

Cellulitis: current insights into pathophysiology and clinical management

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ABSTRACT

Cellulitis is a bacterial skin and soft tissue infection which occurs when the physical skin barrier, the immune system and/or the circulatory system are impaired. Diabetes, obesity and old age are associated with defects in all of these areas and as a result are major predisposing factors for cellulitis. In this review, we summarise current insights into the pathophysiology of cellulitis and place the Dutch guidelines on the clinical management of cellulitis of the lower extremities in perspective. Recent evidence on diagnostic strategies is discussed, the importance of which is underscored by findings that venous insufficiency, eczema, deep vein thrombosis and gout are frequently mistaken for cellulitis. Empiric antibiotic choices are designed against the background of a low prevalence of multi-resistant *Staphylococcus aureus*. Novel antimicrobial agents registered for cellulitis are also discussed. Relapses occur frequently due to a high prevalence of risk factors associated with cellulitis in combination with the occurrence of persistent post-inflammatory lymphatic damage. Lastly, we identify knowledge gaps which, if addressed, will advance our understanding of the pathophysiology of cellulitis and improve its clinical management.

KEYWORDS

Cellulitis, clinical management, pathophysiology, review

INTRODUCTION

Cellulitis (Latin: *cellula* (diminutive of *cella*: cell) + *itis* (suffix denoting inflammation)) and its subtype erysipelas (Greek: *erythrós* (red) + *pella* (skin)), are among the most

frequent infections requiring hospitalisation.¹ The historical distinction between cellulitis and erysipelas, based on different bacterial aetiologies and thus treatment options, is becoming obsolete as increasing evidence suggests a large overlap between these two entities (*textbox 1*). In the Netherlands, the annual incidence is estimated to be 22 per 1000 inhabitants. Approximately 7% of all patients with cellulitis are hospitalised.^{5,6} The mortality rate of hospitalised patients has been reported to be around 2.5%.⁷ Recent epidemiology data on cellulitis in the Netherlands are lacking, but given the rise in the incidence of important risk factors (namely diabetes, obesity and old age), an increase in the incidence of cellulitis is expected.⁸⁻¹⁰ Dutch guidelines on the clinical management of cellulitis of the lower extremities have been available since 2013 (*figure 1*).¹¹ Since their publication, numerous studies have provided novel insights and new antibiotics registered for skin and soft tissue infections have entered the market. This review discusses the current state of evidence regarding pathogenesis, diagnostics, and treatment of cellulitis. The literature search strategy used is documented in *textbox 2*.

Cellulitis: a diagnostic challenge

All that is red is not cellulitis. The classical symptoms of erythema, oedema, warmth and tenderness, are non-specific and vary in severity. The clinical presentation of cellulitis is mimicked by a whole range of diseases (*table 1* and *figure 2*). One recent study revealed that 31% of patients hospitalised with cellulitis were misdiagnosed, the most frequent mimickers being stasis dermatitis, stasis ulcers, gout, congestive heart failure, non-specific oedema and deep venous thrombosis (DVT).¹⁸ Another study in the primary care setting found a similar rate of misdiagnoses.¹⁹ Furthermore, when clinicians specifically consulted dermatologists because of uncertainty about a diagnosis of cellulitis, 74% of the patients turned out not

Textbox 1. Erysipelas vs cellulitis

Historically, physicians distinguish erysipelas, a streptococcal infection of the superficial dermis and superficially located lymphatic vessels, from cellulitis, an infection of all skin layers generally caused by staphylococci. Erysipelas is characterised by sharp demarcation, a palpable edge and salmon-red erythema and is accompanied by high fever.² This distinction has therapeutic implications, as beta-lactamase sensitive penicillins would suffice for erysipelas.

Aetiological evidence, however, contests the concept that erysipelas is solely caused by streptococci. For instance, a systematic review of bacteraemias in erysipelas and cellulitis patients found equal rates of *S. aureus* (14%) in both groups.³ In addition, in a retrospective study of 1142 patients with erysipelas more than half of the positive wound cultures yielded *S. aureus*.² Lastly, streptococci were not found more frequently in patients with all classical erysipelas symptoms than in the general cellulitis population (68%), in a prospective aetiological study.⁴

In addition to being hard to distinguish from cellulitis based on clinical symptoms, the above suggests that diagnosing erysipelas does not help to differentiate between streptococcal and staphylococcal infections. In most studies the two conditions are already grouped together and US guidelines use the term 'skin and soft tissue infections', making management decisions based on the presence of purulence instead.¹³

