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Title: A systematic review showing the lack of diagnostic criteria and tools developed for lower limb cellulitis

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Study registration: PROSPERO registration: CRD42017080466

Conflicts of Interest: None declared
What is already known about this topic?

- Diagnosing lower limb cellulitis on first presentation is challenging.
- Approximately one in three patients admitted from the emergency department with suspected lower limb cellulitis do not have cellulitis and are given another diagnosis on discharge. These patients consequently have potentially avoidable hospital admission and antibiotic prescribing.
- There are no diagnostic criteria available for lower limb cellulitis in the UK.

What does this study add?

- This systematic review has identified a key research gap in the diagnosis of lower limb cellulitis.
- There is a current lack of robustly developed and validated diagnostic criteria or tools for use in clinical practice.
Abstract

Background: Cellulitis can be a difficult diagnosis to make. 31% of patients admitted from the emergency department with suspected lower limb cellulitis are misdiagnosed, with incorrect treatment potentially resulting in avoidable hospital admission and antibiotic prescribing.

Objective: We sought to identify diagnostic criteria or tools that have been developed for lower limb cellulitis.

Methods: We conducted a systematic review using Ovid MEDLINE and Embase databases in May 2018, with the aim of describing diagnostic criteria and tools developed for lower limb cellulitis, and assessing the quality of the studies identified, using the QUADAS-2 tool. We included all types of study describing diagnostic criteria or tools.

Results: Eight observational studies were included. Five studies examined biochemical markers, two studies assessed imaging and one study developed a diagnostic decision model. All eight studies were high risk in at least one domain for bias.

Limitations: The quantity and quality of available data was low. Results could not be pooled due to the heterogeneity in findings.

Conclusion: There is a lack of high quality publications describing criteria or tools for diagnosing lower limb cellulitis. Future studies using prospective designs and validated in both primary and secondary care settings are needed.
Introduction

Cellulitis is an acute bacterial infection of the dermis and associated subcutaneous tissue, with 60% of cases affecting the lower limb. Erysipelas is a form of cellulitis that presents with more marked superficial inflammation.

The diagnosis of cellulitis can be challenging, with 31% of presentations of suspected lower limb cellulitis in the emergency department (ED) subsequently given another diagnosis instead of cellulitis. Routine biochemical and haematology blood tests and blood cultures are not specific for cellulitis. This results in avoidable hospital admissions and unnecessary antibiotic prescribing. Definitive diagnostic criteria would potentially improve clinical care and also improve the validity of clinical research on cellulitis by ensuring appropriate case definition, but there are no agreed diagnostic criteria for cellulitis.

Cellulitis cases commonly present to primary care services or the ED. A recent UK cellulitis research priority setting partnership ranked questions on 'diagnostic criteria' as important for future cellulitis research.

The aim of this systematic review was to identify and critically appraise the quality of studies that have developed or validated diagnostic criteria or tools for lower limb cellulitis.

We define diagnostic criteria or tools as: including a minimum of one variable that has been tested against at least one clinical feature. ‘Cellulitis’ in this paper refers to lower limb cellulitis only. Lower limb erysipelas is included as it is clinically indistinguishable from cellulitis.
A preliminary search found no previous systematic reviews looking at the development or validation of cellulitis diagnostic criteria or tools for cellulitis.

Methods

Protocol and registration

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, with additional reference to the Cochrane Handbook for Diagnostic Test Accuracy Reviews. The protocol was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO, record CRD42017080466, November 2017).

Objectives

The primary objective for this review was to identify and describe diagnostic criteria and tools that have been developed for lower limb cellulitis. The secondary objective was to assess the quality of the studies where diagnostic criteria or tools were developed.

Eligibility criteria

Studies including patients with lower limb cellulitis or erysipelas in primary and secondary care, where diagnostic criteria or tools were used for diagnosis were included.

Inclusion criteria

All study types, all languages, any age, gender and ethnicity, patients with lower limb cellulitis or erysipelas, diagnostic criteria or tools.
Exclusion criteria

Animal studies, laboratory *in vitro* studies, literature and systematic review articles, expert opinions, conference abstracts, only including patients with non-lower limb cellulitis, if the site of cellulitis or erysipelas is not clear, if data from lower limb cellulitis or erysipelas cannot be separated, tools to determine etiology, case series <20 patients, <10 lower limb cellulitis or erysipelas patients included.

Database and searches

The following databases were searched on 25 October 2017: Ovid MEDLINE In-Process & Non-Indexed Citations and Ovid MEDLINE 1946 to present, Ovid Embase (1980 to 2017), Cochrane Library and Web of Science Core Collection. An updated search on 22 May 2018 was also undertaken in all the databases to ensure that the results were up-to-date.

