How can the diagnostic accuracy of lower limb cellulitis be improved?

Dr Mitesh Patel

MRCP (UK), MRCGP, MBChB, BSc, PGCert (Med Ed)

A thesis in fulfilment of the degree of Doctor of Philosophy (By Publication)

University of East Anglia

Faculty of Medicine & Health Sciences

August 2022

Abstract

Introduction

Lower limb cellulitis (cellulitis) affects 1 in 40 people annually in the United Kingdom. However, misdiagnosis is common: approximately a third of those presenting with a red leg and initially managed as cellulitis turn out to have other diagnoses. Incorrect diagnoses lead to inappropriate hospital admissions and antibiotic prescribing.

How to improve the diagnostic accuracy of cellulitis is therefore imperative, and a key research priority from the James Lind Alliance cellulitis priority setting partnership.

Aim

The main aim of this thesis was to explore how the diagnosis of cellulitis can be improved.

Methods

A scoping review and interview studies with health care professionals and people with cellulitis were undertaken to help to identify the key challenges in diagnosing cellulitis. A systematic review to identify diagnostic tools developed for cellulitis was performed. The interview study with health care professionals also identified key clinical features for future diagnostic tools.

Results

The key challenges in diagnosing cellulitis centred on three themes: 1) clinical presentation (subthemes: vague early symptoms, overlapping core features, unclear typical features in certain groups); 2) clinical reasoning (subthemes: specific diagnostic tests, subjectivity, strategic decision making); and 3) learning and education.

The systematic review identified six different diagnostic tools from eleven studies: a biochemical marker, diagnostic criterion, a diagnostic decision support system, a diagnostic predictive model, thermal imaging and light imaging. All studies were considered to have a high risk of bias in at least one domain.

Health care professionals identified key clinical features for a cellulitis diagnosis, which could be considered for inclusion in future diagnostic tools.

Conclusion

Despite a third of suspected cellulitis presentations being misdiagnosed, the solutions to improve the diagnostic accuracy of cellulitis remain limited. This thesis has highlighted the challenges in diagnosing cellulitis and has identified emerging diagnostic tools warranting further investigation.

List of published work included in this thesis

The publications which formed the basis of this thesis and are included in Appendix A are:

- **Patel M**, Lee SI, Thomas KS, Kai J. The red leg dilemma: a scoping review of the challenges of diagnosing lower-limb cellulitis. *Br J Dermatol* 2019; **180**(5): 993-1000.
- **Patel M**, Lee S, Akyea R, et al. A systematic review showing the lack of diagnostic criteria and tools developed for lower limb cellulitis. *Br J Dermatol* 2019; **181**(6): 1156-1165.
- **Patel M**, Lee SI, Levell NJ, et al. Confidence of recurrent cellulitis self-diagnosis among people with lymphooedema: a qualitative interview study. *Br J Gen Pract* 2020; **70**(691): e130-e7.
- **Patel M**, Lee SI, Levell NJ, et al. An interview study to determine the experiences of cellulitis diagnosis amongst health care professionals in the UK. *BMJ Open* 2020; **10**(10): e034692.

Contents

Acknowledgements

I would like to thank my lead supervisor Professor Nick J Levell, who has offered his insight and guidance throughout this journey and assisted me immensely in my clinical and academic dermatology work. He has acted as a mentor and is always willing to provide advice and guidance when I need it. I am also indebted to Professor Tracey Sach, who kindly provided an additional supervisory role and helped to shape this thesis with her expert insight.

I want to thank Professor Kim S Thomas and Professor Joe Kai, who allowed me to develop this research area and everyone at the Centre of Evidence-Based Dermatology, Nottingham and the Division of Primary Care, Nottingham, who supported me along the way.

I am grateful for the backing I received from: the Calverton Surgery; in particular Dr Phil Rayner, the Nottingham General Practice Specialty Training Programme, Birmingham Heartlands Hospital, Sandwell and City Hospital, Birmingham and Kings College Hospital, London, where my colleagues and supervisors enabled me to pursue my academic interests.

I am also obliged to the National Institute of Health Research for funding my academic clinical fellowship and the Clare Wand Fund and Royal College of GP for funding this research.

I want to thank my mother and father, who have supported me every step of the way since I was a young boy dreaming big. Their hard work and sacrifices motivated me to push myself and seize every opportunity, and I will forever be grateful.

Most of all, I would like to thank my partner Dr Siang Ing Lee, who has been by my side through the ups and downs of the last decade. She is my inspiration, my biggest supporter and my most prominent critic! Without her, I would not be in this position today.

Statement of Contribution

I was involved in the study design for all four publications in this thesis and led the data collection and analysis. I drafted and critically revised the manuscripts and approved the final version for publication. I also submitted ethical approval and grant applications for both interview studies.

Professor Thomas, Professor Kai and Professor Levell supervised the design of all four studies. Dr Leighton oversaw the creation of both qualitative studies. Dr Lee assisted with data analysis for all four studies. Dr Akyea helped with data analysis for the systematic review. Dr Smart offered expert insight as a lay representative with lived experience of cellulitis. All co-authors assisted with the drafting, revising and approving of the final version of each respective publication.

All the work presented was completed during my National Institute for Health Research academic clinical fellowship post at the Centre of Evidence Based Dermatology and Division of Primary Care, Nottingham (2017-2019).

None of the work presented has been submitted for any other degree or qualification.

Abbreviations

AI	Artificial intelligence
ALT-70	Asymmetry, Leucocytosis, Tachycardia and age ≥70 years
CEBD	Centre of Evidence Based Dermatology
CRP	C-reactive protein
DVT	Deep vein thrombosis
DNI	Delta neutrophil index
ED	Emergency department
GP	General practitioner
HCP(s)	Health care professional(s)
NEW HAvUN	New onset, Erythema, Warmth, History of associated trauma, Ache, Unilaterality and Number of white blood cells
NHS	National Health Service
LSN	Lymphoedema Support Network
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSP	Priority setting partnership
UK	United Kingdom
USA	United States of America
VisualDx™	Visually based computerised diagnostic decision support system
WCC	White cell count

Introduction

Cellulitis is a common skin infection, with 42.9 million incident cases in 2019 globally.[1] However the diagnosis of lower limb cellulitis (cellulitis henceforth) can be challenging, with 31% of presentations of suspected cases in the emergency department (ED) subsequently given another diagnosis instead of cellulitis.[2] Of the 31% of presentations of cellulitis misdiagnosed, 85% had an avoidable hospital admission, and 92% received unnecessary antibiotics.[2]

This thesis, via a collection of published work, explores how the diagnosis of cellulitis can be improved. To address this question, it is essential to begin by understanding who is affected by cellulitis and how the diagnosis is currently made in both primary and secondary care, focusing on the challenges in diagnosis. Additionally, diagnostic tools developed for cellulitis need to be appraised to determine their roles in improving the diagnostic accuracy.

The diagnostic journey also needs to be captured, involving the patient's experience from symptom onset to diagnosis and the health care professionals' (HCP) decision-making process. A core group of clinical features may then be determined to aid the diagnosis of cellulitis.

Thesis aim

The main aim of this thesis is to explore how the diagnosis of cellulitis can be improved.

Thesis objectives

The main objectives of this thesis are to:

1) Explore the challenges health care professionals experience when diagnosing cellulitis
2) Identify and critically appraise studies that have developed diagnostic tools for cellulitis
3) Identify clinical features that can be incorporated into future diagnostic tools for cellulitis
4) Explore the diagnostic experiences of patients diagnosed with cellulitis

Study designs used to address the objectives

Scoping review

The main aim of my scoping review was to explore the challenges and facilitators identified by patients with cellulitis and HCPs who diagnose cellulitis.

Two databases were searched for papers that discussed the challenges and facilitators of diagnosing cellulitis in primary and secondary care settings. The selected papers were coded by the challenge or facilitator identified and then grouped into themes by thematic analysis.

Three themes were deemed relevant and explored further: clinical cases of misdiagnosis, service development and diagnostic aids.

This study addresses objectives 1,2, and 3.

Systematic review

The main aim of my systematic review was to identify and conduct a critical appraisal of the quality of studies that have developed or validated diagnostic tools for cellulitis.

Four databases were searched to identify and critically appraise studies that have developed or validated diagnostic tools for cellulitis.

Eleven studies were included for data analysis. These studies included six diagnostic tools; a biochemical marker, diagnostic criterion, a diagnostic decision support system, a diagnostic predictive model, thermal imaging and light imaging.

This study addresses objective 2.

Qualitative study with patients diagnosed with cellulitis

The aim of this interview study of patients diagnosed with cellulitis was to explore their experience of receiving a diagnosis. Eighteen patients with recurrent cellulitis in the United Kingdom (UK) were recruited who had a recent experience of being diagnosed with a cellulitis episode. Each participant

took part in a single, semi-structured, qualitative interview. A systematic, multistage thematic analysis was then carried out.

Three key themes were identified: (1) the recurrent nature of cellulitis symptoms; (2) participants' experience of getting a cellulitis diagnosis; and (3) participants' suggestions of how cellulitis diagnosis might be improved.

This study addresses objectives 3 and 4.

Qualitative study with health care professionals

The aim of this interview study was to explore the experiences and challenges faced by HCPs in diagnosing suspected cellulitis. Twenty HCPs from seven different specialities across the UK were recruited with an experience in diagnosing cellulitis. Each participant took part in a single, semi-structured, qualitative interview. A systematic, multistage thematic analysis was then carried out.

Four key themes were identified: (1) the patient presentation; (2) challenges leading to diagnostic uncertainty; (3) strategies to improve diagnosis; and (4) the need for an objective diagnostic aid.

This study addresses objectives 1 and 4.

Chapter 1 – Background

1.1 Chapter introduction

Using evidence from the literature, this chapter summarises cellulitis, describing the disease's distribution and burden, and the impact of misdiagnosis.

Forty per cent of cellulitis cases affect the lower limb.[3] Cellulitis can affect other body parts such as the upper limbs and face, which have different risk factors and presentations to lower limb cellulitis.[3]

This thesis focuses on lower limb cellulitis, as cellulitis most commonly affects the lower limb.[3]

1.2 Pathophysiology

Cellulitis is a skin and soft tissue infection, affecting the deep dermis and associated subcutaneous tissue.[4] Pathogens enter through breaks in the skin.[4]

1.3 Epidemiology

1.3.1 Distribution by age

Cellulitis is more commonly seen in older adults, with the average age of diagnosis being 68.2 years.[5] One observational study found that the incidence of the first episode of cellulitis increased with age, with the incidence per 100,000 population as follows: aged 16-24 years (149.7), 25-44 (156.6), 45-64 (177.2), 65-84 (352.8), 85+ (995.8).[6]

1.3.2 Distribution by sex

There is conflicting evidence on the distribution of cellulitis by sex.[3,5,7,8] This may reflect the small sample sizes in most studies, which do not allow sex-related differences to be determined.[5,7,8]

1.3.3 Distribution by ethnicity

In the UK, approximately 75% of all hospital admissions (of all causes) are patients of White ethnicity.[9] This distribution was also observed for cellulitis: in one secondary care observational study of

inpatients in the UK, 82% of patients diagnosed with cellulitis were of White ethnicity, 10% Asian and 8% Black.[5]

However, there is a lack of literature comparing the risk of cellulitis between different ethnic groups in diverse populations.

1.3.4 Distribution by health care setting

1.3.4.1 Primary care

Cellulitis is more commonly diagnosed and managed in primary care.[10]

Despite this, most epidemiological studies of cellulitis are based in secondary care.[3,6,8,11] A PubMed search found no recent observational studies in the UK describing the epidemiology of cellulitis in primary care.

1.3.4.2 Secondary care

Patients will be referred to secondary care when the cellulitis diagnosis is uncertain or the infection is severe.[12] They are typically seen by ED and acute medical unit generalists.[12]

Patients who do not respond to antibiotic treatment or have recurrent episodes[12] may then be referred onto specialists in dermatology or infectious disease.[12] A prospective observational study recruiting presumed cellulitis cases either in the ED or who had been admitted as an inpatient within the last 24 hours found that early dermatology consultation led to another diagnosis being provided in 39/116 cases (34%).[13]

1.4 Microbiology

The most common pathogens found in cellulitis infections were beta haemolytic streptococci (group A Streptococcus and Streptococcus pyogenes).[14]

1.5 Clinical presentation

The textbook presentation of cellulitis is a well-defined, spreading area of erythema of acute onset, with four cardinal features of general inflammation: erythema, warmth, oedema and pain.[4]

Other signs include inflammation of the proximal lymphatic system, bullae formation and oedema of the skin lymphatic system, which gives a peau d'orange appearance.[4]

1.6 Risk factors

Risk factors of cellulitis include: pre-existing skin diseases (tinea pedis,[11,15] venous eczema[11,16] and leg ulcers[16,17]), skin barrier disruption[5,18,19] and impaired bacterial clearance (lymphoedema[5,18] and leg oedema[16,19]).

1.7 Lymphoedema

A significant risk factor for cellulitis is lymphoedema,[5,18] which occurs when there is an impairment in the drainage of the lymphatic system.[20] Primary lymphoedema is due to a genetic or congenital cause.[20] Numerous causative genes are associated with lymphoedema, including IKBKG, FTL4 and FOXC2.[20]

Secondary lymphoedema is due to acquired causes, with infections such as cellulitis being a common cause.[21] Each episode of cellulitis leads to lymphatic damage, which subsequently can result in secondary lymphoedema, which increases the risk of further episodes of cellulitis.[21]

1.8 Diagnosis

Cellulitis is currently a diagnosis based on the clinical history and examination.[4] Patients who have symptoms for less than 14 days are more likely to have cellulitis than other diagnoses as it is an acute

infection.[22] In cases where the diagnosis is uncertain, additional tests may be undertaken (usually in secondary care), including blood tests, skin cultures and imaging.[12]

1.8.1 Blood tests

There is no single blood test specific to diagnosing cellulitis.[4] One retrospective study found a raised white cell count (WCC) in 50% of cases and a raised C-reactive protein (CRP) in 97% of cases.[23]

However, the WCC and CRP can be raised in numerous infective, inflammatory and neoplastic diseases.[24,25]

1.8.2 Skin cultures

Although performed, skin swabs only sample the epidermis, and not the dermis or subcutaneous tissues, which are the sites affected by cellulitis.[26]

Skin swabs are often colonised with commensal pathogens which do not cause cellulitis.[27] Skin swabs can also provide a mixed growth of pathogens and uncertainties of the significance of the result can lead to inappropriate broad-spectrum antibiotics being prescribed.[27]

The composition of the skin microbiome has been linked to inflammatory skin diseases.[28] However, no specific skin microbiota has been found amongst cellulitis patients.[28]

1.8.3 Blood cultures

Blood cultures are performed when patients with suspected cellulitis are systemically unwell.[29] However, the true pathogen causing cellulitis is rarely isolated with blood cultures.[30] Another limitation is that the results of blood cultures may take 12-36 hours.[31]

1.8.4 Skin biopsies

Skin biopsies are invasive procedures where a tissue sample is taken, and results can take several days to become available.[32] Biopsies on the legs often heal poorly,[32] predisposing to further cellulitis

episodes (as described in *Chapter 1.6 Risk factors*). Skin biopsies are not routinely indicated for cellulitis.[29]

1.8.5 Imaging

Imaging in cellulitis is usually requested when other serious pathologies are suspected, such as necrotising fasciitis.[33] Radiological imaging has been suggested to have a limited role in the diagnosis of cellulitis.[34]

1.9 Management

Cellulitis is usually managed in primary care with antibiotics.[12] The Eron classification guides decisions on whether hospital admission is required for someone with cellulitis.[35] It consists of four classes of severity, ranging from class one (least severe) to class four (most severe).[35]

The choice and route of antibiotics in cellulitis are guided by the severity, local antimicrobial susceptibilities, the experience of HCPs and the causative pathogen (if isolated).[36] In the UK, an expert group of HCPs, called the clinical resource efficiency support team, has developed treatment guidelines for cellulitis.[37]

1.10 Recurrence

Recurrence of a disease is defined as the return of clinical features at the same anatomical site after successful treatment.[38]

A UK retrospective observational study found that 47% of patients had recurrent cellulitis within three years.[39] Risk factors for recurrence of cellulitis are similar to those with a first presentation, in particular oedema.[39]

The UK Prophylactic Antibiotics for the Treatment of Cellulitis at Home (PATCH) study found that taking oral penicillin for six months after an episode of cellulitis reduced recurrent cellulitis by 45% in the first three years after diagnosis.[40] However, this protective effect was not observed after 36 months.[40]

1.11 Misdiagnosis of cellulitis

Misdiagnosis of cellulitis can occur in two ways. Firstly, someone who actually has cellulitis is initially diagnosed with another disease.[41] Secondly, someone with a red leg may be initially diagnosed with cellulitis but is subsequently found to have another disease.[11]

1.11.1 Cellulitis initially misdiagnosed as a different disease

A delay in reaching a correct diagnosis of cellulitis may lead to a delay in starting antibiotic treatment.[4] Such delays can lead to cellulitis progressing to sepsis,[4] osteomyelitis[4] or more rarely, necrotising fasciitis.[12]

1.11.2 A different disease initially misdiagnosed as cellulitis (cellulitis mimickers)

Single centre, retrospective observational studies in the UK[11] and United States of America (USA)[2] have found that approximately a third of suspected presentations of a red leg are initially misdiagnosed as cellulitis.[2,11]

In a large observational study with 1579 patients from a specialist secondary care dermatology cellulitis clinic in the UK, 43% had an alternative diagnosis.[42] The most common mimicker of cellulitis in this study was venous eczema, followed by lymphoedema and lipodermatosclerosis.[42]

1.11.3 Inappropriate use of antibiotics in cellulitis mimickers

Giving antibiotics when they are not required has significant consequences. Increased antibiotic use is associated with increased antibiotic resistance and may limit future antibiotic options.[43] With more

antibiotics being prescribed, Methicillin-susceptible Staphylococcus aureus infections increased by 20% in six years (1998-2004).[43]

1.12 Hospital admissions for cellulitis

This section describes data for cellulitis overall, as separate information is not available for lower limb cellulitis.