Textbox 2. Search strategy

A systematic literature search was performed using the following keywords: (cellulitis[tiab] OR erysipelas[tiab] OR 'skin and skin structure infection'[tiab] OR 'skin and soft tissue infection'[tiab]) AND ((pathogenesis OR etiological OR risk OR precipitating OR predisposing OR pathophysiology OR microbiota) OR (ultrason* OR MRI OR 'magnetic resonance' OR tomography OR CT OR diagnostics OR serology OR serological OR culture OR cultures OR PCR OR microbiota) OR (((duration OR length) AND therapy) OR ((duration OR length) AND treatment) OR ((duration OR length) AND antibiotics) OR flucloxacillin OR dicloxacillin OR clindamycin OR ((therapy OR treatment) AND cessation OR stop OR end)) OR (toxin OR toxins) OR (criteria OR severity OR adjunctive OR prednis* OR pain OR analgesi*) OR (compression OR compressive OR compressing OR stocking OR stockings OR ACT) OR (lymphedema OR lymphatic AND (drain* OR massage)) OR (corticoster* OR steroids OR anti-inflammat* OR grade OR grades OR grading) OR (relapsing OR recurring OR recurrent OR prophylaxis OR prophylactic)) NOT periorbital[ti] NOT postseptal[ti]. Animal and paediatric studies were excluded. Guidelines, statistical sources, previous reviews and bibliographies of relevant studies were also searched for other relevant studies or information. Only studies contributing to the understanding of cellulitis were selected.

to have cellulitis.²⁰ Misdiagnosis results in unnecessary admissions and extra costs for perceived refractory cellulitis.¹⁸ Leucocytosis and elevated C-reactive protein (CRP) levels are present in 34-50% and 77-97% of patients, respectively.^{21,22}

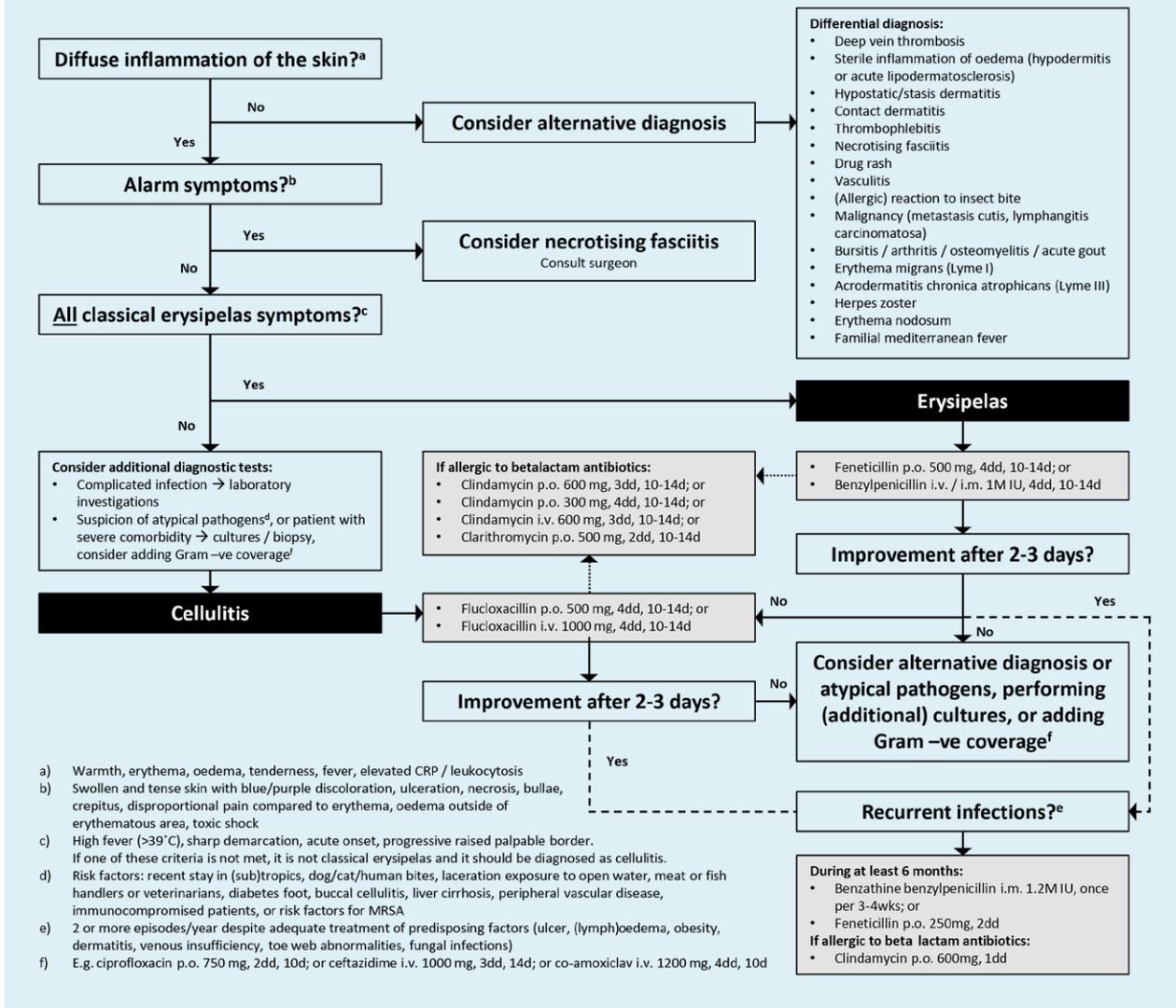
Stasis dermatitis can mimic all symptoms, including mild leucocytosis and/or CRP elevation. Its origin lies in chronic venous insufficiency, which causes proliferation and increased permeability of dermal capillaries. Leucocytes migrate, cause inflammation, stimulate collagen production, and thus induce dermal fibrosis.²³ Erythrocyte extravasation causes brown skin pigmentation.²⁴ Untreated, stasis dermatitis can progress to lipodermatosclerosis, which is characterised by a fibrotic tightening and sometimes ulceration of the skin above the ankles. Compression therapy can correct haemodynamic effects and cytokine levels.¹³

