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What diagnostic strategies can help differentiate cellulitis from other causes of red legs in primary care

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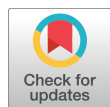
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PRACTICE

UNCERTAINTIES

What diagnostic strategies can help differentiate cellulitis from other causes of red legs in primary care?

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What you need to know

- Red legs owing to non-infectious causes are often misdiagnosed as cellulitis, resulting in unnecessary antibiotics and hospitalisation
- Novel approaches such as thermal imaging, clinical prediction models, point-of-care tests, and a visually based computerised diagnostic decision support system could potentially aid the diagnosis of cellulitis, but there is very limited and weak evidence to support their use in primary care
- Clinically, a unilateral presentation increases the odds of cellulitis, and lack of elevated temperature compared with the unaffected limb can help rule out cellulitis

Cellulitis is the most common bacterial infection causing red legs. It is treated with antibiotics, and patients with severe disease may need to be hospitalised.¹⁻⁴ In 2017-18, 317 522 patients were given a diagnosis of cellulitis in UK hospitals.⁵ The true incidence, including patients managed through primary care, is likely to be higher.

Redness is often accompanied by other classic signs of inflammation: tenderness, warmth, and swelling. Other causes of red legs can present with some, or all, of these common symptoms⁶ (table 1). These conditions may be misdiagnosed as cellulitis. Studies in US emergency departments have reported that between 28% and 30.7%⁷⁻⁹ of cellulitis diagnoses are incorrect. Misdiagnosis can result in unnecessary antibiotic treatment¹⁰ and hospitalisation. Conversely, untreated cellulitis can have complications such as extensive tissue damage and necrosis, disseminated infection, septic shock, and potentially death.¹¹ Figures 1 and 2 show alternative diagnoses for red legs.

Differentiating red legs with bacterial causes from those with non-infectious causes presents a diagnostic dilemma in primary care. A systematic review published in 2019 highlighted the lack of validated diagnostic aids for lower limb cellulitis.^{12 13} In this review we also included studies of patients with cellulitis of any site on the body, and additionally searched conference

abstracts. We excluded any technology or test that was unsuitable for use in primary care.

What is the evidence of uncertainty?

Search strategy and study selection

We searched Medline, Embase, and Web of Science from inception to July 2019 using terms for

Skin or soft tissue infection including: cellulitis (MeSH term) OR bacterial skin disease OR soft tissue infections OR wound infections OR skin diseases OR bacterial OR erysipelas AND

Diagnosis of skin infections including: diagnose* OR detect* OR screen* OR test*

Devices to aid differentiation of infectious from non-infection cases including: point of care testing, skin AND thermometers OR thermography, skin temperature, telethermogra*, bio* OR chem* OR electrochem* sensor OR sensors OR probe

We included studies of patients with skin or soft tissue infections, including cellulitis, erysipelas, and necrotising fasciitis. We included studies if they reported on the detection of skin infections, or investigated the differential of infectious and non-infectious skin

Studies of other infections, management strategies, prognosis, or severity were excluded, as were studies of technologies that were unsuitable for primary care

To find ongoing research we searched UK (ISRCTN), EU (clinicaltrialsregister.eu), and US (clinicaltrials.gov) trial registries for trials concerning diagnosis of cellulitis, erysipelas, bacterial skin disease, skin infections, and skin inflammation

We found eight small observational studies investigating four different diagnostic strategies for cellulitis that are non-invasive and potentially viable in primary care (box 1). Table 2 describes the findings of these studies. There is insufficient evidence to recommend implementation of any of these strategies in primary care. Seven of eight studies recruited patients from emergency departments, who may have had more severe symptoms than those presenting to primary care. All studies used highly selective populations, including only patients who were suspected to have cellulitis by an emergency department clinician or dermatologist and excluding patients with other

relevant diagnoses such as soft tissue abscess, osteomyelitis, and diabetic ulcers.^{8 14 19} In an undifferentiated primary care population test performance may be poorer.

Box 1: Possible diagnostic aids to detect cellulitis in primary care

Thermal imaging

Thermal imaging compares the temperature of an area of suspected cellulitis with a contralateral site on the body. Thermal cameras are available as smartphone attachments

Clinical prediction models

ALT 70

Using final discharge diagnosis of cellulitis as a reference standard, four features were found to be predictive of "true" cellulitis: Asymmetry (3 points), Leucocytosis (1 point), Tachycardia (1 point), and age ≥ 70 (2 points).

