

Some associated signs in patients with erysipelas should not be considered as a complication if they are localized and they resolve with treatment. Bullae are sometimes observed as a consequence of edema, especially in elderly patients with atrophic skin. Purpura may also be observed in the center of the plaque.

Localized abscesses are not rare, and should be suspected when the fever does not respond to antibacterials (figure 4). A localized tender and painful zone can be palpated. Puncture of the lesion will result in the emission of pus, the culture of which is often sterile.

Septicemia and bacteremia are both rare. Blood cultures are positive in less than 5% of patients. Deep venous thrombophlebitis occurs in 1–5% of patients with erysipelas.

Recurrence is relatively high, occurring in 10% of patients 6 months after the first episode and in 30% 3 years after.[14] Erysipelas does not always recur in the same site. The attributable risks for recurrence are leg ulcer (OR 62.5, 95% CI 7–556), athlete's foot (OR 13.9, 95% CI 1.2–27), and skin trauma (OR 10.7, 95% CI 4.8–23.8).[11] Recurrent erysipelas is largely due to the persistence of untreated local factors.

Table IV. Differential diagnosis of erysipelas: noninfectious disorders (reproduced from Vaillant,[5] with permission)

Venous thrombosis
Deep and superficial
Localized diseases
Compartment syndrome
Intolerance to orthopedic prosthesis
Well's cellulitis
Dissecting cellulitis of the scalp
Melkerson-Rosenthal syndrome
Systemic diseases
Periodic disease
Lupus
Sweet's syndrome
Inflammatory neoplasia (e.g. breast)
Angiotropic lymphoma
Crohn's disease
Mercury induced acute exanthematic pustulosis
Others (frequently without fever)
Contact eczema
Angioedema
Adverse effects of drugs (chemotherapy)

Table V. Sensitivity of different laboratory techniques for streptococci (reproduced from Denis et al.,[4] with permission)

Techniques	Sensitivity (%)
Bacteriological skin cultures	14–41
Immunofluorescence	64–70
Latex agglutination	47–58
Serology	30–67
Blood culture	0–5.5
Combined techniques	25–96

7. Treatment

In leg erysipelas as well in cellulitis, the first treatment measure is several days bed rest with the leg elevated. This reduces edema and leg pain, and is also important for the abatement of fever. Once the patient is mobile, an elastic stocking permits leg containment and reduces the recurrence of edema and the risk of lymphedema. We recommend the use of an elastic stocking for a month in previously healthy persons, or longer if they had venous edema or lymphedema.

A great number of clinical trials with antibacterials have been performed in patients with skin and soft tissue infections. Although it is a commercial goal for laboratories to investigate the largest panel of skin infections, it is not possible from these results to find good data concerning specific skin diseases, as they cannot be analyzed from such reports. The reports are not retained for marketing authorization in Europe.

Numerous clinical trials have been performed only in erysipelas and in cellulitis (dermo-hypodermal bacterial infections). A recent review analyzed these studies.[15] Eleven comparative and randomized trials compared numerous antibacterial agents (table VI).[16-26] The number of patients varied from 60 to 492; however in most of these studies, it was difficult to ascertain the results in patients with erysipelas as they were included under those with 'cellulitis'. Some other open and noncomparative studies were reported in the review.[15]

Penicillin G continues to be the standard treatment in uncomplicated erysipelas and it is active in 80% of such cases. The initial daily dose varies according to the study from 10–20MU infused in 4–6 infusions. In most studies, intravenous therapy is continued over 2–3 days and oral penicillin A, daily in three divided doses of 3–6MU, is started as soon as the fever has disappeared. Amoxicillin 3–4.5 g/day may also be used. Treatment should continue for 10–20 days. It has been shown that oral and intravenous treatment are of equivalent efficacy in the treatment of patients with erysipelas.[16]