In 2019-2020, there were 105,644 recorded hospital admissions with cellulitis as the primary diagnosis in England.[44] The average length of a hospital stay in the UK is 6.2 days,[45] with patients diagnosed with cellulitis occupying nearly 1% of hospital beds in England and Wales.[46]

With a 34% decrease in English acute/general hospital beds in the last 30 years,[47] increasing the number of accurate diagnoses of cellulitis would increase available hospital capacity.

1.13 Cellulitis priority setting partnership

The UK James Lind Alliance cellulitis research priority setting partnership (PSP) was undertaken in 2016-2017 to ensure that future cellulitis research focuses on areas that both HCPs and patients consider important.[48]

Three hundred and fifty-three key stakeholders ranked the most important topics for future cellulitis research, out of 846 initial research uncertainties.[48] The top research priorities centred on improving the diagnosis of cellulitis.[48]

This thesis will address three of the key research priorities: 'How can health care professionals be best supported to diagnose cellulitis accurately', 'What are the best diagnostic criteria for cellulitis, and are they different for different patient groups?' and 'What are the early signs and symptoms of cellulitis?'.[48]

1.14 Appraisal of the current evidence base

Cellulitis remains an under-researched area despite its high rate of misdiagnoses. Most of the studies used to provide the current evidence describing the epidemiology and misdiagnoses of cellulitis included studies undertaken over ten years ago with retrospective designs,[2,3,5] based in single centre UK[5] and USA[2,3] secondary care settings. Cellulitis cases in these studies are mainly diagnosed by admitting physicians and not dermatologists and therefore may include patients with other conditions other than cellulitis.[2]

Despite most cellulitis being diagnosed in primary care,[10] there are no primary care epidemiological studies. The demographics and risk factors of those presenting to primary care may differ from those in secondary care.[12] Few studies explore how cellulitis presentation differs in patients of different ethnicity.[5,17]

1.15 Chapter summary

Cellulitis more commonly affects older aged adults[5] and is most often diagnosed in primary care.[10] Cellulitis is a clinical diagnosis, with no specific diagnostic tests currently available.[4] Typically, a third of patients managed with suspected cellulitis later turn out to have another diagnosis instead of cellulitis.[2,11]

This chapter highlights the need to understand why the diagnosis of cellulitis is challenging and determine how the diagnosis can be improved.

For the rest of this thesis, cellulitis refers to lower limb cellulitis. The introduction and methods have been amended to maintain the structure and limit repetition throughout the thesis.

Chapter 2 – The red leg dilemma: a scoping review of the challenges and facilitators of diagnosing cellulitis

2.1 Introduction

No previous studies have looked at the challenges and facilitators of diagnosing cellulitis. This exploratory research question is suited for a scoping review, to gain a broad overview of this topic.[49]

2.2 Aim

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

2.3 Methods

This review was developed using the methodological framework devised by the Joanna Briggs Institute.[49] The protocol was registered on the Centre of Evidence Based Dermatology (CEBD) website in October 2017.[50]

2.3.1 Inclusion criterion

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

2.3.2 Exclusion criterion

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

2.3.3 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). Articles from the first 100 results in Google Scholar were included for grey literature.

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

Table 1: The search terms used in the two databases.

Database	Search terms
OVID Medline	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. or/1-12 14. exp diagnostic errors/ 15. challenge$.mp. 16. error$.mp. 17. mistake$.mp. 18. inaccurac$.mp. 19. delay$.mp. 20. misdiagnos$.mp. 21. mimic$.mp. 22. or/14-21 23. exp cellulitis/ 24. cellulitis.mp. 25. exp erysipelas/ 26. erysipelas.mp. 27. soft tissue infection.mp 28. exp soft tissue infections/ 29. soft tissue infections.mp. 30. skin soft tissue infection.mp. 31. skin soft tissue infections.mp 32. SSTI.mp. 33. or/23-32 34. 13 and 22 and 33
Embase	1. diagnos$.mp. 2. differentiat$.mp. 3. discriminat$.mp. 4. determinin$.mp. 5. confirmat$.mp. 6. ascertainment.mp. 7. detect$.mp. 8. characteris$.mp. 9. characteriz$.mp. 10. identification.mp. 11. identify.mp. 12. exp diagnosis/ 13. or/1-12 14. exp diagnostic errors/ 15. challenge$.mp. 16. error$.mp. 17. mistake$.mp. 18. inaccurac$.mp. 19. delay$.mp. 20. misdiagnos$.mp. 21. mimic$.mp. 22. or/14-21 23. exp cellulitis/ 24. cellulitis.mp. 25. exp erysipelas/ 26. erysipelas.mp. 27. soft tissue infection.mp 28. exp soft tissue infections/ 29. soft tissue infections.mp. 30. skin soft tissue infection.mp. 31. skin soft tissue infections.mp 32. SSTI.mp. 33. or/23-32 34. 13 and 22 and 33

2.3.4 Study selection

Following the search, all identified citations were uploaded into EndNote X8 and duplicates were removed manually. Titles and abstracts were screened by two reviewers independently.

As the results were broad, the selected papers were coded by the challenge or facilitator identified and then grouped into themes by thematic analysis. These themes were reviewed with two other reviewers.

Three themes were further explored, with full-text papers screened by two researchers independently.

2.3.5 Data extraction

Quantitative data were extracted by two reviewers independently.

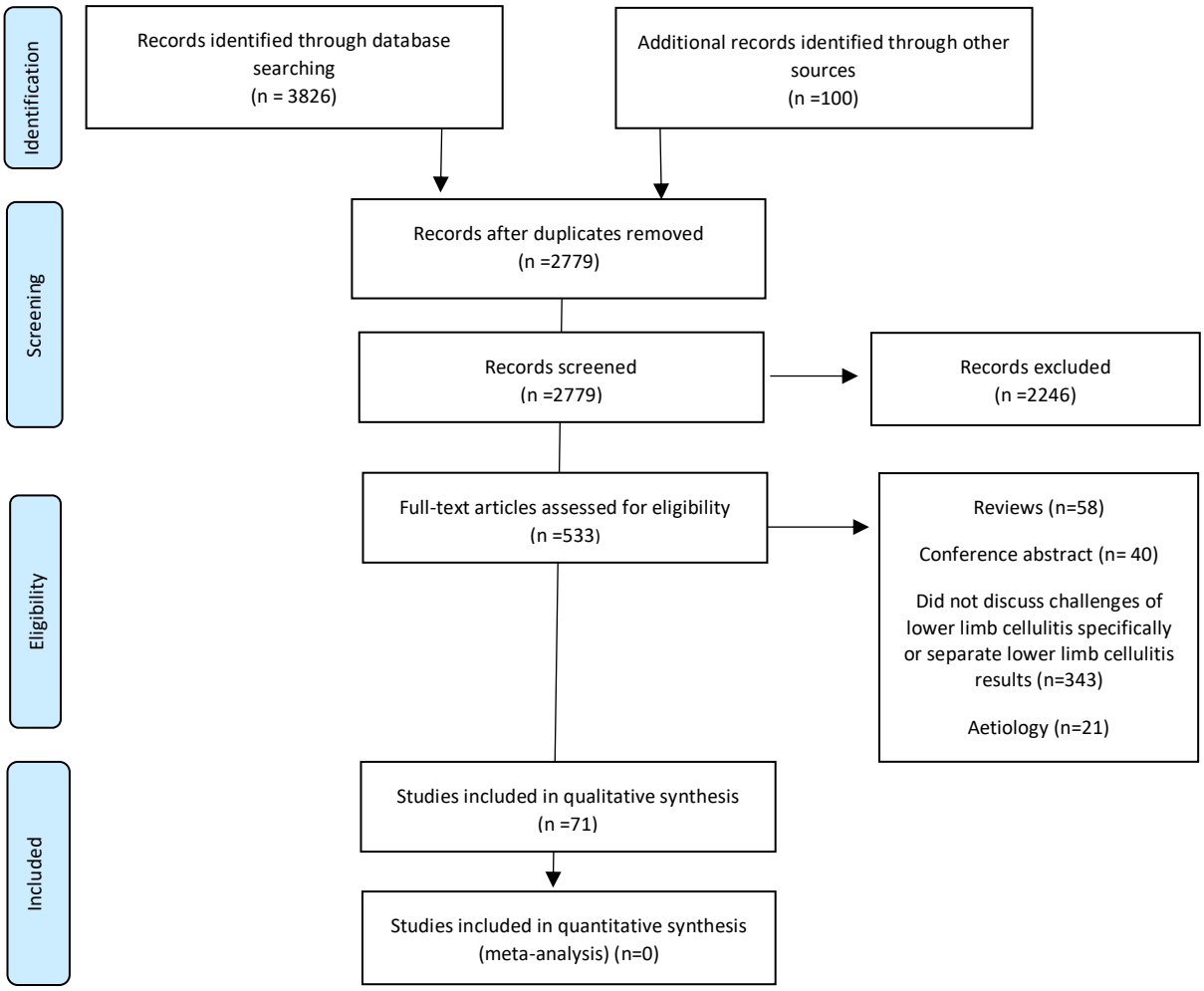
2.3.6 Data presentation

Quantitative data were presented as a narrative synthesis.

2.4 Results

From the 3926 initial search results, 2779 records were screened at the title and abstract stage after duplicates were removed. Five hundred thirty-three full-text articles were assessed for eligibility, and 71 were included for data extraction (Figure 1)(see published paper for a complete list of references).

Figure 1: PRISMA flow diagram of the entire search.



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

Clinical cases of misdiagnosis were studies where 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. *Aetiology* were studies that discussed microbiological causes of cellulitis.

Three themes were deemed relevant and explored further: clinical cases of misdiagnosis, service development and diagnostic tools.

The aetiology theme was not included in this review as the papers highlighted treatment failure due to targeting the wrong organism rather than an incorrect diagnosis of cellulitis.

2.4.1 Clinical cases of misdiagnosis

Sixty-six papers were included for the misdiagnosis theme, with three observational studies [11,51,52] and 63 case reports or series (see published paper in Appendix A for the full list of references).

2.4.1.1 Observational studies

One retrospective observational study showed that in 43 patients with an initial clinical suspicion of deep vein thrombosis (DVT), nine patients were diagnosed with cellulitis.[51] Another study is a specialist cellulitis clinic[11] and will be discussed in *Chapter 2.4.2.1*.

2.4.1.2 Case report and case series

Ninety-four patients were included overall (43 male, mean age 41) (Table 2).

Table 2: The 47 different pathologies misdiagnosed, with the initial and final diagnosis. The pathologies have been grouped into medical specialities. The core features of infection are provided in each case.

Author	**Initial diagnosis**	**Final diagnosis**	**Patient demographics**	**Signs and symptoms**						**Prior treatment with signs and symptoms**
				Pain	Swelling	Erythema	Warmth	Fever	Unilateral or bilateral symptoms	
VASCULAR										
Anderson (2011)	Cellulitis	Constrictive pericarditis	72 years, male		✓				Bilateral	
Corti (2013)	Cellulitis	Angiomatosis	72 years, female		✓	✓		✓	Bilateral	
Cushman (2013)	Cellulitis	Exercise induced vasculitis	58 years, male	✓		✓	✓		Unilateral	
Kaya (2008)	Erysipelas	Deep dissecting haematoma	14 patients	✓ (all)	✓ (all)	✓ (all)			Unilateral	
Laguna (2008)	Cellulitis	Superficial migratory thrombophlebitis	57 years, male			✓	✓		Unilateral	
Noss (2016)	Cellulitis	Stasis dermatitis	81 years, male			✓	✓		Unilateral	Antibiotics for erythema
Patel (2014)	Cellulitis	Haematoma	79 years, male	✓		✓			Unilateral	

Reich – Schupke (2009)	Cellulitis	Hypodermitis	64 years, male 71 years, female 62 years, male 57 years, female 53 years, female	✓ (all)		✓ (all)			Both (cases not separated	Antibiotics for pain and erythema
Demirel (2010)	Cellulitis	Polyarteritis nodosa	75 years, male	✓	✓				Unilateral	Antibiotics for pain and swelling
RHEUMATOLOGY										
Won (2016)	Cellulitis	Sarcoidosis	54 years, female		✓				Unilateral	Treatment (not specified) for swelling
Cheng (2011)			25 years, male	✓	✓	✓			Unilateral	Antibiotics for pain and swelling
Hebel (1993)			23 years, male		✓	✓			Unilateral	Antibiotics for swelling and erythema
Klevtsova (2015)			27 years, female	✓	✓	✓	✓		Bilateral	Antibiotics for pain, swelling and erythema
Amode (2013)	Cellulitis	Puffy hand syndrome	41 years, male		✓	✓		✓	Bilateral	Analgesia for swelling and erythema
Hyland - McGuire (1996)	Cellulitis	Erythema nodosum	36 years, female 36 years, male	✓	 ✓	✓ ✓			Unilateral Unilateral	Antibiotics for pain and erythema
Mines (1996)	Cellulitis	Calcific periarthritis	23 years, male	✓	✓	✓	✓		Unilateral	Analgesia for pain, swelling and erythema
Spierings (2017)	Autoinflammatory disease	Cellulitis	35 years, male					✓	Bilateral	
MUSCULOSKELETAL										
Sobajo (2007)	Cellulitis	Myositis	46 years, female	✓	✓				Unilateral	
Straaton (1991)	Cellulitis	Tibial fracture	47 years, female 73 years, female 46 years, female	✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓	✓ ✓		Unilateral Unilateral Unilateral	Steroids for pain
INFECTION										
Kerhl (2014)	Cellulitis	Necrotising fasciitis	54 years, female	✓		✓		✓	Unilateral	
Navinan (2014)			44 years, male	✓	✓		✓	✓	Unilateral	Antibiotics for pain and fever

Thomas (2014)			70 years, female	✓		✓		✓	Unilateral	
Varma (2006)			58 years, male	✓	✓	✓	✓		Unilateral	
Atcherson (1979)	Cellulitis	Septic arthritis	57 years, male 38 years, male	✓ ✓		✓ ✓ (thigh was red but not ankle)		✓	Unilateral Bilateral	
Fox (2004)	Cellulitis	Pyomyositis	54 years, male 43 years, female 38 years, male	✓ ✓ ✓	 ✓	 ✓	 	✓ ✓ ✓	Bilateral Unilateral Unilateral	Antibiotics for pain and fever
Maida (2017)	Cellulitis	Pretibial abscess	50 years, male	✓	✓	✓		✓	Unilateral	
Sivasubramanian (2010)	Cellulitis	Blastomycosis	28 years, male	✓	✓	✓	✓	✓	Unilateral	
Sweeney (2002)	Cellulitis	Tinea pedis	6 years, male 8 years, female 10 years, male	✓ ✓ Not stated	✓ ✓	✓ ✓			Unilateral Unilateral Unilateral	
van Hulsteijn (2017)	Cellulitis	Appendicitis	73 years, female	✓		✓		✓	Unilateral	
Leveque (2001)	Cellulitis	Osteomyelitis	56 years, male	✓		✓	✓	✓	Unilateral	Analgesia for pain and erythema
ONCOLOGY										
Hussain (2016)	Cellulitis	Lymphoma	20 years, female	✓	✓	✓		✓	Unilateral	Antibiotics and analgesia for pain and swelling
Rodriguez-Vazquez (2005)			34 years, male	✓		✓		✓	Unilateral	Antibiotics for pain and fever
Pan (2013)			72 years, female	✓	✓	✓	✓		Unilateral	Antibiotics
Sedgwick (2015)			81 years, female	✓	✓	✓			Unilateral	Antibiotics for pain and swelling
Cesar (2016)	Cellulitis	Richter's syndrome	85 years, female	Not stated					Unilateral	
Gajraj (1987)	Cellulitis	Lymphangiosarcoma	35 years, male			✓			Unilateral	
Batra (2015)	Cellulitis	Kaposi sarcoma	50 years, male	✓					Bilateral	
Ikawa (2012)	Cellulitis	Malignant melanoma	44 years, female	✓	✓	✓			Unilateral	
Serra (1998)	Cellulitis	Leukaemia	73 years, female			✓			Unilateral	Antibiotics
Cyrulnik (2014)	Cellulitis	Kaposiform hemangioendothelioma	24 days, female	Not stated					Unilateral	
IMMUNOLOGY										
Barghouti (2012)	Allergic reaction	Cellulitis	51 years, male	✓					Unilateral	Analgesia
Gandhi (2011)	Cellulitis	Wells syndrome	50 years, male	✓		✓		✓	Unilateral	Antibiotics for pain,

										erythema and fever
Kulichova (2014)	Cellulitis	Metal hypersensitivity	57 years, female			✓			Unilateral	
DERMATOLOGY										
Eaton (2005)	Cellulitis	Erythromelalgia	55 years, female	✓	✓	✓	✓		Bilateral	Antibiotics for pain, swelling, erythema and warmth
Roux (2000)	Cellulitis	Pyoderma gangrenosum	35 years, male	✓		✓	✓	✓	Unilateral	Antibiotics for fever
Sharma (2014)			60 years, female	✓		✓			Unilateral	
Zhou (2015)	Cellulitis	Pustular dermatosis	73 years, female	✓		✓			Unilateral	
Gach (2006)	Cellulitis	Contact dermatitis	4 years, male 4 years, male		✓	✓ ✓		✓	Unilateral Unilateral	
Augey (2001)			26 years, male	Not stated					Unilateral	
Estines (2003)	Cellulitis	Haemorrhagic cellulitis	75 years, male 69 years, female 56 years, female	 ✓ ✓	 ✓	✓ ✓		✓ ✓	Unilateral Unilateral Unilateral	Antibiotics for erythema and fever Antibiotics
DIABETES RELATED										
Gill (2004)	Cellulitis	Charcot arthropathy	40 years, male 65 years, male	 ✓	✓ ✓		✓		Unilateral Unilateral	Antibiotics for swelling Antibiotics for pain and swelling
Yang (2011)			62 years, female	✓	✓	✓			Unilateral	Antibiotics for pain and swelling
Kermani (2006)	Cellulitis	Diabetic muscle infarct	20 years, female	✓	✓	✓			Unilateral	Antibiotics for pain and swelling
Melikian (2003)			63 years, male	✓	✓		✓	✓	Unilateral	
Joshi (1997)	Cellulitis	Necrobiosis lipoidica	57 years, female	✓		✓	✓		Unilateral	Antibiotics and analgesia for pain, erythema and warmth
MISCELLANEOUS										
Corbeaux (2015)	Cellulitis	Chemotherapy related erythema (gemcitabine and pemetrexed)	66 years, male 70 years, female	✓ ✓	 ✓	 ✓			Bilateral	
Li (2009)			59 years, male	✓	✓	✓	✓		Bilateral	
Tan (2007)			57 years, male	✓		✓			Bilateral	
Tracey (2017)			61 years, female	✓	✓	✓			Bilateral	