Unilateral leg involvement was associated with an adjusted odds ratio of 8.65 for cellulitis, the highest of the four variables in the score¹⁴

NEWHAvUN score system

New onset, Erythema, Warmth/fever, History of trauma, Ache, Unilaterality and Number of white cells¹⁵

Visually based computerised diagnostic decision support system (VCDDSS)

The VCDDSS suggests alternative diagnoses in the form of peer reviewed photographs or diagrams of medical conditions from the most to the least likely, based on symptoms input by the clinician

Procalcitonin

Procalcitonin is an inflammatory response protein which can be measured at the point of care. Procalcitonin levels greater than 0.25 mcg/L are associated with some bacterial infections¹⁶⁻¹⁸

The quality of all studies, assessed using the QUADAS-2 framework (recommended tool to evaluate the risk of bias and applicability of primary diagnostic accuracy studies)²⁰ was poor. In five studies it was unclear whether the researchers using the novel tests were blind to the confirmed diagnosis. Prolonged time intervals between the test of interest and confirmation of disease in most studies and the use of different methods to confirm diagnosis (in two studies) may have biased the results.

Cellulitis is largely a clinical diagnosis and the lack of a diagnostic reference standard poses a key challenge to assessing the performance of diagnostic tests. Most studies rely on diagnosis of cellulitis by a dermatologist as a proxy diagnostic reference standard with little description of how the dermatologists reached their diagnosis.^{21 22} No in vitro diagnostics can give a definitive diagnosis, at least in part because of the lack of obvious substrate for testing. Superficial swab and blood cultures are typically negative even in true cellulitis^{23 24} and rarely alter management.²⁵ Culture and molecular testing of punch biopsy samples may be useful in patients at risk of specific pathogens (eg, animal or water exposure).¹¹

Is ongoing research likely to provide relevant evidence?

We searched UK, EU, and US registries for ongoing studies and found two of potential relevance. The first, a prospective cohort study,²⁶ aims to evaluate the accuracy of non-contact infrared measurement of skin temperature to distinguish limb cellulitis from pseudo cellulitis in 50 adults. The second, a before-and-after study,²⁷ aims to evaluate point-of-care ultrasound to differentiate cellulitis from non-infected insect bite in 304 children. Both of these studies will recruit from emergency department populations, which are likely to be more selective than those consulting to primary care. However, they

use technologies suitable for primary care and one²⁷ appears well powered to evaluate diagnostic accuracy.

What should we do in the light of the uncertainty?

Given the current limitations in the evidence for the use of novel diagnostic approaches in primary care, clinical assessment is the mainstay of diagnosis. Box 2 lists criteria on history that increase the likelihood of cellulitis. On examination, recent overviews describe classic signs of cellulitis as acute unilateral erythema, pain, heat, swelling, and tenderness.^{2 3 5} There may be ascending lymphangitis and tender groin lymphadenopathy. The affected area may be well demarcated or diffuse.²

Box 2: Clinical features that increase the likelihood of cellulitis

History²⁸

- Previous cellulitis
- Lymphoedema/chronic leg oedema
- Excoriating skin diseases
- Tinea pedis or obvious site for infection to have penetrated through
- BMI >30

The observational studies we identified suggest that, in differentiating cellulitis from other causes of red leg, a unilateral presentation greatly increases the odds of cellulitis. Bilateral cellulitis is uncommon but may complicate chronic dependent oedema or lymphoedema.¹¹

In unilaterally affected limbs, a lack of elevated temperature compared with an unaffected limb can help to rule out cellulitis. Consider alternative diagnoses (table 1), the approach supported by VCDSS, in particular, for patients with bilateral red legs and red legs that are not warmer than other body parts. However, given the ongoing uncertainty and risk of complications, antibiotic prescription is reasonable if in doubt. Consider referring patients with signs of systemic toxicity or uncontrolled comorbidities for hospitalisation.⁴ Identifying necrotising fasciitis requires a high index of suspicion as characteristic features may be absent initially (table 1) and emergency referral to hospital for investigation is indicated.²⁹

Education into practice

- What alternative diagnoses would you consider when a patient presents with a red leg?
- What factors would you consider when making a decision to start antibiotics in a patient presenting with red legs? How could you share the decision making around antibiotic prescribing with a patient where you are not confident in the diagnosis of cellulitis or stasis dermatitis?