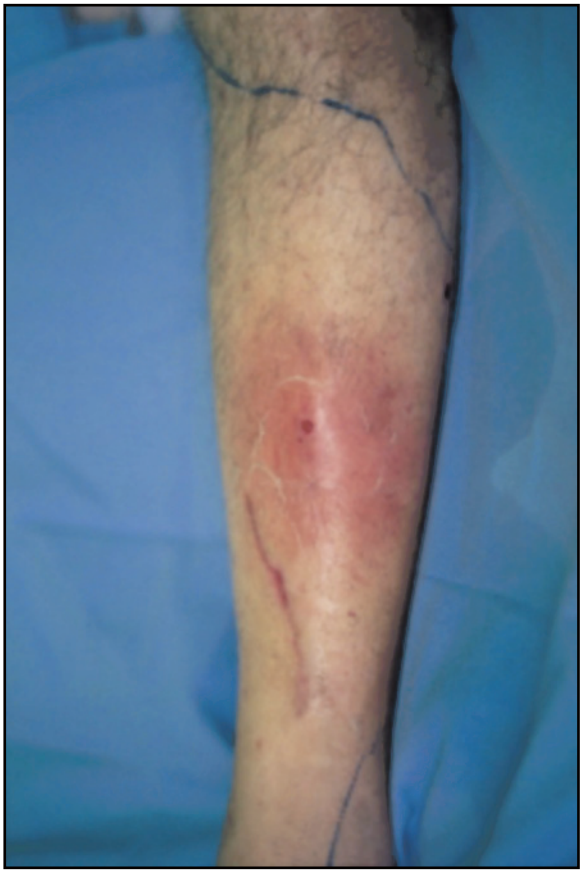

Fig. 4. Localized abscess complicating erysipelas (originally extending to the ink mark).

Other classes of antibacterials have also been used in for erysipelas. Macrolides (erythromycin, roxithromycin and azithromycin), new cephalosporins (cephalexin, cefadroxil and cefotaxime) and fluoroquinolones (ciprofloxacin) have equivalent or slightly more activity than penicillin[15] (table IV). Indications for these drugs are mainly possible complicated cellulitis (bacterial hypodermal type) but their systematic use is also restricted by their cost. In France, pristinamycin (a macrolide related antibacterial) provides a good response but gastrointestinal tolerability (nausea, gastric pain) sometimes limits its use; it is also active against staphylococci. In France, it is the second choice agent used in the treatment of patients with penicillin allergies. To date, macrolides provide the best choice for patients with penicillin allergy when efficacy, tolerability and comfort of the patient are all considered.[3] However, a recent retrospective study of 365 patients found no advantage to using antibacterials other than penicillin, and they suggested that erysipelas could be treated empirically on an outpatient basis.[27]

The use of anticoagulants during the initial period of treatment has been debated for a long time. Now, considering the low prevalence of deep vein thrombosis, subcutaneous heparin is only indicated in patients with a history of venous thrombosis or pulmonary embolism, with varicose veins, or in patients who are obese or confined to bed.

Treatment of the portal of entry is normally required, with treatment depending on where this is. Most of the topical antifungals used in treating athlete's foot have some activity against streptococci. However, they have not been evaluated in the prevention of recurrence of erysipelas. They should be used in association with good hygiene of the toe web. Systemic antibacterials are sufficient in patients with leg ulcer caused by *S. pyogenes*. It is important that the patient understands the requirement of topical treatment in the prevention of recurrence.

The treatment of recurrent erysipelas has been poorly investigated. The use of penicillin V (phenoxymethylpenicillin) and erythromycin, however, has resulted in a significant reduction of recurrences.[14,26]

Table VI. Comparative results of clinical studies of erysipelas treatment (reproduced from Bedane,[15] with permission)

Reference (year)	n	Drug	Results (%)
Jorup-Rönstrom et al.[16] (1984)	60	Penicillin V	90
		Penicillin G	85
Bernard et al.[17] (1992)	72	Penicillin G	76
		Roxithromycin	84
Tan et al.[18] (1993)	111	Piperacillin/tazobactam	80
		Ticarcillin/clavulanic acid	80
Daly et al.[19] (1990)	65	Nafcillin	90
		Cefonicid	90
Daniel[20] (1991)	300	Azithromycin	72
		Erythromycin	74
Daniel[20] (1991)	323	Azithromycin	94
		Cloxacillin	94
Kiani[21] (1991)	179	Azithromycin	91
		Cephalexin	94
Heskel et al.[22] (1992)	105	Erythromycin	95
		Cefadroxil	75
Nelder[23] (1991)	400	Temafloxacin	95
		Cefadroxil	95
Gentry et al.[24] (1989)	184	Ciprofloxacin	75
		Cefotaxime	75
Parish and Jungkind[25] (1992)	197	Ciprofloxacin	95
		Temafloxacin	95

8. Conclusion

Erysipelas is a characteristic clinical type of cellulitis, probably of a unique streptococcal origin. More studies are necessary in order to better understand its mechanism. Therapeutic studies should be devoted specifically to it as, in the past, most studies have been comparative with penicillin G or amoxicillin as the drug reference. Preventative measures need to be studied to reduce the recurrence risk.

Acknowledgements

The authors have provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

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