Iyenger (2014)	Cellulitis	Necrolytic acral erythema	61years, male	✓		✓			Bilateral	
Kluger (2013)	Cellulitis	Tattoo induced oedema	25 years, male 16 years, female	 ✓	✓ ✓	 ✓			Unilateral Bilateral	Antibiotics for oedema
Schwartz farb (2008)	Cellulitis	Foreign body granuloma	40 years, female	✓		✓			Unilateral	Antibiotics for 'skin changes' and fever
Ingen-Housz-Oro (2002)	Cellulitis	Gardner diamond syndrome	21 years, female	✓		✓	✓	✓	Unilateral	

In total, 47 different pathologies were misdiagnosed, including two cases initially diagnosed as another pathology before being correctly diagnosed as cellulitis.[41,53] The pathologies were grouped by speciality: vascular (nine pathologies) was the most common group. Necrotising fasciitis, sarcoidosis, lymphoma and chemotherapy-related pathology had the most case reports/series as a misdiagnosis (see full paper for references). Ten patients (11%) were later diagnosed with a malignancy.

Typical clinical features of cellulitis are erythema, pain, swelling, fever and warmth.[4] 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 a 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.

Key learning points from the included case reports are shown in Box 1.

Box 1

1. If the initial diagnosis is not responding to antibiotics, then an urgent clinical reassessment is warranted, especially before further antibiotic use.[37]
2. Be aware of more serious pathologies in patients with non-specific features that are not improving or if the presentation is out of proportion to clinical findings.[53]
3. The core features of infection: erythema, pain, swelling, fever and warmth are seen in cellulitis but also in numerous other pathologies.[69]
4. If more than one limb has been affected, it is unlikely to be cellulitis. [19]
5. Cellulitis may be a secondary reactive process to another serious underlying pathology that needs urgent investigation. All alternative differentials should be explored.[50]
6. A thorough history from the patient can help distinguish idiosyncratic reactions due to drug treatments or cosmetics that can be managed conservatively.[45]

2.4.2 Specialist cellulitis services

2.4.2.1 Secondary care cellulitis clinic

2.4.2.1.1 Service design

In the UK, a hospital-based cellulitis clinic staffed by specialist nurses and junior doctors was set up to review patients with suspected cellulitis.[11] All those diagnosed with cellulitis were reassessed within 72 hours by a specialist nurse.[11]

2.4.2.1.2 Service results

Over 40 months (2007-2011), 635 patients were reviewed, with 73% of referrals from primary care.[11] 33% were diagnosed with an alternative diagnosis, most commonly venous eczema, lymphoedema and lipodermatosclerosis.[11] Of the 425 cellulitis patients, only 18 needed hospital admission, with the rest given oral antibiotics or intravenous antibiotics in the community/outpatient clinic.[11]

Of the group diagnosed with cellulitis, 28% had pre-existing skin diseases, the most common being eczema (10%), followed by tinea infection (9%).[11] Identifying and treating these known risk factors reduced the risk of recurrent cellulitis.[11]

A re-evaluation of this cellulitis clinic (2015-2018),[54] found that, of the 373 patients referred with suspected cellulitis, 68% had an alternative diagnosis.[54]

2.4.2.2 Nurse-led red legs clinic

2.4.2.2.1 Service design and results

In England, a single centre audit of 50 patients admitted with bilateral redness found that 15 (30%) were misdiagnosed as cellulitis.[55] This hospital subsequently commissioned a nurse-led 'red legs' service to diagnose and manage patients with bilateral red legs.[55] Diagnostic algorithms were developed with relevant clinicians to guide the decision-making of the nurse running this service.[55]

2.4.3 Diagnostic tools to help diagnosis

These will be discussed in Chapter 3.

2.5 Discussion

2.5.1 Main findings

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

The 47 different misdiagnoses in case reports/series emphasise the broad differential diagnoses of cellulitis and the importance of having diagnostic aids and other support to enable clinicians in various settings to make a correct diagnosis.

I found two examples of services developed in the UK to improve cellulitis diagnosis.[11,55] The cellulitis clinic showed that cellulitis experts are more likely to make a correct diagnosis of cellulitis.[11]

2.5.2 Relevance to clinical practice

The clinical misdiagnosis cases highlight the everyday challenge clinicians face when diagnosing cellulitis. Many patients with an alternative diagnosis can present with features that overlap with typical cellulitis.[11] For primary care physicians, who may see patients present with persistent

symptoms despite antibiotic treatment, timely secondary care advice or review should be considered before further antibiotic use.[12]

Regarding the cellulitis services developed,[11,55] both were commissioned to meet the local health needs. The secondary care cellulitis clinic was in a single large dermatology centre, where funding was later made available after demonstrating successful outcomes.[11] Such services may not be feasible for smaller dermatology centres in the UK, where limited resources, workforce capacity and different commissioning priorities may prevent such initiatives from being set up. This clinic closed in 2018 due to competing hospital interests, which remains a threat to similar services in future. The increase in misdiagnosis of cellulitis from 33% to 68% in the re-audit[54] also suggests that the lessons learnt by HCPs in each generation were lost with high staff turnover.

Many areas in the UK with significant dermatology activity do not have local dermatology services to refer patients to.[56] Ten of 123 English hospital trusts (8%) have no consultant dermatologists.[56] Training community HCPs to provide similar hub services locally may be a possible solution.[56]

2.5.3 Strengths and limitations

This scoping review has mapped out the available literature looking at the challenges in diagnosing cellulitis. The search terms were broad to capture all relevant papers, and two reviewers worked independently throughout the data screening and extraction stages.

Due to the scoping nature of this review, only after the title and abstract screening stage was it apparent which themes were emerging. Therefore, 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 venous eczema and lymphoedema[11] were seldom reported. Also, the clinical features were not always clearly described.

This scoping review was not intended to report the epidemiology of cellulitis misdiagnosis, which would be better addressed by observational studies or systematic reviews of prevalence studies.

2.6 Chapter summary

This scoping review found a range of misdiagnoses of which HCPs should be aware. Specific services have been set up but later decommissioned, suggesting this may not be a feasible long-term solution. This review also found emerging diagnostic tools, which will be further explored in Chapter 3.

Chapter 3 – A systematic review identifying diagnostic tools developed for cellulitis

3.1 Introduction

The scoping review highlighted diagnostic tools developed to assist in diagnosing cellulitis.[57] To explore this further, a systematic review was undertaken to provide a comprehensive list of all the diagnostic tools developed for cellulitis.

Diagnostic tools in cellulitis are used to 'rule in' cellulitis so that a diagnosis is not missed, which may then lead to worsening complications, or 'rule out' an alternative diagnosis so that inappropriate antibiotics are not prescribed for cellulitis mimickers.[58]

3.2 Aim

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

3.3 Definition

Diagnostic tools were defined as: including a minimum of one variable that has been tested against at least one clinical feature.

3.4 Methods

3.4.1 Protocol and registration

This systematic review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement,[59] with additional reference to the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[60] The protocol was registered with PROSPERO (CRD42017080466).[61]

3.4.2 Objectives

The primary objective was to identify and describe diagnostic tools developed for cellulitis. The secondary objective was to assess the quality of the studies where diagnostic tools were developed.

3.4.3 Eligibility criteria

Studies included patients with cellulitis in primary and secondary care, where diagnostic tools were used for diagnosis.

3.4.3.1 Inclusion criteria

All study types, all languages, age, gender and ethnicity, patients with cellulitis, and diagnostic tools.

3.4.3.2 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 is not clear, tools to determine aetiology, case series <20 patients, <10 cellulitis patients included, imaging not available in primary care.

3.4.4 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. Updated searches on 22 May 2018 and 2 January 2022 were 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 and in consultation with a cellulitis expert. Concepts were created: 'cellulitis', 'diagnosis' and 'criteria', with controlled vocabulary (MeSH term and Emtree) and free text headings (Table 3). NICE Evidence was also searched using the term 'cellulitis'.

Table 3: Search terms used in each database.

Database	Search terms
OVID MEDLINE	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/ 38. diagnostic feature.mp. 39. diagnostic

	features.mp. 40. exp biomarkers/ 41. biomarker$.mp. 42. marker$.mp. 43. or/37-42 44. or/36 or 43 45. exp cellulitis/ 46. cellulitis.mp. 47. exp erysipelas/ 48. erysipelas.mp. 49. or/45-48 50. and/44 and 49
OVID EMBASE	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$.mp. 23. exp assay/ 24. accura*.mp. 25. exp reproducibility/ 26. reproducibility.mp. 27. exp validation study/ 28. validation studies as topic.mp. 29. validat*.mp. 30. exp ''sensitivity and specificity''/ 31. sensitivity.mp. 32. specificity.mp. 33. exp predictive value/ 34. predictive.mp. 35. or/15-34 36. and/14 and 35 37. exp diagnostic test 38. diagnostic feature.mp. 39. diagnostic features.mp. 40. exp biological marker/ 41. biomarker$.mp. 42. exp marker/ 43. marker$.mp. 44. or/37-43 45. or/36 or 44 46. exp cellulitis/ 47. cellulitis.mp. 48. exp erysipelas/ 49. erysipelas.mp. 50. or/46-49 51. and/45 and 50
Cochrane Database Of Systematic Reviews	1.diagnos* 2. differentiat* 3. discriminat* 4. determinin* 5. confirmat* 6. "ascertainment" 7. detect* 8. characteris* 9. characteriz* 10. "identification" 11. "identify" 12. MeSH descriptor: [Diagnosis] explode all trees 13. MeSH descriptor: [Diagnostic Imaging] explode all trees 14. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 15. "criteria" 16. "criterion" 17. MeSH descriptor: [Classification] explode all trees 18. "classification" 19. "clinical feature" 20. "clinical features" 21. test* 22. tool* 23. imag* 24. "assay" 25. accura* 26. MeSH descriptor: [Reproducibility of Results] explode all trees 27. "reproducibility" 28. MeSH descriptor: [Validation Studies as Topic] explode all trees 29. "validation studies" 30. valid* 31. MeSH descriptor: [Sensitivity and Specificity] explode all trees 32. "sensitivity" 33. "specificity" 34. "predictive" 35. #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 36. #14 and #35 37. MeSH descriptor: [Diagnostic Tests, Routine] explode all trees 38. "diagnostic feature" 39. "diagnostic features" 40. MeSH descriptor: [Biomarkers] explode all trees 41. biomarker* 42. marker* 43. #37 or #38 or #39 or #40 or #41 or#42 44. #36 or #43 45. MeSH descriptor: [Cellulitis] explode all trees 46. "cellulitis" 47. MeSH descriptor: [Erysipelas] explode all trees 48. "erysipelas" 49. #45 or #46 or #47 or #48 50. #44 and #49
Web of Science Core Collection	1.TS = diagnos* 2. TS = differentiat* 3. TS = discriminat* 4. TS = determinin* 5. TS = confirmat* 6. TS = ascertainment 7. TS = detect* 8. TS = characteris* 9. TS = characteriz* 10. TS = identification 11. TS = identify 12. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 13. TS = criterion 14. TS = classification 15. TS = "clinical feature" 16. TS = "clinical features" 17. TS = test* 18. TS = tool* 19. TS = imag* 20. TS = assay 21. TS = accura* 22. TS = reproducibility 23. TS = valid* 24. TS = "validation studies" 25. TS = sensitivity 26. TS = specificity 27. TS = predictive 28. #13 or #14 or #15 or #16 or#17 or#18 or#19 or #20 or #21 or #22 or#23 or #24 or #25 or #26 or #27 29. #12 and #28 30. TS = "diagnostic features" 31. TS = "diagnostic feature" 32. TS = biomarker* 33. TS = marker* 34. #30 or #31 or #32 or #33 35. #29 or #34 36. TS = cellulitis 37. TS = erysipelas 38. #36 or #37 39. #35 and #38

For grey literature, the first 100 articles on Google Scholar were included. The reference lists of all studies selected for critical appraisal were screened for additional studies.

3.4.5 Study selection and data extraction

Following the searches, all citations were uploaded into Covidence (2018): a systematic review management software,[62] with duplicates removed. Title and abstract screening, full-text screening and data extraction was conducted by two independent reviewers using pre-defined templates. Data items sought at the data extraction stage included study aim, type, population, criteria, funding, sample size, index test, reference test and critical findings.

3.4.6 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[63] by two independent reviewers.

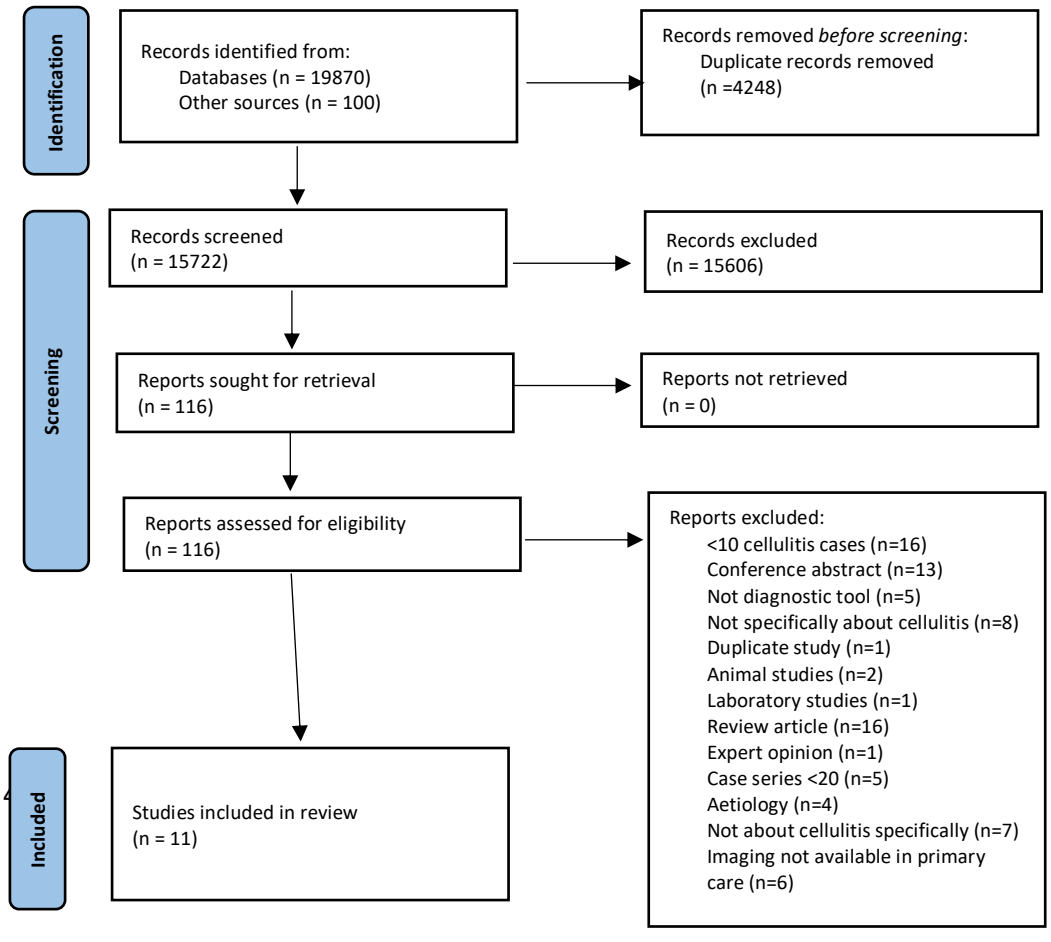
For each domain, studies were judged as 'low risk' if all signalling questions were 'yes'; 'high risk' if at least one signalling question was 'no'; or 'unclear' if in between.[63]

3.5 Results

3.5.1 Study selection

The PRISMA flow diagram shows the result of the complete search after the re-run search on 2 January 2022 (Figure 2). Eleven studies were included for data extraction.[64-74]

Figure 2: PRISMA flowchart of literature search and study selection.