What patients need to know

- Several conditions can cause red legs. One of these is a bacterial infection called cellulitis. Cellulitis should be treated with antibiotics to avoid potentially serious complications
- Emergency department studies have found that up to a third of patients seen with red legs are given antibiotics for cellulitis when they actually have another condition for which these are not the best treatment
- Four different kinds of tests have been evaluated to see if they can help doctors tell whether red legs are caused by cellulitis
- These new tests have been evaluated in only small studies, and no studies were conducted in primary care settings
- Before GPs could start using a new test, research would be needed to show that it was able to identify cellulitis accurately in patients seen in general practice, and to show that by using it patient outcomes were improved

Recommendations for further research

Studies of diagnostic accuracy and randomised controlled trials in primary care settings to address the following clinical questions:

What is the test accuracy of procalcitonin/VCDDSS/clinical prediction models/skin surface temperature in the diagnosis of cellulitis in patients with "red legs" compared with current clinical practice using dermatology assessment to confirm diagnosis?

What are optimal thresholds for these strategies for the diagnosis of cellulitis?

What is the impact of novel diagnostic strategies on rate of misdiagnosis, antibiotic prescription, rate of hospitalisation, and patient outcomes including symptom resolution and quality of life?

How could these diagnostic technologies be used to monitor antibiotic response and guide duration of treatment?

How patients were involved in the creation of this article

We shared the research question and our findings with the NIHR Community Healthcare MedTech and IVD Cooperative's "Appropriate antibiotic prescribing" patient and public involvement group. The group suggested that the focus should be on management outside hospital settings, and we incorporated this into our exclusion criteria. Group members advised that recommendations should take into account the likely discomfort or invasive nature of potential tests and their applicability to home monitoring of antibiotic response. We have included these elements in our discussion. We thank these patients for their input.

Competing interests The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: none.

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Contributorship GE, KF, ML, and GH all contributed to the planning, conduct, and report of the work described in this article. GH is responsible for overall content as guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Tables

Table 1 | Distinguishing cellulitis from other causes of red legs. Major alternatives to consider and diagnostic considerations, adapted from clinical guidelines^{1 2 4}

Unilateral causes of red leg	Bilateral causes of red leg
<p>Infective</p> <p>Cellulitis</p> <p>Acute necrotising soft tissue infection</p> <p>Pain out of proportion to appearance, anaesthesia over affected skin, toxaemia, "woody" hard oedema, blisters, bullae</p> <p>Deep sub-acute/chronic infection, eg, Osteomyelitis</p> <p>Flare of longstanding or recurrent symptoms/ diabetic patient, overlying sinus</p> <p>Septic arthritis/bursitis</p> <p>Localised around a joint.</p> <p>Joint movement severely limited</p> <p>Unusual pathogens</p> <p>Exposure to animals, bites, water</p>	<p>Bilateral true cellulitis</p> <p>Historically considered to be rare¹¹ but is increasingly common, complicating chronic dependent oedema or lymphoedema⁶</p> <p>History of chronic swelling or presence of oedema</p> <p>Infected ulcers (diabetic, vascular)</p> <p>May have different microbiological causes from true cellulitis including potentially antibiotic resistant organisms</p>
<p>Non-infective</p> <p>Vascular disease</p> <p>Deep venous thrombosis</p> <p>Typically features of local and systemic inflammation are less marked than in true cellulitis</p> <p>Venous obstruction</p> <p>Swelling higher in the leg. Lack of features of local and systemic inflammation</p> <p>Compartment syndrome</p> <p>History of trauma, severe pain</p> <p>Arterial compromise</p> <p>Reactive hyperaemia may be confused with cellulitis, tissue necrosis can cause overlying inflammation; signs of poor tissue perfusion</p> <p>Crystal arthropathies</p> <p>Inflammation localised around one or more joint; joint movement severely limited; distribution or history suggestive of gout/pseudogout</p>	<p>Vascular disease</p> <p>Varicose/stasis eczema</p> <p>The commonest misdiagnosis for cellulitis; may be mostly unilateral, itchy, brown chronic skin changes</p> <p>Systemic inflammatory diseases</p> <p>Vasculitis, erythema multiforme, pyoderma gangrenosum</p> <p>Multifocal or ulcerating lesions a characteristic distribution or appearance; features of systemic illness</p>