Imaging is sometimes indicated. As DVT does not occur more often in patients with cellulitis than those without, routine DVT screening is not recommended.²⁵ When ultrasound was only utilised among uncertain 'DVT

vs cellulitis' diagnoses, 17% turned out to have DVT.²⁶ Ultrasound may detect occult abscesses, or disprove 'abscesses' mistakenly diagnosed during physical examination.²⁷ Computed tomography is not warranted due to nonspecific findings.²⁸ Magnetic resonance imaging and the Laboratory Risk Indicator for Necrotising Fasciitis score might help distinguish between necrotising fasciitis and cellulitis, but as yet neither have proven superior to clinical suspicion and subsequent surgical exploration.²⁹ Uncomplicated superficial abscesses with erythema can be difficult to distinguish from primary cellulitis with secondary abscesses.³⁰ Uncomplicated abscesses are treated with incision and drainage,³¹ but two recent trials show cure rate increases from 69-74% to 81-83% with adjunctive antibiotics.^{32,33}

Risk factors

Multiple physical barriers and active protective mechanisms prevent the invasion of skin commensals and thus the occurrence of infection (*figure 3a*). An intact vasculature will help maintain the integrity and function

Figure 1. Management flowchart of cellulitis and erysipelas, adapted from the Dutch 2013 guidelines¹¹

of all these barriers and mechanisms. Deficiencies in skin integrity, immunity or vasculature can be considered risk factors for the development of cellulitis (figure 3b). Old age, diabetes and obesity cause defects in all three of these areas, and thus confer a relatively high risk. This combination of risk factors is often seen in patients with cellulitis who are hospitalised. The biggest risk factor, however, is a positive history for cellulitis.³⁴ Old age comes with skin atrophy, poor circulation, immunosenescence, and comorbidities such as diabetes or congestive heart failure. Malnourishment causes impaired wound healing, decreased skin elasticity and integrity, and relative immunosuppression.³⁵ Incidence, complication (e.g. bacteraemia, osteomyelitis, endocarditis) and hospitalisation rates are all higher in diabetic patients.³³ Most cases of cellulitis in diabetic patients will be attributable to diabetic foot associated skin defects, but

more than a quarter of the cases of culture-positive diabetic cellulitis occur on non-foot locations.³⁴ In morbid obesity, the skin is more susceptible to damage and takes longer to repair.³⁶

Some seasonal variability has been observed. Streptococcal skin infections occur more frequently in the winter in cold countries,^{55,56} while warmer regions see a higher erysipelas incidence during the summer.³⁷

Skin microbiome alterations have been observed in diseases such as atopic dermatitis, where more staphylococci and fewer streptococci are present, but also in acne.⁵⁷ *S. aureus* is shown to be overrepresented in the peri-abscess skin microbiome.⁵⁸ Pioneering studies have revealed that commensals can influence the composition of the local microbiome and alter local immunity,⁵⁹ but future studies will have to reveal relationships between the microbiome and cellulitis.

Table 1. Mimickers of cellulitis and how to recognise them

Mimicker	Signs suggestive for this diagnosis
Stasis dermatitis ¹²	Bilateral nature (is extremely rare for cellulitis), slow onset of symptoms, hyperpigmentation, superficial desquamation
Lipodermatosclerosis ¹²	Acute: pain above the medial malleolus Chronic: Inverted champagne bottle effect (leg diameter narrows below the calf), history of venous insufficiency, bronze-brown skin
Stasis ulcers ¹³	Ulcer in patient with long history of chronic venous insufficiency
Gout ¹⁴	Focal swelling and erythema limited to joints (e.g. knee or first metatarsophalangeal joint), history of gout, tophi, increase in serum uric acid
Deep venous thrombosis ¹⁵	History of immobilisation or cancer, thrombosis on duplex scan; no fever
Ecthyma ¹⁶	Shallow ulcer with punched-out borders and adjacent erythema
Erysipeloid ¹⁶	Red hands, people who work with animals
Impetigo ¹⁶	Crusted blisters, brown-yellow scabs erosions and erythema, mostly in children
Lyme disease ¹⁶	Painless spreading sharply demarcated erythema with central pallor (erythema migrans)
Eosinophilic cellulitis ¹²	Eosinophilia, indurated plaques, itching and burning before plaque formation
Contact dermatitis ¹²	Erythema confined to areas in contact with irritant (soaps, detergents, hobby materials, etc.)
Necrotising fasciitis ¹⁷	Pain disproportionate to clinical findings and outside of lesion margins, rapid onset, systemic toxicity, bullae, purple or blue discoloration of the skin, cutaneous crepitations