3.5.2 Study characteristics

Characteristics of all eleven included studies, describing six different diagnostic tools, are summarised in Table 4.[64-74]

3.5.3 Diagnostic tools for cellulitis

I will now present the eleven studies by the six diagnostic tools.

3.5.3.1 **Biochemical marker**

Biochemical markers (biomarkers) are objective measures that can be used as a diagnostic tool.[75]

A biomarker tested in cellulitis is delta neutrophil index (DNI).[71]

3.5.3.1.1 Study design and results

A retrospective study with 367 adults was undertaken in a single ED in South Korea, looking at DNI as a marker to differentiate cellulitis from acute gout.[71] A DNI >1.7% was an independent factor for predicting cellulitis, compared to WCC, CRP and procalcitonin.[71]

3.5.3.2 Diagnostic criterion

A diagnostic criterion is a cluster of clinical symptoms, signs or test results used to help make a clinical diagnosis.[76]

A criterion developed for cellulitis is the NEW HAVuN criteria (**N**ew onset, **E**rythema, **W**armth, **H**istory of associated trauma, **A**che, **U**nilaterality and **N**umber of white blood cells).[67]

3.5.3.2.1 Study design

A retrospective observational study with 57 adults was conducted in a single centre in the USA.[67]

Through clinical experience and reviewing the literature, seven key diagnostic features were identified for cellulitis; acute onset (<4 days), erythema, pyrexia (>100.4F), history of associated trauma, tenderness, unilaterality and leucocytosis (10.0×10^9 /L) and converted into the NEW HAvUN criterion.[67] This criterion was tested against clinical cases in a dermatology department and medical

record database.[67] Patients who were seen initially as a consultation for possible cellulitis but given a final diagnosis of stasis dermatitis or lipodermatosclerosis were included.[67]

3.5.3.2.2 Study results

A final diagnosis of cellulitis was found in 20 patients. Overall, testing positive for 4 of 7 clinical criteria was 100% sensitive and 95% specific for a diagnosis of cellulitis.[67]

Acute onset (≤3 days) was a clinical feature seen in 80% (16/20) of cellulitis cases and 22% (8/37) of non-cellulitis cases.[67] Erythema was seen in 45% (9/20) vs 65% of the non-cellulitis group (24/37).[67] Pyrexia was found in 85% (17/20) of cellulitis cases and 5% (2/37) of non-cellulitis patients.[67] A history of associated trauma was found in 50% (10/20) of cellulitis cases and 3% (1/37) of non-cellulitis cases.[67] Unilaterality was observed in 100% (20/20) cases of cellulitis and 11 non-cellulitis cases (30%).[67] Leucocytosis was seen in 65% (13/20) of cellulitis cases and 8% (3/37) of non-cellulitis cases.[67]

All these criteria were statistically significant except for erythema and unilaterality.[67]

3.5.3.3 Diagnostic decision support system

Diagnostic decision support systems provide a computerised 'consultation', where clinical data is input, and a list of differential diagnoses is output.[77]

A decision support system developed for cellulitis is the visually based computerised diagnostic decision support system (VisualDx™).[65]

3.5.3.3.1 Study design

A prospective study with 80 patients was undertaken in a single ED in the USA.[65] Admitting physicians were asked to identify their primary diagnosis, a list of differential diagnoses and input presenting skin descriptions, medical history and hospital management into the VisualDx™.[65] A group of differential diagnoses was then provided.[65] A dermatology or infectious disease specialist then reviewed the patients within 24 hours and provided a final diagnosis.[65]

3.5.3.3.2 Study results

In those with cellulitis, both the admitting physician and VisualDx™ included the correct diagnosis in the differential list in every case.[65] Twenty-eight out of 80 patients were misdiagnosed with cellulitis by the admitting physician.[65] Of these, only four had the correct diagnosis included in the differential diagnoses.[65] In comparison, VisualDx™ included the accurate diagnosis in 70 out of the 80 patients, and in the non-cellulitis group, VisualDx™ included the correct diagnosis in 18 cases out of 28.[65]

3.5.3.4 Diagnostic predictive model

A diagnostic predictive model combines several variables or features to estimate the disease risk.[78]

The ALT-70 model has been developed for cellulitis, consisting of **A**symmetry (unilateral leg involvement), **L**eucocytosis, **T**achycardia and age ≥**70** years.[79] The ALT-70 model has been further evaluated at different time points of hospital admission using the same patient dataset.[73] The results of these two studies have been combined as one study in this thesis.[73,79]

3.5.3.4.1 Study design

A retrospective cross-sectional study with 259 adults was undertaken in a single ED in the USA.[79] Adults were included if they were diagnosed with cellulitis by the emergency care or admitting physician.[79]

Charts of included patients were reviewed in the ED, and points ranging from 0 to 7 were assigned as follows for the covariates: **A**symmetry (unilateral leg involvement) (3 points), **L**eucocytosis (1 point), and **T**achycardia (1 point), and age ≥**70** years (2 points).[79]

3.5.3.4.2 Study results

One hundred eighty patients were diagnosed with cellulitis.[79] A score below 3 had a >83.3% likelihood of pseudocellulitis (not cellulitis) and above 4 had a >82.2% likelihood of cellulitis.[79] The authors suggested those with a score of 3-4 were in an intermediate group, where a dermatology review would be advised.[79]

The model was later repeated in a retrospective, single centre study[73] with the ALT-70 score calculated at three-time points; the time of initial ED presentation, 24 hours after the initial presentation and 48 hours after the initial presentation.[73] The median ALT-70 score was significantly higher at all three times points compared with pseudocellulitis.[79] In the cellulitis group, those with an ALT-70 score >2 had a sensitivity of 96.5% at admission and 94.4% at 48 hours.[73]

3.5.3.5 Thermal imaging

Thermal imaging utilises a tool to measure the temperature of the skin.[69] For cellulitis, a thermal camera and hand-held thermometer have been tested in four studies.[66,68-70]

3.5.3.5.1 Study 1 – Thermal camera

3.5.3.5.1.1 Study design

A prospective study with 72 adults was undertaken in a single ED in the USA.[69] All participants with a suspected cellulitis diagnosis provided by the emergency team underwent thermal imaging.[69] They were then randomised to have a consultation with either the dermatology team or standard care (emergency care/medical team).[69]

Only the 40 participants randomised to have a consultation with the dermatology team were analysed in the study.[69]

3.5.3.5.1.2 Study results

Twenty-nine participants were diagnosed with cellulitis, with the average temperature difference between cellulitis and non-cellulitis body parts being 3.7°C.[69] In those with pseudocellulitis, the average temperature difference was 0.2°C.[69] Using a temperature difference of greater than 0.46°C as predictive of cellulitis, 24/24 and 4/8 of pseudocellulitis cases were correctly diagnosed.[69]

3.5.3.5.2 Study 2 – Thermal camera

3.5.3.5.2.1 Study design

A prospective study with 158 adults was undertaken in a single centre in India, recruiting from the outpatient departments of dermatology, surgery and emergency care.[68] Participants were allocated to a development or a validation group.[68]

A thermal camera was used to determine the peak temperature in the affected leg and the corresponding point on the contralateral leg.[68] The temperature gradient was the difference between the two measurements.[68]

3.5.3.5.2.2 Study results

One hundred and eight participants were included in a development group (65 had cellulitis) and 50 in a validation group (25 had cellulitis).[68]

A temperature gradient of >0.6°C in the development group showed a sensitivity of 95% and specificity of 91% for cellulitis, and in the validation group, the sensitivity was 100%, and specificity was 88%.[68]

3.5.3.5.3 Study 3 – Thermal camera

3.5.3.5.3.1 Study design

The ALT-70 predictive model and thermal camera were compared in a prospective study with 67 adults in a single ED in the USA.[70] The emergency team initially diagnosed cellulitis, with all participants then reviewed by a dermatologist who made the final diagnosis.[70]

To maximize sensitivity, a new cut-off for the ALT-70 model was designed, with cellulitis being positive with a score >2 points and negative if <3 points.[70] The skin temperature was taken from affected and unaffected sites using a thermal camera.[70] Cellulitis was diagnosed if the temperature difference was >0.46°C, and pseudocellulitis if the difference was <0.47°C.[70]

Combination testing was then carried out, with cellulitis defined as positive with an ALT-70 score >2 points and temperature difference >0.46°C, and negative if an ALT-70 score of <3 points or temperature difference of <0.47°C.[70]

3.5.3.5.3.2 Study results

The ALT-70 model outperformed thermal imaging in accurately diagnosing cellulitis, providing a sensitivity of 97.8%, compared to 87% with thermal imaging and 85% with combination testing.[70] Combination testing had the highest specificity of 71.4%, compared with 45% with the ALT-70 predictive model.[70] The ALT-70 predictive model provided the highest negative predictive value of 91% for cellulitis.[70]

3.5.3.5.4 Study 4 – Infrared thermometer

3.5.3.5.4.1 Study design

A prospective study was undertaken with 52 adults with suspected cellulitis, presenting to ED, outpatient units and inpatient wards in a single centre in Canada.[66] The final diagnosis was made by an infectious disease specialist.[66] The temperature was taken in the centre of the lesion, followed by measurements of the contralateral limb.[66]

3.5.3.5.4.2 Study results

The mean temperature difference between affected and unaffected limbs was 2.6°C for patients with cellulitis and 0.4°C without cellulitis.[66] An average temperature difference between limbs of 0.8°C or more was 95% sensitive and 69% specific for a diagnosis of cellulitis.[66]

3.5.3.6 Light imaging

Light imaging utilises a tool to measure light reflected or provide a specific signal.[72] For cellulitis, light imaging has been tested in three studies.[64,72,74]

3.5.3.6.1 Study 1 - Diffuse reflectance spectroscopy

Spectroscopy calculates a spectral ratio, comparing oxyhemoglobin and deoxyhemoglobin absorption in the affected skin.[72]

A prospective cohort study with 30 adults was undertaken in a single ED in the USA.[72]

3.5.3.6.1.1 Study design

Spectroscopy was used on 21 participants diagnosed with cellulitis by a dermatologist.[72] Infrared thermal imaging was also tested (as previously described) in combination with diffuse reflectance spectroscopy in the cellulitis group as a combination model.[72]

3.5.3.6.1.2 Study results

Using diffuse reflectance spectroscopy, a spectral ratio of >1.012 corresponded to a sensitivity of 86% and specificity of 56% for cellulitis.[72] As a combination model with infrared thermal imaging, the sensitivity and specificity of cellulitis increased to 95% and 78%, respectively.[72]

3.5.3.6.2 Study 2 – Violet light

Handheld imaging using violet light (MolecuLight) provides a red/cyan fluorescence signal when a high bacterial load is on the skin, identifying the extent and location of infection.[64]

A prospective observational study was undertaken with 236 adults in a wound care clinic in the USA.[64] Fifteen out of 236 patients (6.4%) were diagnosed with wound-related cellulitis.[64] Using MolecuLight, the skin of all 15 patients showed a red fluorescence signal which persisted after targeted cleaning or debridement.[64]

3.5.3.6.3 Study 3 – Tissue oxygen saturation

A prospective study was carried out on 234 adults who presented to a single ED in the USA with a soft tissue infection of the lower leg.[74] Tissue oxygen saturation monitoring (with near-infrared spectroscopy) was used to discriminate between cellulitis and necrotising fasciitis.[74] Biceps and contralateral unaffected leg areas were measured as references.[74]

Lower limbs with necrotising fasciitis had a tissue oxygen saturation reading of 52%±18%, whereas the tissue oxygen saturation reading measured in cellulitis legs was 84%±7%.[74]

Table 4: Characteristics of the 11 included studies.

Diagnostic tool (index test)	Author, publication year	Country, setting	Study type	Number of total patients analysed (number of cellulitis patients analysed)	Reference test	Main results
i)Biochemical marker						
Delta neutrophil index	Pyo et al., 2017[71]	South Korea, a single emergency department	Retrospective observational	367 (183)	Clinical diagnosis (unclear who made the diagnosis)	Delta neutrophil index >1.7% was an independent factor for predicting cellulitis compared to gout.
ii) Diagnostic criteria						
The NEW HAvUN criteria	Ezaldein et al., 2018[67]	USA, a single dermatology department	Retrospective observational	57 (20)	Clinical diagnosis (by a dermatologist)	A final diagnosis of cellulitis was found in 35% (20/57). Overall, testing positive for four of seven clinical criteria was 100% sensitive and 95% specific for a diagnosis of cellulitis.
iii) Diagnostic decision support system						
Visually-based computerised diagnostic decision support system (VisualDx™)	David et al., 2011[65]	USA, a single emergency department	Prospective observational	80 (52)	Clinical diagnosis (by an admitting senior resident physician)	35% (28/80) were misdiagnosed with cellulitis by the admitting physician, and of these, only four had the correct diagnosis included in the differential diagnoses. In comparison, VisualDx™ included the correct diagnosis in 88% (70/80), and the non-cellulitis group included the correct diagnosis in 64% (18/28).
iv) Diagnostic predictive model						

ALT-70	Singer et al., 2019[73]	USA, a single emergency department	Retrospective observational	259 (180)	Clinical diagnosis (by an emergency department physician or admitting team)	The ALT-70 score was calculated at three time-points: the time of initial ED presentation, 24 hours after the initial presentation and 48 hours after the initial presentation. The median ALT-70 score was significantly higher at all three times points compared with pseudocellulitis. In the cellulitis group, those with an ALT-70 score >2 had a sensitivity of 96.5% at admission and 94.4% at 48 hours.
v) Thermal imaging						
FLIR One thermal camera (Generation One; FLIR Systems)	Ko et al., 2018[69]	USA, a single emergency department	Prospective observational	40 (29)	Clinical diagnosis (by a dermatologist)	Cellulitis patients had an average maximum affected skin temperature of 34.1°C, which was 3.7°C warmer than the corresponding unaffected area (95% confidence interval = 2.7-4.8°C, P < 0.00001). A temperature difference of ≥0.47°C conferred a 96.6% sensitivity, 45.5% specificity, 82.4% positive predictive value, and 83.3% negative predictive value for cellulitis diagnosis.
FLIR ONE Pro thermal camera (Generation 3; FLIR	Hanumakka et al., 2021[68]	India, a single centre recruiting from dermatology, surgery and emergency	Prospective observational	158 (90)	Clinical diagnosis (by a dermatologist)	A temperature gradient of >0.6°C in the development group showed a

Systems)		department				sensitivity of 95% and specificity of 91% for cellulitis. In the validation group, the sensitivity was 100%, and specificity was 88%.for cellulitis.
ALT-70 vs FLIR ONE thermal camera (version Gen 2, FLIR Systems)/ iPad (version 10.21, Apple)	Li et al., 2018[70]	USA, a single emergency department	Prospective observational	67 (46)	Clinical diagnosis (by a dermatologist)	ALT-70 model provided a sensitivity of cellulitis of 97.8%, compared to 87% with thermal imaging and 85% with combination testing. Combination testing had the highest specificity of 71.4%, compared with 45% with the ALT-70 predictive model for cellulitis. The ALT-70 predictive model provided the highest negative predictive value of 91% for cellulitis.
MasterCraft Digital Temperature Reader infrared thermometer	Demir et al., 2021[66]	Canada, a single centre recruiting from the emergency department and both inpatient/outpatient settings	Prospective observational	52 (39)	Clinical diagnosis (by an infectious disease specialist)	In the cellulitis group, the affected limb was on average 2.6°C warmer than the contralateral leg. A temperature difference of >0.8°C was 95% sensitive and 69% specific for cellulitis. Using the modified version of ALT-70, with a score >2 being positive for cellulitis, a sensitivity of 97% and specificity of 8% were found.
vi) Light imaging						
Diffuse reflectance spectroscopy	Raff et al., 2021[72]	USA, single emergency department	Prospective observational	30 (21)	Clinical diagnosis (by a dermatologist)	Using diffuse reflectance spectroscopy, a

						spectral ratio of >1.012 corresponded to a sensitivity of 86% and specificity of 56% for cellulitis. As a combination model with infrared thermal imaging, the sensitivity and specificity of cellulitis increased to 95% and 78%, respectively.
Violet light (MolecuLight)	Andersen et al., 2021[64]	USA, a single wound care clinic	Prospective observational	236 (15)	Clinical diagnosis (unclear who made the diagnosis)	The skin of all 15 cellulitis patients provided a red fluorescence signal which persisted after targeted cleaning or debridement.
Tissue oxygen saturation	Wang et al., 2004[74]	USA, a single emergency department	Prospective observational	234 (19)	Clinical diagnosis (unclear who made the diagnosis)	Lower limbs with necrotising fasciitis had a tissue oxygen saturation reading of 52%±18%, whereas the tissue oxygen saturation reading measured in cellulitis legs was 84%±7%.