Table 2| Summary of eight* studies evaluating diagnostic strategies for the differential diagnosis of cellulitis versus non-infectious skin conditions

Diagnostic approach	Study reference	Study population	Site of cellulitis	Design; setting	Reference standard	Clinical question	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Summary
Skin surface temperature	Ko 2018 ⁸	32 adults with presumed cellulitis (validation cohort)	Not specified	Prospective cohort; ED	General hospital physician	Cellulitis v pseudocellulitis	Skin temperature differential of 0.47°C between the affected and non-affected limb				A temperature difference of 0.47°C had a reasonable sensitivity (96.6% and 87.5% respectively) for cellulitis as diagnosed by dermatologists
							96.6	50	85.7	100	
	Li 2018 ²⁰	67 adult patients with presumed lower limb cellulitis	Lower extremity	Prospective cohort; ED	Examination by a dermatologist based on clinical impression	Cellulitis v pseudocellulitis	Skin temperature differential of 0.47°C between the affected and non-affected limb				
							87.5	38.1	75.5	57.1	
	Raff 2018 ^{15**}	30 patients with presumed cellulitis	Not specified	Prospective cohort; ED	Diagnosis by a dermatologist (no further details)	Cellulitis v pseudocellulitis	No threshold specified				This study is only available as an abstract and did not provide a validation cohort
							95.2	77.8	90.9	90.0	
Clinical prediction models	Raff 2017 ¹⁶	259 adults with presumed lower limb cellulitis	Lower extremity cellulitis	Retrospective cohort; ED	Final discharge diagnosis	Cellulitis v pseudocellulitis	ALT-70 score of ≥5				
							61.3	70.9	82.2	45.5	
							ALT-70 score of ≥3				
							96.5	29.1	74.9	79.3	
	Li 2018 ²⁰	67 adult patients with presumed lower limb cellulitis	Lower extremity	Prospective cohort; ED	Examination by a dermatologist based on clinical impression	Cellulitis v pseudocellulitis	ALT-70 score of ≥3				
							97.8	47.6	80.4	90.9	
	Ezaldein ¹⁷ 2018	20 adult patients with dermatologist confirmed cellulitis and 37 with dermatitis	Not specified	Retrospective cohort; Not specified	Diagnosis by a dermatologist (no further details)	Cellulitis v stasis dermatitis	NEW HAVUN criteria 4/7				
							100	95.0	NR	NR	
VCDDSS	David 2011 ⁷	145 adult patients hospitalised with presumed cellulitis (in-patient)	Not specified	Prospective cohort; An inpatient population	NA	Cellulitis v cellulitis misdiagnoses	VCDDSS more frequently included the correct alternative diagnosis amongst non-cellulitis cases than assessment by a clinician (18/28 [64%] versus 4/28 [14%], p=0.0003)				Only preliminary data available. The study did not explore whether use of the VCDDSS by ED physicians resulted in fewer misdiagnoses
Procalcitonin	Rast 2015 ¹⁸	48 adult ED patients (31 with erysipelas, 17 with deep vein thrombosis)	Lower limb	Case-control; ED	Clinical diagnosis by the treating physician team	Erysipelas/cellulitis versus deep vein thrombosis	0.1 µg/L				Patients with erysipelas had significantly higher PCT concentrations than those with DVT
							58.1	82.4	85.7	NR	
	Pallin 2016 ¹⁹	21 ED patients with a diagnosis of cellulitis or dermatitis	Skin lesion in a location other than above the clavicle, or on the hand, foot, or genitals.	Case-control; ED	Confirmed microbiological testing	Cellulitis versus pseudocellulitis	<0.5ng/ml (0.5 µg/L)				In contrast to the study above, none of three histopathologically confirmed cases of bacterial cellulitis had detectable PCT levels
							0	NR	NR	NR	

Table 2 (continued)

Diagnostic approach	Study reference	Study population	Site of cellulitis	Design; setting	Reference standard	Clinical question	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Summary
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* Li et al 2018 reported outcomes for a prediction model and skin surface temperature using thermal imaging