Figure 2. Mimickers of cellulitis. Left: inflamed lower leg due to stasis dermatitis with secondary impetiginisation. Centre: hyperpigmentation due to venous insufficiency. Top right: erythema and swelling of left forefoot due to gout of first metatarsophalangeal joint (podagra). Lower right: chronic venous ulceration and tightened ankle due to lipodermatosclerosis. Top right image licensed under Creative Commons Attribution 3.0 Germany license, author 'Gonzosft', other images courtesy of Dr. A.P.M. Lavrijsen

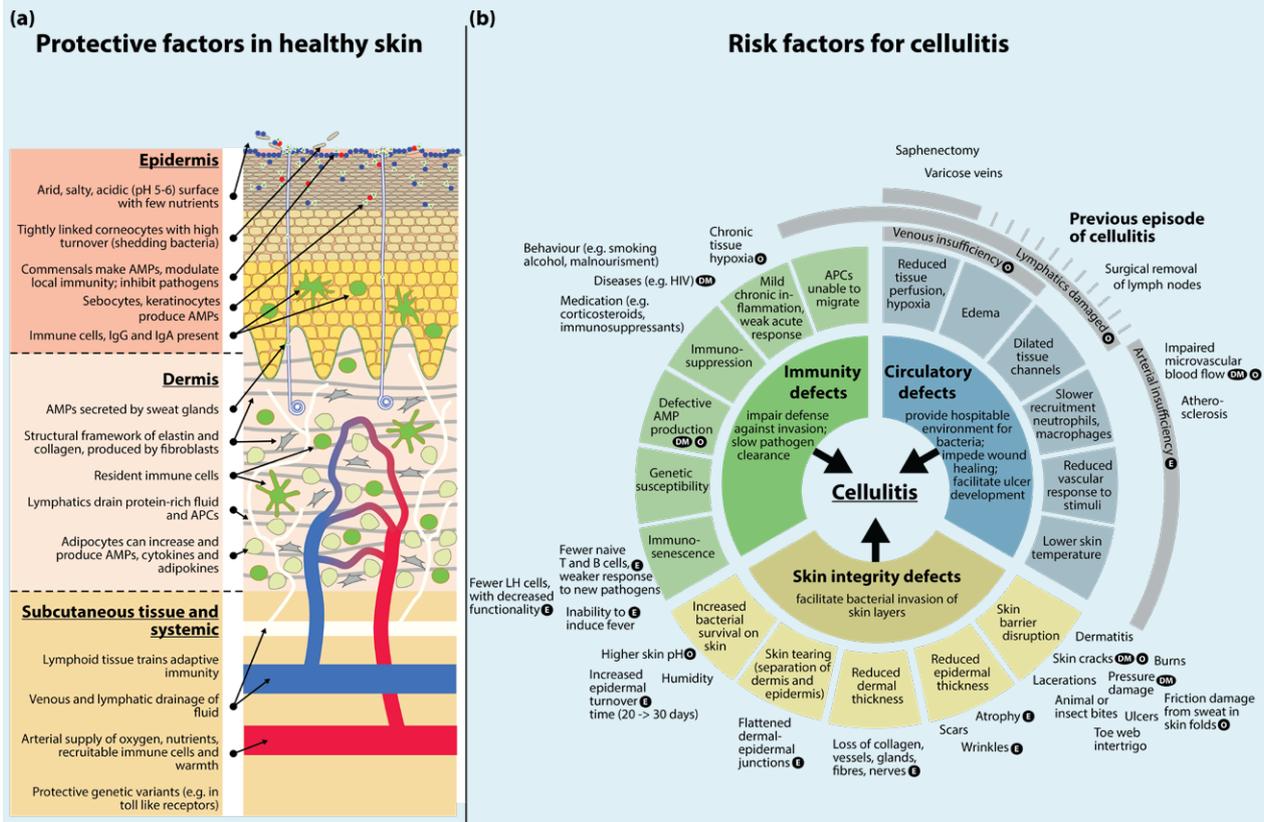


To admit, or not to admit

The 7% of patients who are hospitalised cause 83% of the total healthcare expenditure associated with cellulitis.⁶ Unfortunately, as yet there are no validated, prospectively evaluated admission guidelines. One system distinguishes

classes with supposedly increasing mortality and therapy failure rates based on systemic symptoms, comorbidity and the Standardised Early Warning Scores.^{60,61} Two cohort studies compared this system with current clinical practice: one retrospectively, one prospectively.^{62,63}