*****NEW HAvUN, New onset, Erythema, Warmth, History of associated trauma, Ache, Unilaterality and Number of white blood cells; ALT-70, asymmetry, leucocytosis, tachycardia, age > 70 years.

3.6 Excluded studies

Of the excluded studies, two diagnostic criteria have been postulated for cellulitis but have not been validated in a study.[80,81] These are the CELLULITIS pneumonic[80] and a seven-item checklist.[81] The CELLULITIS mnemonic incorporates Cellulitis history, OEdema, Local warmth, Lymphangitis, Unilateral, Leukocytosis, Injury, Tender, Instant onset, and Systemic signs. A RED Leg RATED tool has also been piloted in emergency care.[82]

One study investigated HLA-DQA1 gene expression levels in cellulitis.[83] Infrared spectroscopy[84] and hyperspectral imaging have also been tested in cellulitis.[85]

3.7 Methodological quality of included studies

The quality of included studies was assessed using the QUADAS-2 tool. [63]

3.7.1 Risk of bias

All included studies were high risk of bias in at least one domain (see Table 5 and Figure 3).[64-74]

In the patient selection domain, the risk of bias was high for all the studies included, except one.[64] Nine studies included inappropriate exclusions of participants such as recent antibiotic use,[66,68-73] 'complicated' infections,[65,68-70,72,73] and abnormal vital signs.[69,72,74] The index test was high risk of bias for six studies as data-driven and not pre-specified thresholds were used.[66,68,69,71,72,74]

The reference standard was high risk of bias in one study,[64] as the reference standard was not interpreted without knowledge of the index test. The reference standard was also of unclear risk of bias for four studies,[65,71,73,74] as it was impossible to determine if the diagnosis of cellulitis was accurate.

The flow and timing domain was high risk of bias in one study,[73] as not all the patients recruited into the study were included in the analysis.

3.7.2 Concerns regarding the applicability

In the patient selection domain, the risk of bias was high in two studies,[64,74] as one study focused on necrotising fasciitis as the primary diagnosis,[74] and the other only included wound-related cellulitis cases.[64] Only one study was deemed low risk of bias for patient selection, as it had an appropriate selection criterion.[65]

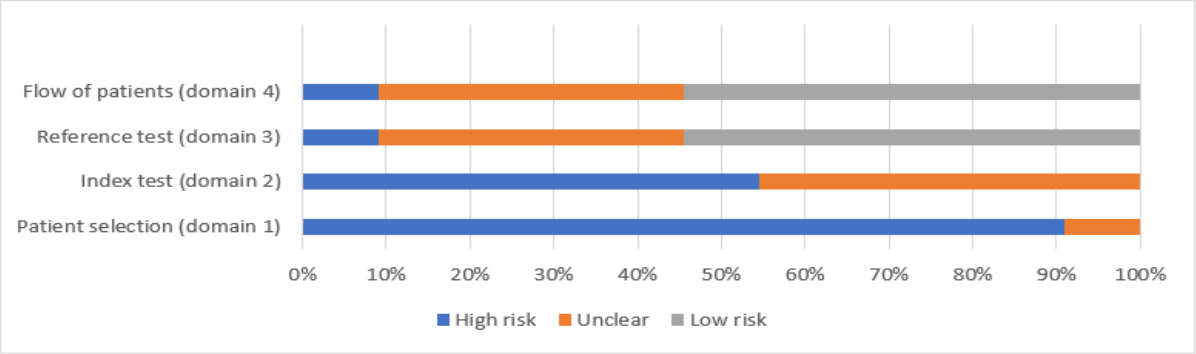
One study was high risk of bias for the index test, as a computerised diagnostic support system provided a list of differential diagnoses of cellulitis, not a single diagnosis.[65] All other studies were low risk of bias for the index test.[64,66-74]

Four studies had an overall unclear risk of bias for the reference standard as it was not possible to determine if a dermatologist made the diagnosis as the reference standard.[64,71,73,74]

Table 5: Risk of bias assessment using the QUADAS-2 diagnostic accuracy critical appraisal tool showing the risk of bias for each domain for individual studies.

	Risk of bias				**Concerns regarding applicability**		
Study	**Patient selection**	**Index test**	**Reference standard**	**Patient flow and timing**	**Patient selection**	**Index test**	**Reference standard**
Pyo et al., 2017[71]	High	High	Unclear	Unclear	Unclear	Low	Unclear
Ezaldein et al., 2018[67]	High	Unclear	Low	Low	Unclear	Low	Lo
David et al., 2011[65]	High	Unclear	Unclear	Low	Low	High	Low
Singer et al., 2019[73]	High	Unclear	Unclear	High	Unclear	Low	Unclear
Ko et al, 2018[69]	High	High	Low	Low	Unclear	Low	Low
Hanumakka et al., 2021[68]	High	High	Low	Low	Unclear	Low	Low
Li et al., 2018[70]	High	Unclear	Low	Unclear	Unclear	Low	Low
Demir et al., 2021[66]	High	High	Low	Low	Unclear	Low	Low
Raff et al., 2021[72]	High	High	Low	Unclear	Unclear	Low	Low
Andersen et al., 2021[64]	Unclear	Unclear	High	Unclear	High	Low	Unclear
Wang et al., 2004[74]	High	High	Unclear	Low	High	Low	Unclear

Figure 3: Graph showing the percentage of studies with a low, high or unclear risk of bias for each of the four domains of the QUADAS-2 tool.



3.8 Appraisal of the current evidence base for diagnostic tools

3.8.1 Applicability of the diagnostic tool

3.8.1.1 Time

The ALT-70 model[70] and thermal imaging[66,68,69] were described in their respective studies as being quick to use. However, no study measured the average additional time per consultation when using each tool to determine how pragmatic it would be to implement each into clinical practice.[64-74]

The VisualDx™ requires the input of clinical details and differential diagnoses,[65] which should be quick to input.

3.8.1.2 Cost

The infrared thermometer costs 30-50 Canadian dollars[66] (£19-£32, July 2022) and is an inexpensive tool. The FLIR ONE devices used for the studies on thermal imaging[69-71] cost approximately £200 on the manufacturer's website.[86] However, it is unclear how many scans a device can complete each day, nor the servicing costs. The VisualDx™ costs approximately £300 per year for individual access.[87] However, group packages may be shared within a hospital or community practice which would allow many HCPs to use the tool and save costs.[87]

3.8.1.3 Applicability in clinical practice

None of the studies specified if the diagnostic tool tested was to rule in or rule out cellulitis.[64-74] Instead, the aim was to develop a tool to 'differentiate' cellulitis from other pathologies.[66-73] With a

third of presentations of suspected cellulitis being misdiagnosed,[2,11] perhaps more emphasis must be placed on ruling out cellulitis.

The ALT-70 model,[70,73,79] NEW HAvUN criteria[67] and DNI[71] incorporate blood tests, which are not easily accessible in primary care and can lead to a time delay in diagnosis.[88]

Thermal imaging,[66,68-70] light imaging[64,72,74] and Visual Dx[65] are all hand-held portable devices which may be used in primary care. One thermal[66] and one light imaging[66,72] tool were described as simple or easy to use. The thermometer was affected by ambient temperatures; therefore, the limbs needed to be exposed for several minutes in one study,[66] limiting outpatient use where consultation times are limited.

Another concern with the thermal and light imaging studies was operator variability, determining how far from the skin the device needs to be held,[66] so this should be standardised in future studies. Three of these studies used tools also tested in upper limb cellulitis,[66,69,72] whereby results may not be generalisable to the lower limb.

The role of spectroscopy is limited in those with darker skin types and obesity due to the absorptive properties of melanin and lipid.[72]

3.8.2 Study methodology

All the studies were carried out in single centres.[64-74] This may limit the generalisability of study findings as the clinical presentation of cellulitis and HCP's behaviour in other centres/countries may differ.

Only five studies included a sample size of over 100 participants.[64,68,71,73,74] Three studies used an observational study design with routine health records,[67,71,73] prone to residual confounding, and key covariates may not have been systematically collected.[89] The ALT-70 model included ED data,[70,73] which are typically busy departments and therefore, all the clinical information may not be documented.[90]

Head to head comparisons between the different tools has only been undertaken in one study.[70] None of the other studies have replicated their findings with further studies to identify whether the results are reproducible and therefore are exploratory.[65,67,71,72,74] All the tools need to be validated in larger multicentre studies.[64-74]

3.8.3 Study setting

Of the eleven studies, ten included patients diagnosed in the ED.[65-74] The ED setting provides a pragmatic group of participants, as emergency care is where a third of suspected cellulitis presentations are misdiagnosed.[2]

However, only three studies described including patients from other settings[64,66,68] and for one of these studies, it was unclear which inpatient and outpatient units were included.[66] Importantly, none of these studies included participants in primary care, despite primary care being the most common setting to diagnose cellulitis.[11]

The ALT-70 model provided a score for an intermediate group, where further advice from dermatology should be sought, when the cellulitis diagnosis was unclear.[73] This helps streamline services to ensure that the specialist sees the patients who are most likely to be misdiagnosed.[73]

Future studies need to be conducted in settings where cellulitis presentations are common, such as acute care, general medical wards with older-aged adults and primary care.[11] This would increase the validity of the tools in different clinical settings.

3.8.4 Study participants

Of the studies that clearly defined the participant's selection criteria: recent antibiotic use,[66,68-71,73] co-existing infections[65,68,69,72,73] and abnormal clinical vital signs[69,72,74] were examples of criteria used to exclude participants. These tools were thereby tested in uncomplicated presentations of suspected cellulitis. However, tools need to be developed for patients with co-morbidities and complications, where the diagnosis is more challenging, as these are the cases often misdiagnosed.[50]

There was also a lack of ethnic diversity, with studies which provided demographic data showing that around 80% of participants were White.[69,70,72] Future studies need to increase the ethnic diversity of included participants.

3.8.5 Physician making the diagnosis of cellulitis

In six studies, the reference standard against which the diagnostic tools were tested was the final diagnosis made by a specialist: five studies included a dermatologist[67-70,72] and one included an infectious disease physician.[66]

Three studies followed up the participants and revised the final diagnosis if needed,[69,72,73] with a cohort of participants in one study receiving a dermatology review two weeks after discharge for re-evaluation of the diagnosis.[69] This pragmatic strategy was employed to help validate the accuracy of the diagnostic tool.

3.9 Discussion

3.9.1 Main findings

This systematic review identified eleven studies that evaluated six different diagnostic tools developed for cellulitis.[64-74] However, these tools have not been validated in large prospective studies or in primary care.[64-74] All the studies had a high risk of bias in at least one domain.[64-74]

3.9.2 Strengths and limitations

The key strength of this review was the comprehensive search strategy supported by an experienced information specialist. Two updated searches were completed to capture any new studies.

The limitations of this review stem from the number and quality of the studies included. Data could not be pooled as the diagnostic tools were not comparable.

3.10 Chapter summary

This chapter discusses six diagnostic tools developed for cellulitis, which currently do not have enough high-quality evidence to support their incorporation into clinical guidelines.[64-74]

To better understand other solutions to improve the accuracy of diagnosis, qualitative research with HCPs and patients diagnosed with cellulitis is required.

Chapter 4 - Confidence of recurrent cellulitis self-diagnosis amongst patients with lymphoedema: An interview study

4.1 Introduction

The cellulitis PSP ranked questions on identifying clinical features in different groups of patients with cellulitis, such as those with lymphoedema, as essential for future cellulitis research.[48]

Qualitative methods enables in-depth exploration of patients lived experiences.[91] Interviewing patients affected by cellulitis would allow the exploration of symptoms they experience, their views of why cellulitis is a challenging diagnosis and what may help to improve the accuracy of diagnosis.

4.2 Aim

The primary aim was to explore the experience of patients with recurrent cellulitis in the diagnosis of cellulitis. The secondary aims were to: explore the key features of cellulitis that prompt patients to seek medical advice; describe experiences where a diagnosis of cellulitis was correct, incorrect or delayed; and describe experiences of getting a diagnosis of cellulitis with different HCPs.

4.3 Methods

4.3.1 Protocol registration and ethics

The protocol was registered on the CEBD website (5 November 2018).[92] Ethical approval was granted by the Faculty of Medicine and Health Sciences Ethics committee, University of Nottingham (5 October 2018). For each participant, verbal consent before the start of the interview and written consent from each participant either before or after the interview.

4.3.2 Eligibility criteria

4.3.2.1 Inclusion criteria

Age >18 years; all ethnicities; patients with a suspected episode of cellulitis in the last twelve months (or two or more episodes within the previous two years); able to give informed consent; speak English.

4.3.2.2 Exclusion criteria

Non lower limb cellulitis.

4.3.3 Selection of participants

Participants were pragmatically recruited from a pre-existing cellulitis research database held at the CEBD (including participants in previous cellulitis trials[40,93] and cellulitis PSP[48]) and from the Lymphoedema Support Network (LSN).[94]

4.3.4 Sampling strategy

Purposive sampling was employed to ensure that participants included individuals aged over fifty years (cellulitis incidence increases with age)[6] and those managed by different types of HCP (so that other pathways to diagnosis might be captured). This was achieved by sending a short questionnaire to eligible participants to determine this information.

Data collection and analysis were undertaken concurrently, and sampling ceased when thematic saturation had been achieved (i.e., new interviews generated no new insight).[95]

4.3.5 Researcher characteristics

One researcher conducted the interviews, and two researchers coded and analysed the interviews. The broader research group includes experienced clinical academics, a patient representative, and research methodologists.

4.3.6 Interview setting

Each participant took part in a single, semi-structured, qualitative interview. These were either face-to-face or via telephone, according to participant preference.

4.3.7 Data collection

In anticipation of the interview, participants were invited to reflect upon their experiences with a cellulitis diagnosis.

A topic guide, informed by a prior review,[57] was used to structure the interview (Figure 4). Participants were encouraged to introduce and develop topics that they felt were most pertinent to their experience of diagnosis.

Figure 4: Topic guide used to structure the interview

Question	Prompts
Can you tell me when you were last told you might have cellulitis?	▪ What did you notice? What made you go and seek medical advice? ▪ How long did you wait to seek help? ▪ Who did you see? ▪ Why did you see this person? ▪ What happened then? ▪ Were any tests done? ▪ What do you think went well? ▪ Was there anything that might have been more helpful? ▪ How was this similar to previous cases of cellulitis you have had?
Can you tell me about any occasion when diagnosing your cellulitis was a problem?	▪ What happened on this occasion? ▪ At what point did you seek medical advice? ▪ What was diagnosed? ▪ Do you know why this was diagnosed? ▪ Did anything change from how you were initially? ▪ What did you do next? ▪ How long did you wait to seek advice again? ▪ What was done differently this time? ▪ Do you know what the final diagnosis was?
We are interested in how different patients receive a cellulitis diagnosis.	▪ Who usually makes the diagnosis of your cellulitis? ▪ Are you confident that they will make the correct diagnosis? ▪ Would you see them again regarding cellulitis? ▪ Has your cellulitis ever been diagnosed by anybody else? ▪ If so, was there a difference in the approach that was used? ▪ What did they ask? ▪ What tests did they do? ▪ Has this changed who you would see in future?

4.3.8 Data processing

Interviews were audio-recorded and transcribed by professional transcribers. Transcripts were checked and data was handled using QSR NVivo 12 software.

4.3.9 Data analysis

Analysis was inductive, finding themes in the data rather than pre-determining concepts of interest. A structured, systematic, multi-stage approach to thematic analysis was followed.[96]

One researcher coded the data, with another researcher independently coding the first six transcripts. All authors and participants agreed upon the final codebook presented in Figure 5.

Figure 5: Standardised codebook used by two independent coders.

Codes used
• Symptoms and signs • Recurrent episodes • Tests • Underlying cause • Seeking medical advice • Relatives involvement • Approach by the HCP • Challenges for the HCP • Participants' confidence • Participants' preferred HCP to see • Seeing different HCPs • Pathways in different countries • Participants' expert knowledge • HCP's trust in the patient • Participants disagree with the HCP • Solutions to help • Participants' concern about a diagnosis • Wanting an early diagnosis • Delayed or incorrect diagnosis • Lymphoedema as a challenge • Other comorbidities as a challenge

4.3.10 Funding sources

This study was funded by the Claire Wand Fund (charity number 220008).

4.4 Results

Eighteen patients with cellulitis were interviewed for a mean duration of 30 minutes (Table 6); all had recurrent cellulitis; all except one had a history of lymphoedema. Interviews were conducted between 29 October and 19 December 2018. A summary of how the codes mapped to the overarching themes are presented in Table 7.

Table 6: Characteristics of the 18 participants.

Participant characteristics	**Number of participants, n (%)**
Gender	
Male	4 (22)
Female	14 (78)
Age	
18-24	0 (0)
25-34	1 (6)
35-44	1 (6)
45-54	2 (11)
55-64	8 (44)
65-74	6 (33)
75+	0
Ethnicity	
White	18 (100)
Total number of cellulitis episodes in their lifetime	
1-5	6 (33)
6-10	2 (11)
10+	10 (56)
History of lymphoedema	
Yes	17 (94)
No	1 (6)

Table 7: Summary of how the codes map to the overarching themes.

