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# The red leg dilemma: a scoping review of the challenges of diagnosing lower limb cellulitis

Running head: Challenges and facilitators in the diagnosis of lower limb cellulitis

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## What is already known about this topic?

Lower limb cellulitis is a common infection presenting in primary and secondary care. Almost a third of cases are misdiagnoses, leading to avoidable antibiotic prescribing or hospital admission.

Research to improve diagnosis of cellulitis is a major priority for patients and clinicians, but evidential review of the challenges of diagnosis and what may help is lacking.

## What does this study add?

This review highlights the current lack of evidence on diagnosis of lower limb cellulitis, wide clinical diversity in its misdiagnosis and emerging approaches to service improvement and diagnostic aids. Challenges for diagnosis and ways of addressing these are illustrated.


## Abstract

**Background:**

Suspected lower limb cellulitis presentations are commonly misdiagnoses, resulting in avoidable antibiotic prescribing or hospital admissions. Understanding the challenges posed in diagnosing cellulitis may help enhance future care.

**Objectives:**

To examine and map out the challenges and facilitators identified by patients and health professionals in diagnosing lower limb cellulitis.

**Methods:**

A scoping systematic review was performed in MEDLINE and Embase in October 2017. Thematic analysis was used to identify key themes. Quantitative data was summarised by narrative synthesis.

**Results:**

Three themes were explored: (i) clinical case reports of misdiagnosis, (ii) service development and (iii) diagnostic aids. Forty-seven different pathologies were misdiagnosed, including seven malignancies. Two different services have been piloted to reduce the misdiagnosis rates of lower limb cellulitis and save costs. Four studies have looked at biochemical markers, imaging and a scoring tool to aid diagnosis.

**Conclusions:**

This review highlights the range of alternative pathologies that can be misdiagnosed as cellulitis, and emerging services and diagnostic aids developed to minimise misdiagnosis. Future work should focus on gaining a greater qualitative understanding of the diagnostic challenges from the perspective of patients and clinicians.

## Introduction

Cellulitis is a common infection of the deep dermis and subcutaneous tissue, with 60% of cases affecting the lower limb [1]. Clinical presentation is typically an acute infection with signs of inflammation including pain, warmth, redness and swelling [2]. A subtype of cellulitis with more pronounced superficial inflammation is known as erysipelas [3].

Unfortunately, 31% of patients admitted from the emergency department (ED) and diagnosed as having lower limb cellulitis are misdiagnoses [4]. Within this group of misdiagnoses, 85% have an avoidable hospital admission and 92% receive unnecessary antibiotics [4]. This burden is significant: in 2016-2017 there were 132,896 recorded cases of cellulitis managed in secondary care in the UK, with a mean length of stay of six days [5].

An important priority for cellulitis research, identified by both patients and health care professionals at the cellulitis priority setting partnership (PSP), is diagnosis [6]. This includes research to assist clinicians in making an accurate diagnosis, identifying atypical presentation of cellulitis in patients with comorbidities and assessing for early signs or symptoms to allow prompt treatment.

A search of Cochrane Database of Systematic Reviews, Prospero and PubMed found no previous systematic reviews looking at the challenges and facilitators when making a diagnosis of cellulitis.

Identifying challenges and facilitators is an exploratory research question suited to a scoping review to gain a broad overview of this topic [7]. Such a review may also assist in identifying gaps for future research on diagnosis in lower limb cellulitis.

The main aim of this scoping review was to explore the challenges and facilitators identified by patients and health professionals in diagnosing lower limb cellulitis.

'Cellulitis' in this paper refers to lower limb cellulitis only.

## Methods

This review was developed using the methodological framework devised by the Joanna Briggs Institute [7]. The protocol was registered on the Centre of Evidence Based Dermatology website in October 2017 [8].

We searched for papers that discussed the challenges and facilitators of diagnosing lower limb cellulitis in primary and secondary care settings.

**Inclusion criterion** – All study designs, any language, misdiagnosis of lower limb cellulitis, erysipelas or skin and soft tissue infection, all age groups, gender, ethnicity, health care settings.

**Exclusion criterion** – Animal studies, laboratory in-vitro studies, the terms 'cellulitis', 'erysipelas' or 'skin and soft tissue infection' were not in the title or abstract, 'diagnosis' not discussed in the abstract, explicitly discussed non-lower limb cellulitis only, conference abstracts, review articles, not a patient, carer or health care professionals' views.

### Databases and search strategy

The following databases were searched on 9 October 2017: Ovid MEDLINE In-Process & Non-Indexed Citations and Ovid MEDLINE 1946 to present (Ovid) and Ovid Embase (1980 to 2017). For grey literature, articles from the first 100 results in Google Scholar were included when entering the search 'challenges in the diagnosis of lower limb cellulitis'.