Figure 3. An aetiological approach to factors protecting against (a) or predisposing for (b) cellulitis



Factors associated with elderly (E), diabetic (DM) or obese (O) patients are marked with black circles. AMPs = antimicrobial peptides; IgG = immunoglobulin G; IgA = immunoglobulin A; APCs = antigen presenting cells; HIV = human immunodeficiency virus; LH = Langerhans.³⁴⁻³²

Overtreatment of infections that the system classified as mild (class I and II) was very common, while most of the severest infections (class IV) were undertreated. In one of the two studies, only 5 of 6 (83%) class IV patients had achieved complete resolution of symptoms at the end of therapy, compared with 100%, 98% and 96% in classes I-III.^{62,63} One explanation for this is that factors not incorporated in this system currently have a substantial effect on admission and treatment practices.

Pragmatically, one could consider admission for patients with (1) poor disease perception, (2) intake problems, (3) an altered mental status, or (4) disease progression despite adequately dosed oral antibiotics. Severity or dysregulation of comorbidity (e.g. diabetes, immunodeficiency, obesity, or cardiac, renal or venous insufficiencies) and severity of infection (e.g. systemic symptoms, organ failure) should also be taken into account.^{11,64}

Factors predicting oral therapy failure may also be indications for admission for intravenous antibiotics. Retrospectively identified factors associated with failure of oral antibiotic therapy include fever, chronic leg ulcers, chronic oedema and lymphoedema, prior cellulitis in the same area, and wound infections.^{65,66} Additionally, after treatment in an observation unit for 24 hours, patients

with cellulitis of the hand, an elevated lactate, fever, history thereof, or multiple comorbidities were more likely to be admitted.^{67,68} However, this mainly reflects clinical practice rather than need for admission.

Alternatively, outpatient parenteral antibiotic therapy, where intravenous antibiotics are given at home or on outpatient basis, can avoid or shorten hospitalisation for selected patients and is usually preferred by patients.⁶⁹

Antibiotic treatment

One might wonder if a proportion of cases of cellulitis are self-limiting and do not require antimicrobial agents. It is noteworthy that in clinical trials performed in the pre-antibiotic era, in which the effects of horse serum and ultraviolet light were evaluated, cure rates of 70% were observed.⁷⁰ On the other hand, it has also been demonstrated that inadequate empirical antibiotics are associated with prolonged treatment durations and length of hospital stay.⁷¹ Current treatment recommendations are summarised in figure 1.

Streptococci and *S. aureus* are the most common pathogens identified in patients with cellulitis (table 2), and accumulating evidence from prospective convalescent serology studies suggests that > 70% are caused by

Table 2. *Causative agent of cellulitis depending on culture methodology*

Culture method	Cultured/total patients, % positive cultures	Pathogen distribution	Factors which increase yield	Notes
Blood culture	2731/unknown, 4% (+3% contamination) ^{3*} 555/1142, 9% (+2%) ² 250/476, 4.8% (+1.6%) ⁷²	GAS: 24-26% OS: 37-58% SA: 8-25% GNB: 0-23%	Increased blood volume cultured, extensive infection, high CRP, fever, diabetes, chronic ulcer, alcoholism, impaired immunity, immersion injuries, animal bites. ⁷² Age >65, non-lower extremity involvement, cirrhosis, systemic inflammatory response syndrome ⁷³	Unknown if patients with Gram-negative bacteraemia had risk factors. ³ Blood cultures rarely elicit change of antibiotic class ⁷⁴
(Wound) swab culture	343/1142, 72% ² 127/216, 75% ⁴	GAS: 21-23% OS: 26-39% SA: 62-74% GNB: 10-12%	Debridement and irrigation of wound before swabbing, to avoid culturing colonisers ⁷⁵	Role of <i>S. aureus</i> and Gram negatives unknown (coloniser vs pathogen), as BHS aetiology was often confirmed or probable despite <i>S. aureus</i> growth in cultures ⁴
Punch biopsy / needle aspiration culture	541/808, 24% ^{76*}	GAS: 27% OS: 11% SA: 51% Others: 17%	Take from point of maximum inflammation, not leading edge ⁷⁷	
Combination of wound culture, blood culture and/or serology	432/465, 48% (83% of purulent infections, 36% of non-purulent) ⁷⁸	BHS: 46% (5% purulent, 70% non-purulent) SA: 30% (60%, 12%) GNB: 11% (13%, 10%) Polymicrobial: 10% (19%, 5%)		

*Systematic review; GAS = group A streptococci; OS = other streptococci; SA = *Staphylococcus aureus*; GNB = gram-negative bacteria; BHS = beta-haemolytic streptococci.