Theme	**Code**
The recurrent nature of cellulitis symptoms	• Symptoms and signs
	• Delayed or incorrect diagnosis
	• Lymphoedema as a challenge
	• Recurrent episodes
	• Relatives involvement
	• Challenges for the HCP
Participants' experience of getting a cellulitis diagnosis	• Participants' expert knowledge
	• Seeking medical advice
	• HCP's trust in the patient
	• Wanting an early diagnosis
	• Seeing different HCPs
	• Approach by the HCP

	• Participants' confidence in the HCP
	• Participants' preferred HCP to see
	• Participants disagree with the HCP
Participants' suggestions of how cellulitis diagnosis might be improved	• Solutions to help
	• Tests

4.4.1 Main findings

Three key themes were identified in the data: 1) the recurrent nature of cellulitis symptoms, 2) participants' experience of getting a cellulitis diagnosis, and 3) participants' suggestions of how cellulitis diagnosis might be improved.

Participant quotes are shown in Table 8.

4.4.1.1 The recurrent nature of cellulitis symptoms

Participants described a red, warm, painful limb as being the core symptoms (Participant (P)2). Having a history of lymphoedema meant that swelling alone was not an essential feature and made identifying other features of cellulitis more difficult in the early stages (P7).

However, most interviewees felt that the clinical features of cellulitis during recurrent episodes were similar and helped them recognise the diagnosis (P9). These similar features made participants more confident in seeking a medical review or starting emergency antibiotics provided to them in advance by their general practitioner (GP) (P8). The recurrent pattern of the clinical presentation of cellulitis also allowed family members to identify features to look out for (P1).

Some participants diagnosed with cellulitis experienced vague constitutional 'flu-like' symptoms such as fever and fatigue, typically in the first 24 hours (P14), and wanted antibiotics prescribed at the onset of these early constitutional symptoms, hoping to prevent hospital admission (P11).

4.4.1.2 The experience of the participant getting a cellulitis diagnosis

Learning from recurrent episodes of cellulitis allowed participants to become more 'expert' in making a self-diagnosis before seeing a HCP (P1).

Continuity in care was important for participants. Some discussed how seeing their usual HCP assisted the diagnosis as they were familiar with their typical presentation of cellulitis (P1). Previously recorded episodes of cellulitis can also influence diagnosis in the out-of-hours setting and the ED (P9).

Many participants wanted a diagnosis quickly and sought medical advice as soon as the first symptom appeared (P7). This was not always easy (especially in primary care due to limited acute appointments), leading some to rely upon out-of-hours and the ED (P9).

Some participants were content to wait for changes in the limb before seeking help (P11), while others started treatment with oral antibiotics at home before seeking medical advice (P8).

Participants consulted various HCPs: GPs, emergency physicians, dermatologists, lymphoedema nurses, nurses in primary care, and pharmacists. Despite this variation, the HCP assessment of possible cellulitis was similar across all professional groups (P8).

A later presentation, with the development of more clinical features in secondary care, was suggested as a reason diagnosis may be less challenging in this setting (P8).

Participants were generally confident that all HCPs (irrespective of setting) would make the correct diagnosis of cellulitis (P9). One participant felt that the lymphoedema nurse and community nursing team were good at diagnosing cellulitis as they are more familiar with their usual features (P5).

As participants felt confident in making a self-diagnosis of cellulitis, they would become more determined for the HCP to accept their judgement (P1). Some would seek a second opinion if a professional did not concur (P11).

Some participants would push for a diagnosis even when a HCP is unsure (P2). This often stemmed from the impact cellulitis had on them in the workplace or socially and their urgency to get a quick diagnosis and treatment (P2).

4.4.1.3 Participants' suggestions of how cellulitis diagnosis can be improved

When asked about resources that may help a HCP to make an accurate diagnosis more quickly, further education, with prompts and pictures, was suggested (P7). Educating professionals on how cellulitis can present in lymphoedema was a specific area where more education would be beneficial (P4). Other resources mentioned to assist diagnosis included a specific blood test (P11).

Participants seen in a cellulitis clinic stated that a specialist clinic was ideal to provide an accurate diagnosis (P1).

Some participants thought a symptom checklist could help (both for themselves and HCPs) (P13). However, any self-diagnostic guide should have clear instructions about when to seek medical advice from the HCP (P18).

Table 8: Examples of participant quotes mapped to the themes.

Themes	**Participant quotes**
Core cellulitis symptoms and recurrence	'I get a real bad bruise pain ... It's the pain, a bit like when you break a leg….Generally speaking, if I get that pain, I check my leg out to see where it's red, or raised or hot' (P2, 56-year-old female) 'There is the heat in the leg, swelling in my leg, and that swelling, could be confused with the lymphoedema side of things. But it's the heat and the swelling, not just the swelling' (P4, 74-year-old male) 'Because this was my second episode.. symptoms I felt were very similar to the first time around, but obviously, I recognised them this time around' (P9, 71-year-old male) 'My husband says I don't look well [when I get cellulitis]…I go much paler, glassy-eyed' (P15, 62-year-old female)
Experience of getting a cellulitis diagnosis	'Until the symptoms show themselves totally…they [doctors] are reluctant to make that [diagnosis], that it is cellulitis, but they are quite happy the day after when it's more apparent that this is it' (P4) 'As I've had it so many times, my [self] diagnosis has got better. Simply because I know more about it myself… There are a lot of GPs who appreciate that I have had it so often, and they know what is happening, and they will go with my instinct' (P1) 'He looked at my records [in urgent care], and he noticed that I had a record of cellulitis, and he said, "It certainly looks like it, and I'm not going to take any chances" (P9)

	'I have antibiotics that I keep at home so that if this happens, I can start taking them, but I started taking them, and it hadn't gone away, so I made an emergency appointment to see my GP' (P8, 36-year-old female) 'I don't actually think that they [emergency department] asked anything particularly different [to the GP]' (P8) 'I suppose by that point [in the emergency department], basically, everyone had already thought the day before that it was probably cellulitis….I actually went there with the diagnosis whereas because I was sort of a bit further down the line' (P8) 'Funnily enough, the best person I have found for picking it up has been one of my district nurses. She's had previous experience with cellulitis…I think that they see it more' (P5) 'If I was sure it was cellulitis, and someone was saying definitely not, then I would say look, I know it is cellulitis, we need to get someone else to look at it because I know now what I am looking at' (P11)
Suggestions of how cellulitis diagnosis might be improved	'Education - because I'm sure it's not something they come across every day so they'll just think, they need to be shown examples, pictures, anything or even have somebody speak to them who suffers with it' (P7) 'A specific blood test or antigen that they could test for and they can find out if that is what the problem was' (P2) 'A dedicated clinic for me would be amazing. Because then you are dealing with people who know what cellulitis is on a regular basis and familiar with it and everything' (P1) 'If I had a checklist that once I had completed, it said yes, it is definitely cellulitis, this is how you treat it….I would certainly do it myself' (P13, 55-year-old female) '[With a self-diagnostic guide] I think you have to be very clear about if it reaches [a particular] stage, you need to get a health professional involved' (P18)

4.5 Discussion

4.5.1 Main findings

This qualitative study found that patients with lymphoedema experience similar clinical features during each recurrent cellulitis episode and generally feel confident in making their own clinical diagnosis. Patients often experience constitutional 'flu-like' symptoms and fatigue, typically before the inflammatory features of pain, warmth and erythema were noticed.

However, swelling associated with cellulitis, particularly amongst patients with lymphoedema, can be difficult to differentiate from pre-existing swelling. In addition, the typical features of cellulitis can also present in many differential diagnoses,[11] making the diagnosis challenging.

Patients felt that the clinical diagnostic approach of various HCPs they consulted were comparable, with the speed of being seen and seeing a known HCP as key determining factors of whom to consult. Patients were generally confident that a HCP would make the correct diagnosis of recurrent cellulitis episodes due to their previous history.

Patients consider themselves to have a significant amount of knowledge in diagnosing their own cellulitis episodes, and many perceive they have the trust of their HCP in making a diagnosis and starting treatment. More education and a diagnostic checklist that both HCPs and patients with cellulitis could use were suggested as ways to improve the cellulitis diagnosis.

4.5.2 Relevance to clinical practice and research

The study findings can be applied to patients with recurrent cellulitis and lymphoedema, which predisposes them to recurrent cellulitis.[21] The key clinical features described and the diagnostic overlap of these features with other pathologies are well-known in clinical practice,[11] and this study confirms this. The similarity of clinical features in recurrent cases is likely to be something HCPs consider when making a diagnosis, given that they seem more willing to diagnose cellulitis in a person with multiple previous episodes.

Constitutional features could be an indication of viral illness that does not require antibiotics[97] or an early feature of infection, but the source of infection is not apparent yet. This poses significant challenges to professionals in diagnosing cellulitis: not over-diagnosing and maintaining antibiotic stewardship versus not delaying cellulitis diagnosis is a delicate balance to tread.

With increasing pressures on health care in the UK and a growing cohort of 'expert patients', empowering individuals to self-diagnose and self-manage may become more common.[98] However,

this must be done cautiously by professionals who know the person with cellulitis well and have transparent safety nets. A shared validated diagnostic tool or set of criteria that both HCPs and patients with recurrent cellulitis can use may allow this to be done safely, similar to those available in asthma.[99] Regarding the interview findings that some patients find it difficult to access their primary care provider quickly during an acute episode, having a self-management plan becomes even more relevant. Other methods proposed to aid diagnosis include educational resources such as clinical images of cellulitis presentations made available to HCPs or specialist cellulitis clinics, which have been shown to improve accurate diagnosis.[11]

4.5.3 Strengths and limitations

A key strength is that efforts were made to ensure the inclusion of individuals >50 years of age, who are often harder to recruit in research studies.[100] This was important as the incidence of cellulitis increases with age.[6]

Participants included are those at higher risk of experiencing recurrent cellulitis.[21] Some of these expert patients provided valuable insights on other approaches employed by different HCPs when making a diagnosis of cellulitis. This select group also provided insight into distinguishing the early diagnosis of cellulitis from their underlying lymphoedema, a common diagnostic dilemma.[11] Another strength is that participants provided feedback on the final themes.

A fundamental limitation is that this study recruited patients pragmatically from a cellulitis research trial database,[40,93] the cellulitis PSP,[48] and the UK LSN.[94] This led to selection bias as the patients who volunteer from such groups are likely to be inherently different from the general population with cellulitis. Consequently, all the interview participants were of White ethnicity, had recurrent cellulitis, and all but one had lymphoedema. This limits the generalisability of the findings, as it did not provide insight into the experiences of those with a first-time diagnosis of cellulitis, without co-existing lymphoedema, or from minority ethnic groups. However, the wealth of experience that people with recurrent cellulitis have gained over the years on their symptoms and when to seek treatment are invaluable.

In future, screening primary and secondary care health records with the appropriate ethical approval could improve the sampling strategy.

4.6 Chapter summary

This interview study has shown that selected adult individuals with recurrent cellulitis know when they have an acute episode of cellulitis. Therefore, some patients could be involved in diagnostic decision-making. The initial features of cellulitis were discussed, alongside suggestions to improve clinical diagnosis, including educational resources, specific blood tests, and a diagnostic checklist. It was clear that patients felt HCPs sometimes struggled to make an accurate diagnosis. This needs to be further explored with HCPs.

Chapter 5 - An interview study to determine the experiences of cellulitis diagnosis amongst health care professionals in the UK

5.1 Introduction

In the interview study of patients with recurrent cellulitis, challenges in diagnosis and a cluster of early and 'typical' features of cellulitis, were described.[101] To determine if HCPs corroborated these findings and to explore their opinions, a qualitative interview is the optimal study design.[91]

5.2 Aims

The primary aim of this study was to describe the key clinical features which inform the diagnosis of cellulitis. The secondary outcome was to explore the difficulties in diagnosing cellulitis.

5.3 Methods

5.3.1 Protocol registration and ethics

The protocol was registered on the CEBD website (9 May 2019).[102] Ethical approval was granted by the Health Research Authority and Health and Care Research Wales (19/HRA/0485) (30 November 2018). Verbal and written consent was obtained from each participant.

5.3.2 Eligibility criteria

Participants were qualified HCPs with a minimum of two years of clinical experience as a HCP in the National Health Service (NHS) and managed a clinical case of suspected cellulitis in the UK. Two years' experience was the minimum requirement as HCPs will have gained adequate exposure to cellulitis cases. HCPs were recruited from dermatology departments (including a specialist cellulitis clinic), general practice, tissue viability, lymphoedema services, general surgery, emergency care, and acute medicine.

Purposive sampling was employed to ensure that participants included consultant doctors, trainee doctors, and nurses across the above specialities. Participants were recruited through:

- National networks

- HCPs who contributed to the cellulitis PSP
- UK Dermatology Clinical Trials Network
- Snowball sampling where participants helped recruit other participants
- Personal networks of the authors

Potential participants were approached and recruited by email. Data collection and analysis were undertaken concurrently, and sampling ceased when thematic saturation had been achieved.[95]

5.3.3 Researcher characteristics

Interviews were conducted by one researcher and coded and analysed independently with another researcher. The broader research group includes experienced clinical academics, a patient representative, and research methodologists.

5.3.4 Interview setting

Each participant took part in a single, semi-structured, qualitative interview. These were either face-to-face or via telephone, according to participant preference.

5.3.5 Data collection

Before the interview, participants were asked to reflect upon their most recent experiences of making a cellulitis diagnosis, focusing on the typical presentations, challenging cases, and differential diagnoses.

The topic guide was informed by prior systematic reviews and interview study,[57,101,103] and was used to structure the interview (Figure 6). However, participants were urged to propose and expand on topics that were relevant to their diagnosis experience. New topics were then added to the topic guide for subsequent interviews.

Figure 6: Interview topic guide.

Question	Prompts
Can you tell me about a case of cellulitis that you diagnosed? Repeat the above for a maximum two cases that the participants may have for the interview (repeat twice only if the participant has no delayed/incorrect cases below).	• What thoughts go through your head when you are considering a diagnosis of cellulitis? • What symptoms do you ask about? Local? General? • What signs do you look for? Local? General? • Are there any specific signs/symptoms you rely on to help? • Did you do any tests? • Did you seek advice from anyone else? • Were you concerned that this may not be cellulitis? • If you were concerned, why? • Was there anything challenging about this case? • How did you address these challenges? • How confident were you that this was cellulitis on a 1-10 scale when you first saw the patient? • Did the patient discuss any self-diagnoses? • Did any external factors such as time influence your decision? • Did the patient come back to see you again? • Would you change your approach if the same case presented again? • Is this a typical case you see? • What are the main differential diagnoses you see?
If the participant has a case where the diagnosis was delayed or incorrect (can be initially either seen by same health care professional or a colleague, but preferably the same person)	• Did you see the patient on initial presentation or was it a colleague? • If it was another colleague, what specialty did they work in? • What symptoms did they present with? • What signs did they have? • What was the initial diagnosis? And why? • Were any tests done? • Did any external factors influence the decision for the initial diagnosis? • When did they see you or another colleague again? • If it was another colleague, what specialty did they work in? • Did anything change with the signs/symptoms? • What happened next? • Do you know what the final diagnosis was? • What were the reasons for the delay in the diagnosis? • Why was it difficult to make an accurate diagnosis on first consultation?
We want to establish if it is possible to determine a core group of features that can be used to help diagnose lower limb cellulitis	• What symptoms are you asking about? • Of these symptoms, which do you think are more suggestive of cellulitis? • Are there any symptoms that make cellulitis less likely? • Are there other features in the history which make cellulitis more/less likely? (prompt – other conditions, previous history, drugs, family history)

	• What signs are you looking for? • Of these signs, which do you think are more suggestive of cellulitis? • Would you request any tests if it was available to you on the same day? • If so, what tests would these be? • Are there any signs in a 'red leg' that would make cellulitis less likely as the diagnosis? • Are there any signs in a red leg which would make cellulitis more likely as the diagnosis? • How has your approach to diagnosing cellulitis changed after managing previous cases? • If the patient has had previous cellulitis, does this influence your diagnosis? • From your experience, what differential diagnoses do you think about? • How do you distinguish cellulitis from these differential diagnoses? • Specifically, how do you differentiate cellulitis from lymphoedema? • Specifically, how do you differentiate cellulitis from venous eczema? • Specifically, how do you differentiate cellulitis from infected venous eczema? • Specifically, how do you differentiate cellulitis from lipodermatosclerosis? • Do you feel that a list of key diagnostic features of cellulitis would help when assessing patients?
We want your views on some aspects of diagnosis that patients with recurrent cellulitis and lymphoedema have discussed	• Patients felt that they were confident in making a self-diagnosis of cellulitis and valued greater trust in self-management at home with treatment. What are your thoughts on patients self-diagnosing? • Would a photograph with a proforma taken and filled in by the patient and sent to you be helpful in managing patients with recurrent cellulitis? • In the instance where you may not agree with the patients self-diagnosis of cellulitis, how would you manage the diagnosis? • Do you feel that any further training or resources should be set up to help improve our diagnosis of cellulitis? For example, a specialist cellulitis clinic to refer patients to? • What are your thoughts on HCPs having a guide such as checklist to help diagnosis? • Do you think patients should have this checklist? If so why or why not?

5.3.6 Data processing

Interviews were audio-recorded and transcribed by professional transcribers. Transcripts were checked and data managed using QSR NVivo 12 software.

5.3.7 Data analysis

Analysis was inductive, searching for themes in the data. A structured, systematic, multi-stage approach to thematic analysis was followed.[96] One researcher coded the data, with another researcher independently coding a third of the transcripts.

A list of each code, with a brief description, was then used to group the codes into theme piles. Themes were defined and refined, with sub-themes also developed.