A search strategy was developed with an information specialist (DG), using the concepts 'cellulitis', 'diagnosis' and 'challenges' with controlled vocabulary (MeSH term and Emtree) and free text headings (Supplementary Table 1).

### Study selection

Following the search, all identified citations were uploaded into EndNote X8 and duplicates removed manually by one reviewer (MP). Titles and abstracts were screened by two reviewers independently (MP and SIL) using a protocol that was initially piloted.

As the results were broad, the selected papers were coded by the challenge or facilitator identified and then grouped into themes by thematic analysis by one reviewer (MP). These themes were reviewed with all other reviewers (SIL, KST and JK).

Three themes were further explored, with full text papers screened by MP and SIL independently.

Disagreements between the two reviewers were resolved through discussion with a third independent reviewer (KST or JK).

### Data extraction

Data was extracted by two independent reviewers (MP and SIL). A data extraction pilot using three papers was initially carried out by two reviewers (MP and SIL). Non-English papers were translated by colleagues proficient in that language or Google Translate.

### Data presentation

Quantitative data was presented as a narrative synthesis.

## Results

From the 3926 initial search results, 2779 records were screened at the title and abstract stage after duplicates were removed. 533 full text articles were assessed for eligibility and 71 included for data extraction [9-79] (Figure 1). Nine papers were foreign language texts: six French, two Spanish and one Turkish.

The articles were first grouped into four themes: clinical cases of misdiagnosis, diagnostic aid, service development and etiology.

*Clinical cases of misdiagnosis* were studies where lower limb cellulitis was the incorrect initial diagnosis or was initially misdiagnosed as another pathology. *Service development* were studies looking at how services set-up may reduce misdiagnosis. *Diagnostic aid* included studies that developed or tested tools to help diagnosis. *Etiology* were studies that discussed microbiological causes of cellulitis.

Three themes were deemed to be of particular relevance and explored further: clinical cases of misdiagnosis, service development and diagnostic aids.

The etiology theme, identifying the microbiological cause of cellulitis, is also an important research topic from the cellulitis PSP [6] . We did not include this theme in this review as the papers identified highlighted treatment failure due to targeting the wrong organism, rather than a wrong diagnosis of cellulitis.

For the themes service development and diagnostic aids, 11 papers were excluded as the site of cellulitis was not specified or the results of lower limb cellulitis were not separated [80-90].

### (i) Clinical cases of misdiagnosis

For the misdiagnosis theme, 66 papers were included, with three observational studies [9,10,11] and 63 case reports or series [12-74].

*Observational studies*

One prospective study found that of the 635 patients referred with lower limb cellulitis to a cellulitis clinic, 210 patients had 44 other diagnoses. Of these other diagnoses, the most common was eczema (118 patients), lymphoedema (14 patients) and lipodermatosclerosis (nine patients) [9]. Another prospective study of children aged under 15, found 19 out of 50 osteomyelitis patients were initially misdiagnosed as cellulitis [10]. One retrospective observational study showed that in 43 patients with an initial clinical suspicion of deep vein thrombosis, nine patients were diagnosed with cellulitis [11].

*Case report and case series*

A total of 94 patients were included overall (43 male, mean age 41) (Supplementary Table 2).

In total, 47 different pathologies were misdiagnosed, with two initially diagnosed as another pathology before being correctly diagnosed as cellulitis [6,39,64]. The pathologies were grouped by specialty: vascular (nine pathologies) was the most common group [13,21,22,24,39,45,52,54,55]. Necrotising fasciitis [40,51,68,71], sarcoidosis [19,32,42,72], lymphoma [33,53,56,59] and chemotherapy related pathology [20,47,67,69] had the most case reports/series as a misdiagnosis.

Typical symptoms and signs of inflammation seen in cellulitis are erythema, pain, swelling, fever and warmth. Of the patients subsequently found to have been misdiagnosed, 74 (79%) had erythema of the skin, 73 (78%) patients experienced pain, 52 (55%) had swelling, 23 (24%) had fever and 19 (20%) had increased warmth of the skin. Unilateral features were present in 73 patients (78%) and bilateral features in 15 (16%) patients. Prior antibiotics were given to 26 (28%) patients.

Ten patients (11%) were later diagnosed with a malignancy [17,18,23,29,33,35,53,56,59,60], including one case of metastatic malignant melanoma [35] and a neonatal case with kaposiform hemangioendothelioma [23].