** Thermal imaging together with diffuse reflectance spectroscopy

ED=emergency department; PPV=positive predictive value; NPV=negative predictive value; VCDDSS=visually based computerised diagnostic decision support system; NA=not applicable; NR=not reported

Figures

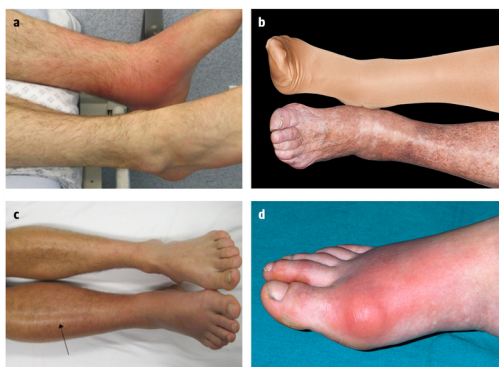


Fig 1 Alternative diagnoses of red legs: (a) cellulitis, (b) varicose eczema, (c) deep vein thrombosis, (d) gout



Fig 2 Concurrent cellulitis and deep vein thrombosis. The manifestation of skin diseases can vary between ethnic groups and skin colours

thebmj Visual summary

Erythema of the leg

Differentiating cellulitis from other causes of red legs in primary care

Cellulitis is the most common bacterial infection causing red legs. It is treated with antibiotics, and patients with severe disease may need to be hospitalised. Studies have reported that between 28% and 30.7% of cellulitis diagnoses are incorrect. Misdiagnosis can result in unnecessary antibiotic treatment and hospitalisation. In its early stages, necrotising fasciitis may resemble cellulitis.



Evidence for diagnostic aids

There is very limited evidence to support the use of any of the following diagnostic aids

Study	Population	Diagnostic aid	Threshold	Sensitivity %	Specificity %
Ezaldein 2018	57	Clinical Prediction Model - New HAVUN ¹	4/7	100	95.0
Raff 2017	259	Clinical prediction model - ALT-70 ²	≥5	61.3	70.9
Li 2018	67	Clinical prediction model - ALT-70 ²	≥3	97.8	47.6
Raff 2017	259	Clinical prediction model - ALT-70 ²	≥3	96.5	29.1
Raff 2018	30	Skin surface temperature ³	None specified	95.2	77.8
Ko 2018	32	Skin surface temperature ³	Differential of 0.47°C	96.6	50.0
Li 2018	67	Skin surface temperature ³	Differential of 0.47°C	87.5	38.1
Rast 2015	48	Procalcitonin	0.1 µg/L	58.1	82.4
Pallin 2016	21	Procalcitonin	0.5 µg/L	0/3 cases were identified	Not reported
David 2011	145	VCDDSS: Visually based computerised diagnostic decision support system	Only preliminary data available	More frequently included the correct alternative diagnosis amongst non-cellulitis cases than assessment by a clinician (18/28 [64%] versus 4/28 [14%], p=0.0003)	

What to do when uncertain

Clinical features that increase the likelihood of cellulitis

Refer to patient history

Previous cellulitis BMI >30
Lymphoedema/chronic leg oedema
Excoriating skin diseases
Tinea pedis or obvious site for infection to have penetrated through

Examine patient for

Acute unilateral erythema, pain, heat, swelling, and tenderness
Can be associated with ascending lymphangitis and tender groin lymphadenopathy
Affected area may be well demarcated or diffuse

What else could it be?

Major alternatives to consider and diagnostic considerations, adapted from clinical guidelines

Unilateral redness

Infective

Acute necrotising soft tissue infection
Deep sub-acute/chronic infection
Septic arthritis/bursitis Unusual pathogens

Non-infective

Vascular disease
Crystal arthropathies

Bilateral redness

Infective

Bilateral true cellulitis
Infected ulcers

Non-infective

Vascular disease
Systemic inflammatory diseases

1. New onset, Erythema, Warmth/fever, History of trauma, Ache, Unilaterality and Number of white cells

2. Asymmetry (3 points), Leucocytosis (1 point), Tachycardia (1 point), and age ≥70 (2 points)

3. Skin temperature differential between the affected and non-affected limb

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