Data collection and analysis were concurrent. All authors agreed upon the final codebook, which is presented in Figure 7.

Figure 7: Final codes used**.**

- Trial of treatment guides diagnosis
- Discussing diagnosis with colleagues
- Time and safety netting approach
- Patients who self-diagnose and treat
- Approach when HCPs do not agree with the patient's self-diagnosis
- Patients involved with the diagnosis with the HCP
- Typical cellulitis presentations
- Clinical features of cellulitis
- Factors that increase the likelihood of cellulitis diagnosis
- Factors that decrease the likelihood of cellulitis diagnosis
- Investigations to aid diagnosis
- Missed/delayed diagnosis of cellulitis (final diagnosis)
- Missed/delayed diagnosis of cellulitis (initial diagnosis)
- Patient finds it difficult to accept it is not cellulitis
- Reasons why cellulitis diagnosis is challenging
- Suggestions on what may improve diagnosis
- Views on diagnostic aids for HCP
- Views on diagnostic aids for patients
- Views on how well HCPs make a diagnosis
- Experience guides diagnosis
- Seeing patients part way through assessment and management
- Differential diagnoses
- Sepsis as a concern
- Medico legal issues as a factor
- Follow up of patients
- Most suitable HCP to diagnose cellulitis
- Fear of missing more serious differentials
- Clinical features to include in diagnostic algorithm
- Other factors influencing diagnosis

5.3.8 Funding sources

This study was funded by the Royal College of General Practitioners (RCGP) Practitioners Allowance Grant (SFB 2018-31).

5.4 Results

Twenty HCPs were interviewed (Table 9). Interviews were conducted between 19 March and 11 June 2019, with a mean duration of 29 minutes.

Table 9: Characteristics of the participants.

Participant	Gender	Age	Ethnicity	Clinical role	Years of clinical experience	Number of times they have diagnosed cellulitis	Time since they last diagnosed cellulitis
1	Female	41	British Asian	GP	>13	>50	One week ago
2	Female	52	British Caucasian	Acute medicine/infectious disease consultant	25	>50	One week ago
3	Female	42	Irish Caucasian	GP	18	>50	Three weeks ago
4	Male	39	British Caucasian	Acute medicine consultant	17	>50	Last four weeks
5	Male	39	British Caucasian	Acute medicine consultant	16	>50	One week ago
6	Female	51	British Caucasian	Tissue viability nurse	11	10-50	Less than one week
7	Female	50	British Caucasian	Lymphoedema specialist nurse	26	>50	One week ago
8	Male	50	British Asian	Emergency medicine consultant	20	>50	Less than one week
9	Female	38	British Asian	Dermatology consultant	10	10-50	Four weeks ago
10	Female	57	British Caucasian	District nurse	25	>50	Last three months
11	Female	29	Black	GP trainee	6	10-50	Less than one week

12	Male	30	British Asian	GP locum	7	10-50	Two weeks ago
13	Female	42	British Asian	GP out of hours	20	>50	Two weeks ago
14	Female	47	British Caucasian	Dermatology specialist nurse	9	>50	Last three months
15	Female	42	British Caucasian	Dermatology consultant	18	10-50	Last 12 months
16	Female	29	Mixed	Surgical trainee	5	10-50	Last four weeks
17	Female	49	British Caucasian	Community advanced nurse practitioner	20	>50	Less than one week
18	Female	32	British Caucasian	Dermatology trainee	8	>50	Four weeks ago
19	Female	35	British Caucasian	Emergency medicine consultant	10	>50	Last three months
20	Male	67	British Caucasian	Dermatology consultant	42	>50	Less than one week

5.4.1 Main findings

Four key themes were identified: 1) The patient presentation; 2) The challenges leading to diagnostic uncertainty; 3) The strategies to improve diagnosis; 4) The need for an objective diagnostic aid, with further classification into sub-themes. How the codes mapped onto the overarching themes are shown in Table 10. Quotes from participants are shown in Table 11.

Table 10: How the codes mapped onto themes

Themes	Sub-themes	Codes
The patient presentation	The typical patient and risk factors	• Typical cellulitis presentations
		• Factors that increase the likelihood of cellulitis diagnosis
	Confidence in diagnosis	• Most suitable HCP to diagnose cellulitis
		• Experience guides diagnosis
	Cases of misdiagnoses	• Missed/delayed diagnosis of cellulitis (final diagnosis)
		• Missed/delayed diagnosis of cellulitis (initial diagnosis)
	Differential diagnoses	• List of alternative diagnosis

Challenges leading to diagnostic uncertainty	Continuum of clinical features	• Changes in clinical presentation
	A subjective diagnosis	• Reasons why cellulitis diagnosis is challenging
	Community challenges	• Seeing patients part way through assessment and management
		• Follow up of patients
	The role of 'defensive' medicine	• Sepsis as a concern
		• Medico legal issues as a factor
		• Fear of missing more serious differentials
	Patient specific factors	• Other factors influencing diagnosis
Strategies to improve diagnosis	Using time as a guide	• Time and safety netting approach •
	Trial of treatment	• Trial of treatment guides diagnosis •
	Biochemical investigations	• Investigations to aid diagnosis
	Seeking advice	• Discussing diagnosis with colleagues
	Further education	• Suggestions on what may improve diagnosis
The need for an objective diagnostic aid	A diagnostic algorithm	• Views on diagnostic aids for HCP
	Indices for an algorithm	• Clinical features to include in a diagnostic algorithm

Table 11: Participant quotes

Themes	**Sub-themes**	**Participant quotes**
The patient presentation	Confidence in diagnosis	'*I would say it is just experience [helping a diagnosis], a lot of the juniors that come into A&E have not seen that many cellulitis [cases]*' (P19, emergency care consultant) '*I probably thought more presentations were [cellulitis] as a junior doctor… I probably didn't really recognise that sort of stretched skin appearance.. I think that has come along as part of just experience over the years, so I probably diagnosed more cellulitis inappropriately as a more junior doctor*' (P13, GP out of hours)
	Cases of misdiagnoses	'*One of the nurse practitioners had seen [a patient with] ankle swelling … he played some cricket two or three days ago and after one or two days the swelling appeared and she thought that it was just a sprain but next day he represented, I saw him and it looked more like cellulitis because it was quite red, localised area… on close examination I could see a couple of scratches around the ankle so that was maybe the source of cellulitis spreading on the leg'* (P8, emergency care consultant) *'We did see [patients] coming in with "oh this must be a resistant cellulitis", have got a swollen limb that might be a little bit red and it turns out to be some horrible form of lymphoma. You maybe get one or two of those every year where the assumption is that this must be cellulitis because they are really sick and it's a bit red and those can be quite difficult to tease out sometimes, simply because they are sick and the assumption is that it is an infection'* (P2, infectious disease consultant) '*Generally anything that is red and hot and on the legs is treated with antibiotics*' (P1, GP)

		'*There are too many chronic rashes that get referred [to dermatology] as cellulitis*' (P18, dermatology trainee)
	Differential diagnoses	'*One thing that is always a problem in leg swelling…it is difficult to ascertain between DVT and cellulitis*' (P8, emergency care consultant)
Challenges leading to diagnostic uncertainty	Continuum of clinical features	'*Usually the patient is already admitted ….. [the referring team] have tried [multiple antibiotics], but nothing is happening, "please can you come and tell us what is going on?*" (P9, dermatology consultant) '*There are varying ranges of erythema, from a little bit of light pinkness to rip roaring hot red, tender, well demarcated, unilateral; the classic sort of textbook stuff*' (P18, dermatology trainee) '*I learnt to appreciate much more that [cellulitis] is coming up, it is happening and that it is fading away. A lot of what happened when I was [junior], I was seeing [cellulitis] at the beginning and middle stages, trying to diagnose it, but in dermatology you're seeing it more at that other end of the spectrum..so I think there is a lot [to be] learnt about seeing that pattern developing and progressing and then resolving '* (P18, dermatology trainee) '*Virtually every patient that I see...they have had their d-dimer and their duplex done so [DVT] is usually a diagnosis that has been excluded*' (P20, dermatology consultant)
	A subjective diagnosis	*'I think the fact that there is no specific diagnostic test… and two different people can look at [possible cellulitis] and come up with two different answers'* (P1, GP)
	Community challenges	'*You've not met the patient before and sometimes you're not going to be able to follow them up so you probably are more likely to give antibiotics*' (P12, GP locum) '*If you know the patient and you know that they have recurrent cellulitis, someone had seen it like a district nurse and it is Friday afternoon and you can't get out [for a visit].. you would make a judgement call*' (P1, GP)
	The role of 'defensive' medicine	'*I think you would want to rule out DVT first because if you miss that then that is… a problem*' (P1,GP; P16,surgical trainee) '*We're so much more aware of things like sepsis… looking at any kind of signs of infection*' (P10, district nurse) '*We're all risk adverse aren't we? We would rather make sure we weren't sued because we had missed someone with an infection*' (P2, infectious disease consultant)
	Patient specific factors	'*One of these classical patients that comes in hasn't got a rash and hasn't necessarily got the features that I said of swelling, redness, rash and pain in the leg but they come in none specifically unwell and they may have described a bit of an ache in the leg or something like that but there is nothing else to go on examining the patient for signs, so I think those patients are much trickier'* (P5, acute medicine consultant) *'People with chronic red [legs], their legs are red most of the time.. the skin takes so long to settle, so they could have had cellulitis four weeks ago and it is still red'* (P17, advanced nurse practitioner)
Strategies to improve diagnosis	Using time as a guide	*'All you can really do is reassure the patient and say…I don't see any clear evidence of cellulitis but we will keep an eye on it…. you give safety net advice to the patients'* (P18, dermatology trainee) '*So, if they were well.. then I would bring them back to clinic the next day or two*' (P4, acute medicine consultant)
	Trial of treatment	'*Cellulitis…was the easiest thing to try and treat so I think that definitely pushed [me] to try some antibiotics and see if this is an infection*' (P11, GP trainee)

		'[*My concerns with this approach] are antibiotic resistance and side effects…especially in older groups..I would say probably that is not the best approach'* (P3, GP)
	Biochemical investigations	'*If I am thinking about doing blood tests…it is unlikely that I am going to continue managing them in the community*' (P11, GP trainee) '*[With cellulitis]….you expect a) it is unilateral, b) you want some inflammatory markers which are raised, at least a reasonable WCC and CRP and if it is normal, it is not going to be cellulitis'* (P9, dermatology consultant) '*I would never not diagnose somebody [with cellulitis] just because their inflammatory markers are normal*' (P5, acute medicine consultant)
	Further education	*'You very quickly just get entrenched in…your preferences for diagnoses and it is often good to refresh*' (P11, GP trainee) *'I only did two weeks [of dermatology] as a medical student… but certainly increasing dermatology teaching at an earlier stage would make a massive difference'* (P13, GP). '*It is all very well seeing pictures but pictures aren't that helpful sometimes, it is how it feels sometimes that makes a difference and actually seeing it in the flesh is very different to seeing even good quality pictures, so I do think that clinical exposure [is important]*' (P13, GP). '*It is not something people will have put a lot of thought into, the differentials, and I think the focus needs to be on teaching the frontline staff*' (P15, dermatology consultant). '*Pattern recognition and [seeing] variation in the progression of the rash [are important]*', thereby appreciating the '*life of rashes*' (P18, dermatology trainee).
The need for an objective diagnostic aid	A diagnostic algorithm	'*I think it can be helpful to have those objective measures [of an algorithm], if it was accepted and validated as a reasonable measure of cellulitis, I think I would actually use that*' (P11, GP trainee). *'[A checklist] could help people that weren't experienced or confident enough. To have a checklist as a learning tool is fabulous, it just gives you something to think about like "oh I hadn't thought about the smell, I hadn't thought about the heat"….and I use checklists all of the time'* (P14, dermatology nurse). '*For a diagnostic checklist you almost want it to be provided as an education tool with photographs and descriptions…. so that people can put these differential diagnoses into their head*' (P15, dermatology consultant). '*You would have to develop a criterion that can pick up the beginning, it is in the middle and it is resolving at the end*' (P18, dermatology trainee). '*Because there is such a wide differential…how would you exclude all of those and also it can be quite nonspecific sometimes in the early stages*' (P12, GP locum). '*Sometimes the trouble with guidelines, algorithms…. you could probably cover 95% but does it mean that actually the atypical 5% then [do not] get diagnosed?*' (P20, dermatology consultant).

5.4.1.1 Diagnosis of cellulitis

5.4.1.1.1 The typical patient and risk factors

In general practice, the typical patient described by participants included older adults with co-morbidities (P3); district nursing colleagues often raised concerns about possible cellulitis cases (P1). Emergency care (P19) and acute services (P5) described patients who presented with features of systemic compromise. General surgery services often managed intravenous drug users at risk of a deeper infection (P16).

According to HCP participants, factors that increased the likelihood of cellulitis were: features of systemic upset, including fever, malaise, rigors; co-existing injury or infection such as tinea, superficial ulceration, previous history of cellulitis, previous history of dermatological conditions such as eczema, diabetes, immunosuppressive medications and those with no fixed abode with social and health risks. Bilateral symptoms were commonly described by participants as a factor increasing the likelihood of chronic, systemic pathologies rather than cellulitis (P2,P9,P20).

5.4.1.1.2 Confidence in diagnosis

One dermatologist explained how being more aware of the differential diagnoses made senior dermatologists more likely to accurately diagnose cellulitis, especially compared to junior colleagues (P15). Generally, HCPs with more clinical experience felt more confident in diagnosing cellulitis, as they have managed more cases (P19).

A dermatology trainee felt seeing fewer cellulitis cases during their training compared to their senior colleagues historically, and therefore not getting as much exposure hindered accurate diagnosis (P18).

5.4.1.1.3 Cases of misdiagnoses

Trauma-related skin changes were frequently an initial misdiagnosis in the ED (P8). When discussing cases of uncertainty, where cellulitis was the initial suspected diagnosis, one GP described a case of venous eczema which was managed with repeated antibiotics (P1). Chronic rashes were frequently seen by dermatology, and infectious disease discussed lymphoma cases initially referred to as cellulitis (P2).

The importance of a correct diagnosis is vital, as two participants discussed the possibility of prophylactic antibiotics for patients with recurrent cellulitis (P9,P15). A dermatology consultant explained how misdiagnosis could result in inappropriate and costly admissions to the ward (P9).

5.4.1.1.4 Specific groups of patients where the typical features of cellulitis are unclear

Participants described specific groups of patients where the clinical features were often not clear, making the diagnosis more challenging (P5, P14). These are patients with lymphoedema (P5) and chronic red legs (P14) who are over diagnosed and anecdotally, those of darker skin types who are underdiagnosed.

Distinguishing the signs of a new episode of acute cellulitis from post-inflammatory changes, following a recent cellulitis episode was also a specific challenge (P17). A clinical decision then needs to be made whether to treat with more antibiotics (as a suspected relapse or recurrence of cellulitis) or not (P17).

5.4.1.1.5 Differential diagnoses

A frequent diagnosis of uncertainty for primary and emergency care was DVT, as the clinical features of cellulitis can overlap (P8). Common differential diagnoses discussed by participants, which they observed in their clinical practice, with discriminating features from cellulitis are shown in Table 12.

Table 12: Differential diagnoses of lower limb cellulitis discussed by participants

Differential diagnoses	**Key differentiating factors from cellulitis**
Chronic heart failure causing oedema	Chronic, bilateral, lack of mobility, breathless, cardiac history (P1,GP;P14,dermatology specialist nurse)
Venous eczema	Chronic with hemosiderin, scaling, itching, crusting, likely bilateral, possibly eczema elsewhere on body, less well defined, (P3,GP;P15, dermatology consultant)
Thrombophlebitis	Tender, localised, hard, lumpy rash around an often-thickened vein (P3,GP;P5,acute medicine consultant;P12,GP locum)
Erythema nodosum	Multiple, discrete swellings (P13,GP out of hours)

Deep vein thrombosis	Pain is usually deep in calf rather than superficial, less sharply demarcated and less intense erythema, diffuse swelling of limb, can be young, can be intravenous drug users, high DVT wells score, fewer systemic features (P2,infectious disease consultant;P12,GP locum;P13,GP out of hours)
Lymphoedema	Chronic, bilateral, usually less painful, thickened warty skin in the long-term, normal inflammatory markers (P9,dermatology consultant;P18,dermatology trainee)
Allergic reaction to insect bites	Central puncture mark, itch, when acute, developing lichenified erythema when chronic (P2,infectious disease consultant)
Lipodermatosclerosis	Often bilateral, systemically well, tight non tender skin with inverted champagne bottle appearance (P4,acute medicine consultant; P20,dermatology consultant)
Necrotising fasciitis	Crepitus, rapidly spreading, septic, very tender (P5,acute medicine consultant; P16, surgical trainee)
Wound infection	Local to the wound, covers small area, yellow exudate, strong odour (P10,district nurse; P16,surgical trainee)
Baker's cyst	Unilateral popliteal swelling, suddenly more tender on rupture (P15,dermatology consultant)

5.4.1.2 Challenges leading to diagnostic uncertainty

5.4.1.2.1 The continuum of clinical features

An important observation highlighted, was that erythema differs depending on where in the trajectory of the cellulitis episode, the person is being assessed (P18).

Erythema is an important feature, where the intensity of redness can determine how confident a HCP is in the diagnosis. For instance, a physician may be more confident in diagnosing cellulitis in lighter coloured skin when the leg appears vivid red in the later stages, compared to a light pink rash seen in the early stages (P18).