Box 1

1. If the initial diagnosis is not responding to antibiotics, then an urgent clinical reassessment is warranted, especially prior to further antibiotic use [33].
2. Be aware of more serious pathologies in patients who have non-specific features that are not improving, or if the presentation is out of proportion to clinical findings [51].
3. The core features of infection: erythema, pain, swelling, fever and warmth are seen in cellulitis, but also in numerous other pathologies [67].
4. If more than one limb has been affected, it is unlikely to be cellulitis [17].
5. Cellulitis may be a secondary reactive process to another serious underlying pathology that needs urgent investigation. All alternative differentials should be explored [48].
6. A thorough history from the patient can help distinguish idiosyncratic reactions due to drug treatments or cosmetics, that can be managed conservatively [43].

Key learning points suggested by the authors of included case reports are shown in Box 1.

### (ii) Service development

Two studies had developed services to help reduce the rates of cellulitis misdiagnosis within both primary and secondary care.

*Cellulitis clinic*

One study initiated a new care model with a 'cellulitis clinic' in a single hospital in the UK, operated by nurses and junior doctors from 0900-1700 on weekdays, with faxed or telephone referrals from clinicians for patients diagnosed with suspected cellulitis [9]. Six hundred and thirty-five patients were treated through the specialist service, of which 425 (67%) had cellulitis. 41% were given intravenous antibiotics in the community, with 512 patients avoiding admission for intravenous treatment in the hospital, with a bed day saving of £818,000 over 40 months. In total, 1470 days of antibiotic use was avoided in the non-cellulitis patients.

*Red legs service*

In one hospital in the UK, a retrospective audit of patients who were admitted with bilateral red legs found that 15/50 were misdiagnosed as cellulitis [75]. This hospital subsequently commissioned a nurse led 'red legs' service to manage patients with bilateral red legs. Diagnostic algorithms were developed with relevant clinicians. Clinical photographs were shared with the lead clinicians via the hospital computer system. 77 patients were seen by the service, of which 58 (75%) were discharged and 19 (25%) required a follow up appointment. The cost saving was estimated to be £100,000. From the feedback available, 23 (82 %) patients were extremely satisfied with their level of care.

### (iii) Diagnostic aids to help diagnosis

Four papers looked at developing or using an existing tool to help differentiate lower limb cellulitis from alternative pathologies [76-79] (Table 1). Raff *et al* explored cellulitis as the main pathology [79]. Three studies included lower limb cellulitis patients as a comparison group, where cellulitis and other diagnoses were compared. All four studies were observational studies conducted in different health care specialties.

*Predictive test*

An ALT-70 model was designed that involved assessment of asymmetry (unilateral involvement), leukocytosis (white blood cell count ≥10,000/uL), tachycardia (heart rate ≥90 bpm) and age ≥70 years. A score below 3 had a >83.3% likelihood of pseudocellulitis (an alternative diagnosis to cellulitis) and above 4 had a >82.2% likelihood of cellulitis [79].

*Biochemical test*

When compared to acute gout, delta neutrophil index > 1.7% was the only independent factor for predicting cellulitis (P = 0.002) compared to white blood cell (p=0.41), c-reactive protein (p=0.277) and procalcitonin (PCT) (p=0.122) [78].

*Imaging*

In comparison to patients with Dercum's disease, in cellulitis, attenuation was more linear, diffuse, and non-mass like on computed tomography (CT) and magnetic resonance imaging (MRI). In addition, there was post-contrast enhancement in all three cases of contrast provided to cellulitis patients [77].

Three phase immunoscintigraphy using $^{99}Tc^{m}$-labelled anti-granulocyte monoclonal antibodies was used in patients with infectious diabetic foot, with six out of nine cellulitis lesions showing significantly increased uptake [76].

**Excluded studies**

*Service development*

Looking at service development, four papers were excluded because the site of cellulitis was not specified: three studies in the USA showed that dermatology consultation improves the accuracy of cellulitis diagnosis [80-82] often done in a single consultation [81]. Jain *et al* showed that input from an infectious disease specialist cellulitis clinic improved differentiation from pseudocellulitis, reduced rates of hospitalization and cellulitis recurrence [83].

*Diagnostic aids*

Four studies did not state the site of cellulitis. Of these, David *et al* used a visually-based computerized diagnostic decision support system for patients admitted with cellulitis from the emergency department [84]. Palin *et al* looked at PCT and HLA-DQA1 gene expression amongst cellulitis cases and mimickers [85]. Schmid *et al* and Rosenthall *et al* used MRI [86] and radiophosphate imaging [87] respectively.