Search strategies for these databases were developed with an information specialist (DG) and in consultation with a cellulitis expert (NJL). Concepts were developed: ‘cellulitis’, ‘diagnosis’ and ‘criteria’, with controlled vocabulary (MeSH term and Emtree) and free text headings (Table 1). NICE Evidence was also searched using the term ‘cellulitis’.

For grey literature, the first 100 articles on Google Scholar were included using the search ‘diagnostic criteria for cellulitis’, sorted by relevance.

The reference lists of all studies selected for critical appraisal were screened for additional studies.

Study selection and data extraction
Following the searches, all citations were uploaded into Covidence (2018): a systematic review management software, with duplicates removed by one reviewer (MP). Title and abstract screening, full text screening and data extraction were conducted by two independent reviewers (MP and SL/RKA) using pre-defined templates. Any disagreements that arose between any reviewers were resolved through discussion, or with a third independent reviewer (KST, JK or NJL). Data items sought at the data extraction stage included study aim, type, population, criteria, funding, sample size, index test, reference test and key findings.

Evidence synthesis and risk of bias assessment

All included studies were described in a narrative synthesis. To assess the methodological quality, all studies were assessed using signalling questions in the QUADAS-2 tool by two reviewers (MP and RKA), with disagreements resolved with a third reviewer (SL or EBT). If the information was not clearly provided in the study, then the reviewers assessed the signalling question as ‘unclear’.

For each domain, studies were judged as ‘low risk’ if all signalling questions were ‘yes’; ‘high risk’ if at least one signalling question was ‘no’; or ‘unclear’ if in between.
Results

Study selection

The PRISMA flow diagram shows the result of the complete search (Figure 1). A total of 98 papers were included for full text screening. Of these, 90 papers were subsequently excluded: including 20 studies that did not specify the site of cellulitis and eight studies that did not separate the results of lower limb cellulitis from other sites. Eight studies were included for data extraction.

Study characteristics

Characteristics of all eight included studies are summarised in Table 2. Raff et al explored lower limb cellulitis as the main pathology. Seven studies included lower limb cellulitis patients as a comparison group, where cellulitis and other diagnoses were compared. Six studies were case control studies, with one cohort study and one cross sectional study. The most common setting, in three studies, was the ED. The studies were conducted in six different countries. Kato et al did not include exclusion criteria.

Reference tests
The reference test for cellulitis was a clinical diagnosis in seven studies,\textsuperscript{14-20} with a bone scan used by Fleischer et al.\textsuperscript{13} However, only Rabuka et al clearly stated which specialty made the cellulitis diagnosis.\textsuperscript{17} Two studies followed up patients for up to thirty days to determine the final diagnosis.\textsuperscript{18,19}

**Index tests**

**Studies where cellulitis was the main pathology**

**Predictive score**

In a study to compare cellulitis from pseudocellulitis, Raff et al developed an ALT-70 score out of 7: asymmetry (unilateral involvement, 3 points), leukocytosis (white blood cell count $\geq 10,000$/uL, 1 point), tachycardia (heart rate $\geq 90$ bpm, 1 point) and age $\geq 70$ years (2 points).\textsuperscript{18} An ALT-70 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.\textsuperscript{18}

**Studies where cellulitis was used as a comparator**

**Clinical features**

One study comparing cellulitis and osteomyelitis amongst diabetic patient found that a temperature higher than 37.2°C was predictive of osteomyelitis,\textsuperscript{13} however Malabu et al showed no significant differences in clinical parameters between these groups.\textsuperscript{15}
Rabuka et al showed that distinct margins of erythema were seen in 6 (8%) cellulitis patients vs 0 (0%) in deep vein thrombosis (DVT) (p=0.008). However, when comparing erysipelas and DVT, Rast et al found no significant differences between any physical signs.

**Biochemical and haematological tests**

In a study comparing cellulitis with acute gout, delta neutrophil index (DNI: immature granulocyte count) > 1.7% was the only independent factor for predicting cellulitis (P = 0.002), compared to white blood cell count (WBC) (p=0.41), C-reactive protein (CRP) (p=0.277) and procalcitonin (PCT) (p=0.122). Creatine kinase (CK) was significantly higher in all cases of necrotising fasciitis (NF) compared to cellulitis.