streptococci.^{4,79} Atypical pathogens can be observed in patients with selected conditions (table 3). In contrast to diabetic foot infections, diabetic non-foot infections are generally not caused by atypical pathogens.⁸⁷ In the Netherlands, the preferred small spectrum agent covering both methicillin-susceptible *S. aureus* and beta-haemolytic streptococci is flucloxacillin. Confirmed streptococcal infections can be treated with benzylpenicillin or feneticillin. Co-amoxiclav and clindamycin are alternative options. Clindamycin is recommended in case of beta-lactam allergies, and inhibits streptococcal and staphylococcal toxin production. Clindamycin is also thought to have better tissue penetration than beta-lactams. However, clindamycin is highly concentrated intracellularly, and studies measuring tissue concentrations used homogenised tissues and thus also measured intracellular clindamycin.⁸⁸ This overestimates relevant clindamycin levels in the extracellular fluid, while the primarily extracellular beta-lactam concentration is diluted by the released intracellular volume and thus underestimated.⁸⁸ Of note, some *S. aureus* strains have inducible resistance

for clindamycin, showing growth inhibition in vitro but resistance in vivo.^{89,90} In the Netherlands, around 10% of *S. aureus* from selected general practice patients and hospital patients show (inducible) resistance to clindamycin, compared with less than 3% for flucloxacillin.⁹⁰ This makes clindamycin less preferable as an empirical choice. Evidence does not favour one agent over others, although there is a major lack of evidence in this area.⁹¹ One study found pristinamycin to be slightly more efficacious than penicillin in a non-blinded trial, but did not account for penicillin not covering *S. aureus*.^{3,92} Beta-lactams were as effective as non-beta-lactams in a cohort study.⁹³ A recent meta-analysis comparing penicillins or cephalosporins with macrolides or lincosamides (such as clindamycin) found similar efficacy between the two groups.⁹⁴ If one needs to cover multi-resistant *Staphylococcus aureus* (MRSA), vancomycin remains the first choice of treatment, with linezolid as an alternative.⁹⁵ Additionally, three novel antibiotics have recently been approved by the European Medicines Agency for treatment of skin infections: oritavancin and dalbavancin, two (lipo)glycopeptides, and

Table 3. Conditions with possible atypical pathogens

Condition	Possible atypical pathogens
Neutropenia ⁸⁰	<i>Escherichia coli</i> Enterobacteriaceae <i>Pseudomonas aeruginosa</i>
Liver cirrhosis ^{81,82}	<i>E. coli</i> , <i>Klebsiella</i> spp, <i>Pseudomonas</i> spp, <i>Proteus</i> spp, <i>Aeromonas</i> spp, <i>Vibrio</i> spp, <i>Acinetobacter</i> spp
Diabetic foot infection ⁸³	
- Chronic ulcer, or ulcer previously treated with antibiotics	Enterobacteriaceae
- Macerated ulcer	<i>P. aeruginosa</i> (in combination with other organisms)
- Long duration nonhealing wounds with prolonged, broad-spectrum antibiotic treatment	Enterococci, diphtheroids, Enterobacteriaceae, <i>Pseudomonas</i> spp, nonfermentative gram-negative rods
Fresh or salt water exposure ⁸⁴	<i>Aeromonas hydrophila</i> , <i>Edwardsiella tarda</i> , <i>Erysipelothrix rhusiopathiae</i> , <i>Mycobacterium fortuitum</i> , <i>Mycobacterium marinum</i> , <i>Shewanella putrefaciens</i> , <i>Streptococcus iniae</i>
- Tropical/warm water	<i>Chromobacterium violaceum</i> , <i>Vibrio vulnificus</i>
Fish fin or bone injuries ^{84,85}	<i>Enterobacter</i> spp, <i>Erysipelothrix rhusiopathiae</i> , <i>Klebsiella pneumoniae</i> , <i>Mycobacteria marinum</i> , <i>Streptococcus iniae</i> , <i>Vibrio vulnificus</i>
Human bites ⁸⁶	<i>Eikenella corrodens</i> , <i>Haemophilus</i> spp, Enterobacteriaceae, <i>Gemella morbillorum</i> , <i>Neisseria</i> spp, <i>Prevotella</i> spp, <i>Fusobacterium</i> spp, <i>Eubacterium</i> spp, <i>Veillonella</i> spp, <i>Peptostreptococcus</i> spp
Cat or dog bites ⁸⁶	<i>Pasteurella</i> spp, <i>Neisseria</i> spp, <i>Corynebacterium</i> spp, <i>Moraxella</i> spp, <i>Enterococcus</i> spp, <i>Fusobacterium</i> spp, <i>Porphyromonas</i> spp, <i>Prevotella</i> spp, <i>Propionibacterium</i> spp, <i>Bacteriodes</i> spp, <i>Peptostreptococcus</i> spp

tedizolid, an oxazolidinone, all showing potent activity against MRSA similar to vancomycin and linezolid (table 4).⁹⁶ Oritavancin and dalbavancin both have terminal half-lives of over two weeks and thus only require a single intravenous dose to reach cure rates non-inferior to a 2-week course of vancomycin.^{98,103} Whether this actually reduces the number of admissions or total treatment costs remains to be evaluated.