Three studies did not separate the results for lower limb cellulitis: Borschitz *et al* utilised a modified Laboratory Risk Indicator for Necrotizing Fasciitis score to differentiate cellulitis from necrotising fasciitis [88], Rahmouni *et al* used MRI [89] and Sullivan *et al* looked at nuclear scintigraphy [90].

## Discussion

### Main findings relevant to clinical practice

This scoping review has identified a lack of research on the challenges and facilitators in diagnosing lower limb cellulitis. Existing literature on misdiagnoses are mainly limited to case reports and studies and were not always specific for lower limb cellulitis.

The 47 different misdiagnoses in case reports/series emphasise the wide differential diagnoses of cellulitis and how important it is to have diagnostic aids and other support to enable clinicians in different settings to make a correct diagnosis.

We found two examples of services developed in the UK to improve cellulitis diagnosis and care. One service showed having cellulitis experts who are more likely to make a correct diagnoses of cellulitis can prevent inappropriate antibiotic use [9]. Another integrated 'red legs' service demonstrated how access to expert advice led to high patient satisfaction and economic savings [75]. This multidisciplinary approach may optimise correct diagnosis for red legs and merits further investigation.

Unfortunately, there is a lack of diagnostic aids for lower limb cellulitis. So far, these have used biochemical tests or imaging, which may be unfeasible in some settings. All four studies were conducted in secondary care, have not been repeated prospectively and did not compare cellulitis with the same differential diagnoses, which is required to improve the validity. Tests that differentiate cellulitis from only one other differential are only useful in very specific clinical presentations. A diagnostic aid to help rule in or rule out cellulitis in a red leg presentation is required.

The clinical cases of misdiagnosis highlight the everyday challenge faced by clinicians when diagnosing lower limb cellulitis. Many patients with an alternative diagnosis can present with features that overlap with typical cellulitis. For primary care physicians, who may see patients present with persistent symptoms despite antibiotic treatment, timely secondary care advice or review should be considered prior to further antibiotic use.

Regarding the diagnostic aids, the ALT-70 model may be a quick tool that would be feasible in the hospital setting, but is not practical in primary care where point of care blood tests cannot always be carried out in a timely way. It is also unlikely that CT and MRI imaging would be used as a first line investigation for cellulitis.

### Strengths and limitations

This scoping review has mapped out the available literature looking at the challenges in the diagnosis of lower limb cellulitis. It is an important research priority topic that was proposed by patients and clinicians. The search terms were broad to capture all relevant papers and two reviewers worked independently throughout when screening and extracting data.

Studies were only included if they discussed lower limb cellulitis, therefore this review can be applied to future lower limb cellulitis research. However, papers that contained useful information were excluded if the site of cellulitis was not clear or results not separated.

Due to the scoping nature of this review, only after the title and abstract screening stage was it apparent that themes were developing. Coding by a second reviewer would have been ideal, although the themes were discussed with all reviewers. Also, as the themes were developed after the initial search, the search terms used may not include all the papers for each theme.

Case reports and case series highlight rare pathologies, which explains why commonly seen diagnoses such as lymphoedema and eczema [9], were seldom reported. This scoping review is not intended to report the epidemiology of cellulitis misdiagnosis, which would be better addressed by observational studies or systematic reviews of prevalence studies.

The clinical features described in the case reports and series, both prior to any treatment and when seen by the authors, were not always clearly separated. Nine foreign text were translated, but it is possible that information could still be misinterpreted.

## Conclusion

This scoping review highlights the current lack of evidence on diagnosis of lower limb cellulitis, wide clinical diversity in its misdiagnosis and emerging approaches to service improvement and diagnostic aids. Further research to gain greater understanding of the challenges and facilitators in diagnosis of lower limb cellulitis through qualitative research, involving patients and clinicians, is required.

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Table 1

| Study, year | Country, setting | Years of study | Study type | Funding source | Number of patient analysed | Mean age (years) | Male, number (%) | Index Test | Reference test for cellulitis | Timeframe for follow up |
|---|---|---|---|---|---|---|---|---|---|---|
| Dominguez-Gadea *et al* (1993) [76] | Spain, department of nuclear medicine and rheumatology (single centre) | 1990 - 1991 | Cohort | None stated | 25 patients with 38 foot lesions. 9 patients had cellulitis | Not provided | Not provided | $^{99}$ Tc$^{m}$- AA scintiraphy | Clinical diagnosis of cellulitis by nuclear medicine physicians | No follow up |
| Petscavage-Thomas *et al* (2015) [77] | USA, department of radiology (single centre) | Not stated | Case series | None stated | 17 – 10 with Dercum's disease and 7 with cellulitis | 52.3 in the cellulitis group | 4 (40%) in cellulitis group | CT, MRI and ultrasound | Clinical diagnosis of cellulitis (unclear who made diagnosis) | No follow up |
| Pyo *et al*, (2017) [78] | South Korea, division of rheumatology (single centre) | 2010-2015 | Case control | Korean health industry development institute | 367 – 184 with acute gout and 183 with cellulitis | 62 | 285 (78%) | Delta neutrophil index | Clinical diagnosis of cellulitis (unclear who made for gout | No follow up |
| Raff *et al*, (2017) [79] | USA, emergency department (single centre) | 2010-2012 | Cross sectional | None stated | 259 – 180 cellulitis and 79 with pseudocellulitis | 63 | 118 (46%) | ALT-70 | Clinical diagnosis by ED physician | 30 days post discharge |