Malabu et al found that in diabetic patients, haemoglobin (p<0.0001) and haematocrit (p<0.0001) were higher in cellulitis patients than in osteomyelitis. However, erythrocyte sedimentation rate (ESR) (p <0.0001), CRP (p <0.0001), platelet count (p<0.01), WBC (p<0.05) and red cell width (RDW) (p<0.05) were higher in osteomyelitis than in patients with cellulitis.

One study compared PCT concentrations in patients with erysipelas and (DVT). Patients with erysipelas had significantly higher concentrations of PCT (p = 0.001). At a PCT threshold of > 0.25 ug/L, the specificity and positive predictive value for erysipelas was 100%. No significant differences were seen between the two groups with regard to CRP concentrations (p = 0.20) and WBC counts (p = 0.14).

In contrast, Rabuka et al found a raised WBC in 21.3% of cellulitis patients versus 50% of DVT patients (p=0.038). This study also found that CK was higher in the cellulitis group compared to DVT.

**Imaging**
In a study comparing cellulitis with lymphoedema using computed tomography (CT) scanning, Shin et al found specific features that were more frequently associated with cellulitis. These were fluid collection ($P = 0.009$); fascial enhancement ($P = 0.043$); inguinal lymph node enlargement at the affected side ($P < 0.001$) and inguinal lymph node medullary fat obliteration ($P < 0.001$).

Rabuka et al looked at ultrasound imaging in patients with a presentation suggestive of cellulitis, with 72 (80%) patients diagnosed with cellulitis after having a negative duplex scan.

**Methodological quality**

**Risk of bias**

The risk of bias for patient selection was high for all eight studies: six used a case control method and the exclusion criteria were not deemed appropriate in two studies as they excluded patients who are more difficult to diagnose (Table 3 and Figure 2). Shin et al had low risk of bias for the index test, by including a pre-specified threshold, whilst the other seven studies did not. Rabuka et al was high risk for the reference standard as some patients received the reference test after the index test, increasing observer bias, whilst the risk was unclear in the remaining seven studies as it is not possible to determine how accurate the diagnosis of cellulitis was. The flow of timing was unclear in seven studies as it was not stated if all the patients received the same reference standard test. Fleischer et al was high risk for the flow of timing as not all the patients were analysed.

**Concerns regarding applicability**

For patient selection and reference standard applicability, all eight studies included patients who had already been diagnosed with cellulitis and we cannot definitely state that the correct diagnosis...
had been made. However, five studies were high risk for patient selection as they either included
a rare differential diagnoses for cellulitis: osteomyelitis and NF 13-15 or only included patients with
an initial suspected DVT.17, 20 The index test in four studies were high risk: two studies only
included investigations for diabetic foot ulcers 13,15 and two studies included imaging for suspected
DVT.17,20

Excluded studies

Of the excluded studies, twenty did not specify the site of cellulitis. Of these, David et al developed
a visually-based computerized diagnostic decision support system.5 Pallin et al looked at PCT
and HLA-DQA1 expression,81 with Kini et al looking at ESR 52 and three examining the Laboratory
Risk Indicator for Necrotizing Fasciitis (LRINEC) score.63, 78,109 Six studies explored radio
nucleotide or bone imaging,37,45,69,70,93,102 five looked at magnetic resonance imaging (MRI)
49,50,91,95,97 and two considered ultrasound imaging in the paediatric setting.46,72 Smirnova et al
looked at antibodies in erysipelas.100

Eight studies did not present the results of lower limb cellulitis separately. Of these, Rahmouni et
al examined MRI in cellulitis 90 and Chao et al utilised ultrasound imaging for soft tissue infections
in the paediatric population.29 Bonnetblanc et al looked at a modification of the LRINEC score,26
two studies focused on multiple laboratory and clinical markers 98,99 and Radkevich et al
investigated coagulable factors.87 Wang et al discussed tissue oxygen saturation monitoring 107
with Ko et al looking at thermal imaging camera.54,55
Discussion

Main findings

We found no robustly developed and validated diagnostic tools or criteria for lower limb cellulitis. A variety of potential tools have been explored so far: biochemical tests, imaging, predictive scoring and clinical features. However, in seven of the eight included studies, cellulitis was not the main pathology of interest and used as a comparator. Three studies compared cellulitis with rare differential diagnoses such as osteomyelitis, which provide limited clinical applicability. This diversity in tools explored emphasises the difficulty in making a correct diagnosis on first presentation.
All eight included studies identified in this review were observational studies.\textsuperscript{16-19} The sample sizes were small, with only two studies including more than 100 patients with cellulitis.\textsuperscript{16, 18} No criteria or tools have been validated subsequently in a large, prospective study.