Optimising antibiotic use

For oral flucloxacillin, proper timing of intake (before or long after meals) optimises the bioavailability to ~55%.¹⁰⁴ Beta-lactams reach lower serum concentrations in obese patients due to altered distribution volumes and clearance, so these patients might benefit from higher oral dosing, or more frequent intravenous dosing.¹⁰⁵ This is underscored by the fact that obese patients tend to have lower cure rates.^{106,107}

The optimal duration of antibiotic treatment of cellulitis is unknown. One study suggested that patients with cellulitis who are treated on an outpatient basis only require 5 days of therapy when signs of improvement are seen.¹⁰⁸ However, this study used unconventional

numbers for its power calculation, had a dropout rate of 30% before randomisation due to non-improvement, included relatively young and healthy subjects and made use of levofloxacin as study drug.¹¹ Community-acquired pneumonia, pyelonephritis and intraabdominal infections require shorter antibiotic treatments than we previously thought necessary.¹⁰⁹⁻¹¹¹ Whether cellulitis treatment can also be shortened is under investigation.¹¹²

Some patients have an increased risk of a complicated infection. Obesity predisposes to local complications such as bullae, abscess formation, haemorrhagic lesions and necrosis.^{113,114} Smoking and delays in antibiotic treatment are also linked to abscess formation.¹¹³ Patients with congestive heart failure, neutropenia, hypoalbuminaemia, an altered mental status or discharge from the lesion have an increased risk of experiencing adverse outcomes, in terms of death, local complications (e.g. requiring surgical drainage) or systemic complications (e.g. multi-organ failure).⁷

Non-antibiotic management

Additional non-antibiotic management options can potentially improve outcomes. Compression therapy has

Table 4. *New antibiotics for skin and soft tissue infections*

Agent	Dosing	Dose adjustments for kidney function	Early clinical response (mITT)*	Investigator assessed clinical cure post-treatment (mITT)*	Cellulitis specific*	Inclusion criteria for study population	Notes
Dalbavancin ^{96,97}	1500 mg iv once, or two once-weekly doses of 1000 mg iv and 500 mg iv	75% of dose in creatinine clearance <30 ml/min	80% vs 80%	96% vs 97%	79% vs 77% ECR; 91% vs 92% CSEOT	<ul style="list-style-type: none"> - 85 ≥ age ≥ 18 - Wound infection, cellulitis or major cutaneous abscess, each with a minimum surface area of 75 cm² (or 50 cm² for face cellulitis) - Suspected or confirmed gram-positive bacteria - Hospitalised for at least 3 days of intravenous antibiotics - At least two local and one systemic signs of infection 	<p>Comparator is vancomycin</p> <p>CSEOT = decrease in lesion size from baseline, temp ≤ 37.6, no fluctuance or heat/warmth, tenderness/induration no worse than mild, at end of therapy. Increased ALT/AST levels, 12% of patients have reduced platelets</p>
Oritavancin ^{96,98,99}	1200 mg iv once	None	80-82% vs 79-83%	80%-83% vs 80-81%	67% vs 75% ECR; 71% vs 76% PTE	<ul style="list-style-type: none"> - Age ≥ 18 - Wound infection, cellulitis/erysipelas (onset within 7 days prior) or major cutaneous abscess, each with a minimum surface area of 75 cm² - Suspected or confirmed gram-positive bacteria - Hospitalised for at least 7 days of intravenous antibiotics - At least two local and one systemic signs of infection 	<p>Comparator is vancomycin</p> <p>Serious hypersensitivity reactions reported. Caution warranted in case of allergy to other glycopeptides, including vancomycin. Falsely elevated PT and PTT, increases bleeding risk of warfarin. Relatively healthy study population in registration trials</p>

Agent	Dosing	Dose adjustments for kidney function	Early clinical response (mITT)*	Investigator assessed clinical cure post-treatment (mITT)*	Cellulitis specific*	Inclusion criteria for study population	Notes
Tedizolid ¹⁰⁰⁻¹⁰²	Once daily 200 mg iv or po, 6 days	None	82% vs 79%	87% vs 87%	78% vs 76% ECR; 88% vs 82% IACPT	<ul style="list-style-type: none"> - Age ≥ 12 - Wound infection, cellulitis/ erysipelas or major cutaneous abscess, each with a minimum surface area of 75 cm² and onset within 7 days prior - Suspected or confirmed gram-positive bacteria - Minimum of local and systemic signs of infection depend on infection type 	<p>Comparator is linezolid</p> <p>Cellulitis-specific investigator-assessed post-treatment cure rate only available from ESTABLISH-I</p>

mITT = modified intention to treat; IV = intravenous; *all percentages are listed as success chance in investigational treatment group vs comparator group, no differences were statistically significant; ECR = early clinical response; CSEOT = clinical status at end of therapy; WBC = white blood cell; IACPT = investigator-assessed cure post treatment; PTE = post-treatment evaluation.