Key features of the four studies included using diagnostic tools or criteria, including the index and reference test for lower limb cellulitis

CT= Computed tomography MRI = Magnetic Resonance Imaging ACR = American College of Rheumatology ED= emergency department

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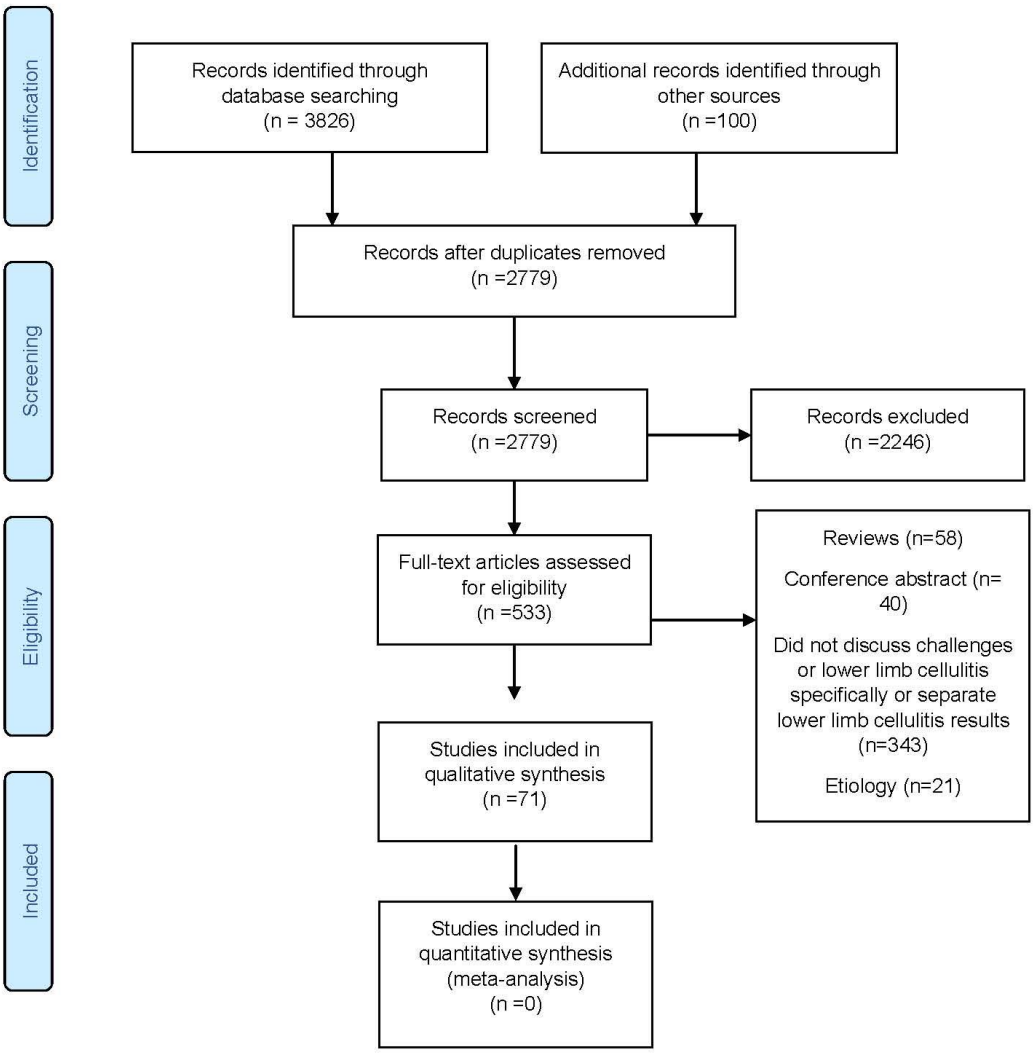
**Figure 1:**




PRISMA flow diagram of the entire search