Despite cellulitis being a common presentation in the community, all the tools identified to date have been developed and tested in secondary care, with limited evidence of validity or applicability in community settings. No study stated that the gold standard reference for clinical diagnosis was a board certified dermatologist or other specialist with cellulitis expertise. Only one study clearly stated who made the cellulitis diagnosis.\textsuperscript{17}

Relevance to clinical practice

All the tools developed to date can be accessed by secondary care, are already available, and with the exception of CT imaging, are inexpensive. The severity of cellulitis is likely to be worse in secondary care. However, none of these tools can be used until they are validated in higher quality studies.

Three studies included rare pathologies that provide very limited clinical relevance, as they are not common misdiagnoses of cellulitis.\textsuperscript{110} Blood tests need to be interpreted with caution, as ESR, CRP and WCC are non-discriminatory markers, but can be used to guide a clinician when the differential diagnoses have been narrowed. High levels of these markers can also help point towards rarer pathologies such as NF.

Only one study included paediatric patients,\textsuperscript{20} therefore findings cannot be translated to this under researched population.

Strengths and limitations of this review
This is the first systematic review identifying diagnostic criteria or tools that have been developed for lower limb cellulitis. The key strengths of this review are the comprehensive search strategy used, supported by an experienced information specialist. The focus of this review was lower limb cellulitis and therefore if the site of cellulitis was not specified or a study did not present the results of lower limb cellulitis separately, then they were excluded.

The limitations of this review stem from the number and quality of the studies included. Data could not be pooled as the index tests were not comparable. Also, twenty-eight papers were excluded as the site of cellulitis was not specified or the results of lower limb cellulitis were not separated. These papers did include diagnostic criteria or tools that need to be further evaluated. Due to time constraints, only the first 100 results on Google Scholar were included.

Conclusion

This systematic review has identified an important research gap in the diagnosis of lower limb cellulitis. There is currently insufficient evidence available to support the validity of any diagnostic criteria or tools that have been developed for lower limb cellulitis. As such, their utility for clinical practice or research remains unclear.

Future studies should employ prospective designs, using diagnosis by board certified specialists with cellulitis expertise as the reference diagnostic standard and be validated in both primary and
secondary care settings. To better understand what should be included in diagnostic criteria or tools, qualitative research including input from a range of healthcare professionals and patients with experience of managing lower limb cellulitis could helpfully be undertaken.

Acknowledgements

We would like to thank Dr Esther Burden-Teh for independently reviewing the protocol internally and helping assess the methodological quality. We also thank Dr Yana Vinogradova for translating and full text screening the Russian transcripts.

References


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Table 1: Search terms used in each database

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<tr>
<th>Database</th>
<th>Search terms</th>
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<tr>
<td>OVID MEDLINE</td>
<td>1. diagnos$.mp. 2. differentiat$.mp. 3. discriminat$.mp. 4. determinin$.mp. 5. confirmat$.mp. 6. ascertainment.mp. 7. detect$.mp. 8. characteris$.mp. 9. characteriz$.mp. 10. identification.mp. 11. identify.mp. 12. exp diagnosis/ 13. exp diagnostic imaging/ 14. or/1-13 15. criteria.mp. 16. criterion.mp. 17. classification.mp. 18. clinical feature.mp. 19. clinical features.mp. 20. test$.mp. 21. tool$.mp. 22. imag$.mp. 23. assay$.mp. 24. accura$.mp. 25. validat$.mp. 26. exp reproducibility of results/ 27. reproducibility.mp. 28. exp validation studies/ 29. exp validation studies as topic/ 30. exp sensitivity and specificity/ 31. sensitivity.mp. 32. specificity.mp. 33. exp predictive value of tests/ 34. predictive.mp. 35. or/15-34 36. and/14 and 35 37. exp diagnostic test, routine/</td>
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LRINEC = The Laboratory Risk Indicator for Necrotizing Fasciitis  CK = creatine kinase  PCT = procalcitonin  ESR=erythrocyte sedimentation rate  WBC = white cell count  DNI = delta neutrophil index  ALT-70 = asymmetry, leucocytosis, tachycardia, age >70  CRP= C- reactive protein  DVT= deep vein thrombosis  ED = emergency department  CT = computed tomography

**Table 3:** Risk of bias assessment using the QUADAS-2 diagnostic accuracy critical appraisal tool showing risk of bias for each domain for individual studies
<table>
<thead>
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<tr>
<td>Shin et al 20</td>
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</table>

= high risk of bias  = unclear risk of bias  = low risk of bias