long been, and still is, cause for debate. Advocates claim there is an accelerated reduction of oedema and pain, and shorter time to cure. Currently, no evidence supports this claim. Patients, however, often report side effects such as pain, dry skin, itching, constriction and slipping.^{115,116} It is unknown if the altered haemodynamics affect the time to microbiological cure. The adequacy of applied bandages varies in clinical practice, and inadequately applied bandages can cause pressure ulceration, thus unnecessary harm.^{117,118} An alternative to reduce oedema in the acute phase is passive leg elevation. To prevent persisting lymphoedema from causing recurrences, compression therapy is indicated when lymphoedema persists for several weeks after antibiotic treatment.¹¹ Compression stockings should follow initial bandaging, provided the patient's arterial disease status allows it.¹¹⁸

The use of anti-inflammatory drugs in addition to antibiotic therapy might be beneficial. In a proof-of-concept study, adjunctive non-steroidal anti-inflammatory drugs (NSAIDs) led to faster regression and resolution of symptoms.¹¹⁹ Similarly, patients receiving adjunctive oral prednisone (2 days 30 mg, 2 days 15 mg, 2 days 10 mg, 2 days 5 mg) had earlier resolution of symptoms and

intravenous to oral antibiotic switches.^{120,121} Whether these drugs also affect microbial eradication is as yet unknown.

Recurrent cellulitis

Almost 30% of admissions for cellulitis are for recurrent cellulitis.¹²² Two, three and five year recurrence rates are 17%, 29-47% and 47%, respectively.^{38,123-125} Five-year recurrence rate is 57% in patients with a history of recurrence.¹²⁵ For HIV-infected patients, one- and three-year recurrence rates are 29% and 47%.¹²⁶ Independent of persisting risk factors that might explain recurrences, the first episode's inflammation has also likely damaged local lymphatic channels. Drainage is then insufficient, antigen presenting cells cannot migrate, and accumulating protein-rich fluid accommodates invading bacteria.¹²⁷

Lymphoedema is the most important risk factor for recurring cellulitis, and 25-60% of recurrent cellulitis patients suffer from chronic oedema.^{122,124} Obese patients have more recurrences and CRP and leucocyte counts are higher in these recurrences.³⁹ For HIV-infected patients specifically, non-hepatitis liver disease, intravenous catheters or intravenous drug use increase the recurrence

Textbox 3. Questions for future research

What is the best way to...

- ... distinguish cellulitis from its mimickers?
- ... obtain a representative microbiological diagnosis?
- ... effectively reduce recurrences?

What is the role of...

- ... the skin microbiota in the aetiology of cellulitis?
- ... compression therapy in its management?
- ... anti-inflammatory agents in disease management?
- ... pathogen reservoirs in recurrences?

Which patients are likely to...

- ... not require antibiotics at all?
- ... succeed with a shortened treatment duration?
- ... fail on outpatient therapy?
- ... require higher doses of antibiotics?
- ... require extended treatments?

risk.¹²⁶ All persisting risk factors are also likely to increase the chance of recurrences, and should be treated vigorously when possible. Lymphoedema warrants treatment with compression therapy. Tinea pedis should be treated with topical azoles in order to decrease the chance of recurrence. Frequent and meticulous interdigital web space cleansing prevents skin damage, bacterial overgrowth and bacterial invasion.¹²⁷

S. pyogenes is able to survive and replicate within macrophages.¹²⁸ Theoretically this might elicit recurrences. However, recurrence rates are similar between patients receiving antibiotics with or without intracellular activity.¹²⁹ When infections recur despite adequately treating risk factors, prophylactic antibiotics prevent recurrences.¹³⁰ In the PATCH I trial, which randomised 274 patients with two or more episodes to either twice daily low-dose oral penicillin or placebo, recurrence rates were significantly lower in the penicillin group (22% vs 37%) after one year, although this effect wore off after cessation of treatment.¹³¹ For recurring *S. aureus* infections, on-demand therapy can be considered. *S. aureus* eradication or hygiene measures do not prevent recurrent *S. aureus* skin infections.^{132,133}

Future perspectives

An overview of knowledge gaps which, if addressed, could advance our understanding of the pathophysiology of cellulitis and improve its clinical management is given in *textbox 3*. A major challenge is the high rate of misdiagnoses which can bias clinical trials towards non-inferiority.⁷⁰ To determine applicability and reliability of trial results, it is imperative to document results

from abscesses and cellulites separately, to accurately describe criteria and definitions, to extensively document clinical and microbiological characteristics, and to report information on additional procedures such as surgical drainage or limb immobilisation.¹³⁴ For this relatively simple infection which has plagued humanity for so long, there still is a lot to discover.

ACKNOWLEDGEMENT

We thank Dr. Harjeet Singh Virk for critically reviewing the manuscript.

DISCLOSURES

The authors were supported by the Netherlands Organisation for Health Research and Development (ZonMW; grant no. 836011024). We have no conflicts of interest to report.

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