5.4.1.2.2 A subjective diagnosis

Cellulitis is a clinical diagnosis based on the clinician's interpretation of the medical history and clinical examination. The assessment of a red leg may vary between two clinicians (P1). This subjectivity is further compounded by the lack of an objective diagnostic test (P1).

Whilst exploring this theme, some HCPs could not fully describe the clinical rationale behind their diagnostic decisions.

5.4.1.2.3 Community challenges

In the community, additional challenges for GPs were not being familiar with the patient's background history, seeing a patient for the first time, or taking over care part way through the patient journey (P12). Working as a locum doctor with a lack of follow-up often led to treatment when unsure of the diagnosis (P12). Limited resources to see patients, such as being unable to conduct an urgent home visit, also influenced diagnosis and subsequent management by GPs (P1).

5.4.1.2.4 Acute care challenges

In acute hospital settings, when assessing a red leg, the priority for HCPs is to exclude life-threatening causes (P1, P16). Blood tests (e.g., d-dimer) and ultrasound imaging is often performed by frontline services for patients presenting with a unilateral red leg, to exclude a DVT, before a cellulitis diagnosis is provided (P19). These patients may be discharged with oral or intravenous antibiotics or admitted for further management of cellulitis.

5.4.1.2.5 The role of 'defensive' medicine

HCPs in the community (P1), acute care (P5), and surgery (P16) were particularly wary of missing a more serious diagnosis, such as DVT and necrotising fasciitis, which needed to be ruled out first. Many HCPs also mentioned '*sepsis*' when discussing clinical features and diagnosis (P1, P2, P13,P14). This may be leading to an overdiagnosis of cellulitis due to concerns of medico-legal complaints of missing an infection which could then get worse (P2).

5.4.1.3 Strategies used to reduce uncertainty

5.4.1.3.1 Using time as a guide

In cases where the HCP was not sure of the diagnosis, different strategies were employed. Using time to allow additional clinical features to develop with appropriate safety netting was one approach used (P4). This was easier when follow-up appointments were available in the community but was also

done in the acute setting (P4). Follow-up in secondary care was difficult, often not done, and can be a missed opportunity to learn from incorrect diagnoses (P2).

5.4.1.3.2 Trial of treatment

Some HCPs started antibiotics for suspected cellulitis and reviewed the response to help provide the diagnosis retrospectively (P11). One GP highlighted this approach's primary concern was antibiotic resistance and side effects (P3). However, overall, there was a common understanding in primary care about why this approach was taken in some instances (P3).

5.4.1.3.3 Investigations

In primary care, one doctor described how blood tests and cultures were rarely done to diagnose cellulitis, as such patients would need to be seen in secondary care (P1). The infectious disease physician requested blood cultures if it was an atypical infection (P2), but a challenge described by one dermatology consultant was that organisms are not isolated in the majority of patients (P20). Swabs were done for suspected wound infections, mainly by district nurses (P10) or before discussion with microbiology when seen by dermatologists (P15).

The blood tests commonly requested by secondary care HCPs were WCC and CRP, with one dermatologist stating how changes in blood test results were important when taking referrals for suspected cellulitis (P9). However, the interpretation of these blood tests also varied. For some clinicians, when the diagnosis of cellulitis is unclear, raised inflammatory markers may help to confirm their diagnosis (P9). Others would still diagnose cellulitis despite normal inflammatory markers, when the clinical suspicion of cellulitis was high (P4).

However, one challenge with interpreting blood tests was in the group partially treated with antibiotics, who have improving blood tests but a limited clinical response (P18).

A biomarker or point of care test for cellulitis was suggested as an investigation to aid diagnosis by one dermatology consultant (P20) and one GP respectively (P1).

5.4.1.3.4 Seeking advice

Another approach during uncertainty was to discuss with colleagues. Nurses may ask the GP to review in the community (P10). In the hospital, specialists in infectious disease, dermatology, microbiology, and general/plastic surgeons are most often contacted for review.

5.4.1.3.5 Further education

It was mentioned that more dermatology teaching may help improve the diagnosis at the undergraduate and postgraduate levels (P13). One GP stated that real-life clinical cases were more critical for teaching rather than focusing on pictures (P13).

A dermatology consultant suggested that a key area of education among HCPs was being aware of differential diagnoses for frontline services (P15). One trainee who worked in a specialist cellulitis clinic found that seeing many cases helped improve her recognition of cellulitis (P18). Part of experiential learning is reviewing the final diagnosis and reflecting on the diagnostic approach.

5.4.1.4 The need for an objective diagnostic aid

5.4.1.4.1 A diagnostic tool

Many participants mentioned developing a diagnostic algorithm similar to the Wells score[104] for DVT. One GP explained how this might also help GPs make a validated clinical decision when colleagues such as district nurses suspect cellulitis and the patient cannot be seen quickly (P1). A dermatology nurse described how she often used checklists and how an algorithm would help HCPs not to miss any clinical features (P14). One dermatology consultant suggested that a diagnostic checklist should be more of an educational tool to help rule out other differential diagnoses (P15).

A dermatology trainee felt that the indices of a checklist would have to reflect how cellulitis changes through the course of the episode (P18). Other challenges described by participants regarding developing an algorithm were the number of alternative diagnoses, with features that often overlapped with cellulitis and initial vague constitutional features. Another concern highlighted by a

dermatology consultant was that algorithms would miss patients who may present with atypical features, referred to as '*outliers*' (P20).

5.4.1.4.2 Indices for a diagnostic criterion

The key clinical features HCPs suggested to include in a diagnostic criterion for lower limb cellulitis were: unilateral, pain, erythema, the warmth of the limb, pyrexia, swelling, acute onset, trauma to the limb, a break in the skin, a single area affected, clear demarcation, exudate, flu-like malaise, tracking rash, shiny, tenser skin, previous cellulitis, co-existing immunosuppression, co-existing skin conditions, clinical observations for sepsis, negative Wells score and patient concern.

No HCP suggested blood tests were a priority in the algorithm, but a GP trainee suggested it could be included in a modified algorithm in secondary care, similar to the CURB-65 (Confusion, urea, respiratory rate, blood pressure, age >65) score used for pneumonia (P11).

5.5 Discussion

5.5.1 Main findings

This study found that the presentation of cellulitis changes as the episode progresses, leading to variation in the clinical features seen in different clinical settings. This may be reflected in the range of differential diagnoses that specialities discussed and have been described in the literature.[105]

A core group of clinical features to diagnose cellulitis was suggested. But the challenge is that these features overlap with other pathologies *(see Chapter 2.4.1 Clinical cases of misdiagnoses – case reports and series)*. More serious pathologies must be ruled out first, for patient's safety and to avoid medico-legal consequences.

Clinical experience was described as an essential factor in making a more accurate diagnosis. Beyond theoretical learning, a critical way HCPs build their expertise is experiential learning. They can do so by following patients along the diagnostic pathway. The initial diagnosis may be revisited if new features present or if there is a lack of response to the initial treatment. For instance, clinicians in this

interview study described one fundamental way of improving the diagnosis of cellulitis was to learn from cases of misdiagnoses. In recent years, this experiential learning has been limited by the clinical workload, how healthcare is structured, and shift work patterns.[106]

Frontline workers such as those in emergency and acute care see an undifferentiated take. After the initial assessment of an acute presentation of a red leg, the care is handed over to the general medical team. This impedes the completion of the learning cycle, as they were only involved in the early stages of patient care.

A great understanding of the decision-making processes undertaken by frontline services has been gained, including why empirical antibiotics are sometimes given and why urgent investigations are requested to rule out other pathologies.

Suggestions to improve the accuracy of diagnoses included developing a diagnostic algorithm that could objectively help HCPs with different levels of experience. The challenge with a diagnostic algorithm is that it would need to incorporate the various stages of a cellulitis episode and, therefore, multiple versions of an algorithm might be required.

5.5.2 Relevance to clinical practice and future research

This study has highlighted that HCPs need to be aware that cellulitis can present with different features at various stages of the acute episode, and the need to consider the cellulitis mimickers. With a current shift in healthcare resulting in trained nurses now managing more acute presentations,[107] upskilling nurses in cellulitis is also essential.

Key indices and risk factors for a diagnostic algorithm have been identified in this study, as well as key distinguishing features from cellulitis mimickers, but these need validating in larger studies. A key question when developing a cellulitis diagnostic algorithm is who should use it? Cellulitis is predominantly managed in primary care, where more typical cases are seen and more easily diagnosed. Should the diagnostic algorithm be developed for this larger group to ensure they are more

accurately diagnosed? Or should the algorithm be reserved for the smaller group of patients with multiple comorbidities who are more challenging and more likely to present in secondary care? Future diagnostic tools would need to be tested in all these scenarios to determine where they have the most significant clinical impact.

Importantly, more dermatology teaching for frontline services with a greater emphasis on the alternative diagnoses of cellulitis is required, especially when the features are vague, atypical, or not responding to antibiotic treatment. For example, a cellulitis visual summary has been designed as a teaching tool in the UK for primary care, with a series of steps discussing what to do when the clinical features are uncertain and discussing alternative diagnoses.[10] The challenge with teaching tools are that they need to meet the learning requirements of all learners, and also need to be updated when new information develops.[108]

Currently, around 75% of all NHS consultations for skin problems take place in primary care.[56] However, less than 10% of general practice trainee posts are based in secondary care dermatology.[56] Optimisation of dermatology training is a crucial goal from a recent dermatology national speciality report in England.[56]

5.5.3 Strengths and limitations

A key strength of this study is that participants were included nationally around the UK, across seven specialities that commonly diagnose cellulitis, with nurses and doctors of varying clinical experience. A variety of experiences were captured, made possible by offering the option of telephone interviews and flexible timeslots to cater to the busy schedules of HCPs.

It was important to gather the experiences of both generalists and specialists because most cellulitis cases are diagnosed by generalists such as general practitioners and acute physicians.[11] However, responder bias was evident as many of the generalist group participants had a specialist interest in dermatology and therefore had more dermatology experience than their peers.[109] Therefore, their

experience may not truly reflect the experiences of a generalist. International participants could not be recruited due to time and funding constraints.

Another limitation of this study was that some participants could not fully describe their clinical rationale behind diagnostic decisions during the interview. This may be because they have developed an intuitive, pattern-recognition approach to decision-making with experience. Such heuristic diagnostic processes in dermatology are well documented.[110] Using pictures and case scenarios of red legs to guide this process or a focus group discussion may help further unpack the clinical rationale of diagnostic decisions.[111] Some senior HCPs also may have felt obliged to provide clinically or socially appropriate answers.[112]

5.6 Chapter summary

This interview study showed that cellulitis is a complex diagnosis. Not only do the core features overlap with other diagnoses, but the presentation of cellulitis changes as the episode progresses. This study ascertained a cluster of features that may help diagnose cellulitis. Still, many of these features overlap with cellulitis mimickers, suggesting that a single diagnostic criterion is unlikely to apply to everyone.

Chapter 6- Discussion

6.1 Chapter introduction

The aim of this thesis was to explore how to improve the diagnosis of cellulitis. To answer this, a series of linked studies were carried out. This included a scoping review,[57] a systematic review,[103] and two interview studies[101,113] to identify the key challenges in diagnosing cellulitis and diagnostic tools to help improve the diagnostic accuracy of cellulitis.

This final chapter summarises the key findings, comparing existing literature and the implications for clinical practice and future research.

6.2 Summary of key findings, comparison with existing literature, clinical and research implications

The key findings are presented by the objectives in this thesis.

6.2.1 Objective 1: Exploring the challenges health care professionals experience when diagnosing cellulitis

No primary studies have directly explored the challenges HCPs experience when diagnosing cellulitis. The scoping review summarised potential misdiagnoses of cellulitis and accompanying clinical features reported in literature. [57] The qualitative study with HCPs specifically addressed this objective. [113] Both studies found several reasons why cellulitis is a challenging diagnosis.

Firstly, the early vague constitutional symptoms of cellulitis are commonly found in other diseases.[97] Their presence do not necessarily indicate an infection nor help distinguish between a viral or bacterial cause.[97]

Secondly, the core features of cellulitis (erythema, warmth, oedema, and pain) are non-specific.[57] For example, over 75% of patients diagnosed with cellulitis mimickers in the case reports/series in the scoping review had erythema or pain.[57] The clinical features of cellulitis, specifically erythema, change as the infection progresses, leading to variation in the core clinical features.[113]

Thirdly, there are a wide range of differential diagnoses that HCPs should be aware of, from common pathologies such as venous eczema[113] to malignancies such as angiosarcoma.[57]

Fourthly, the typical features of cellulitis may not be easily distinguished in certain groups of patients.[113] This includes patients with underlying chronic skin diseases (oedema in patients with lymphoedema[101] and erythema in inflammatory skin disease[113]) and patients of darker skin types, where in particular, erythema may not be a key feature.

HCPs should be advised to seek dermatology or infectious disease specialist input when a patient with suspected cellulitis does not have the typical features of cellulitis or does not respond to antibiotic treatment after 48 hours.[12] This advice may be sought through telemedicine which has become standard practice in many parts of the UK since the Coronavirus disease pandemic, with high-quality photos, when used, facilitating a rapid, accurate diagnosis.[56]

6.2.2 Objective 2: Identifying studies that have developed diagnostic tools for cellulitis

For the first time, the systematic review synthesised the findings from studies that evaluated diagnostic tools for cellulitis.[103]

The systematic review identified six different diagnostic tools: a biochemical marker, diagnostic criterion, a diagnostic decision support system, a diagnostic predictive model, thermal imaging, and light imaging.[103] Of the included studies, the most recent ones have focused on an ALT-70 predictive model,[73] thermal imaging,[66,68-70] and light imaging[64,72,74] as diagnostic tools.

However, all the included studies had small sample sizes[64-74] and were not validated in larger prospective studies,[64-74] with many excluding complicated cases of cellulitis.[65,68-70,72,73] None of the tools have been investigated in primary care.[64-74] All these limitations needs to be addressed in future studies.

6.2.3 Objective 3: Identifying clinical features that can be incorporated into future diagnostic tools for cellulitis

The scoping review[57] and qualitative studies[101,113] determined a core list of clinical features that could be included in a diagnostic tool. These features were: co-existing immunosuppression, co-existing skin diseases, preceding trauma, skin barrier disruption, flu-like malaise, acute onset, unilaterality, pain, erythema, warmth, pyrexia, swelling, shiny tense skin, clear demarcation, exudate, spreading rash, previous cellulitis, clinical observations for sepsis, Wells score (DVT risk score) and patient concern.[113] Importantly, no HCP suggested that blood tests were obligatory.[113] This initial list of clinical features may be further prioritised in a future survey of HCPs across the UK.

6.2.4 Objective 4: Exploring the diagnostic experiences of patients diagnosed with cellulitis

Two previous interview studies with cellulitis patients showed that many individuals demonstrate a degree of uncertainty about the cause and management of cellulitis, and that some feel ill-informed about the recurrent nature of cellulitis.[114,115]

In contrast, this interview study explored in-depth the whole patient journey of obtaining a cellulitis diagnosis from the onset of early constitutional symptoms, in both primary and secondary care.[101] As the study interviewed patients who have both lymphoedema and recurrent cellulitis, it presented a patient population who know how to manage their cellulitis and who are confident in navigating the healthcare system.[101]

Patients described having similar clinical features during each recurrent cellulitis episode and constitutional 'flu-like' symptoms, typically before they noticed the inflammatory features of pain, warmth, and erythema.[101] The symptoms described by patients corroborated with the clinical features described by HCPs.[113]

One concern highlighted was a delayed diagnosis due to the limited availability of timely appointments with their usual doctor.[101] Therefore, patients want to self-diagnose and start oral antibiotics at home.[101] Future studies are required to evaluate this strategy to ensure accurate diagnosis and

appropriate prescribing of antibiotics. A shared validated diagnostic tool or set of criteria that both HCPs and people with recurrent cellulitis can use may allow this to be done safely, similar to those available in asthma.[99]

6.3 Future research recommendations

There remains a lack of research on cellulitis. Further population-based studies are required to ascertain updated evidence of the incidence and prevalence of cellulitis, especially in primary care and amongst minority ethnic groups. Gaining qualitative insight from dermatologists in other countries may help to improve cellulitis diagnosis in darker skin in the UK.

Large observational studies are needed to determine risk factors, presenting features, and cellulitis mimickers in different populations, with an emphasis on harder-to-diagnose groups such as patients with lymphoedema. Further understanding of the timeline and trajectory of clinical features (which features appear first and for how long) may allow an earlier diagnosis to be made.

We are still in need of diagnostic tools that are validated for cellulitis. One possible diagnostic tool discussed further in *Chapter 3.5.3.2* is diagnostic criterion, using key clinical features identified in the literature reviews[57,103] and interview studies[101,113] in *Chapter 5.4.1.4.2.* The next step may involve conducting an international Delphi survey[116] to triangulate these findings and identify the core features that should be included in the proposed diagnostic criteria. This should then be tested in a diagnostic accuracy study,[117] comparing it against a diagnosis made by a panel of dermatologists as the reference standard. Importantly, it should be tested in diverse populations and be applicable in both primary and secondary care.

Chapter 3.5.3 highlighted potential diagnostic tools that would benefit from further evaluation in multisite studies, especially in primary care. This included hand-held thermal imaging,[66,68-70] the ALT-70 predictive model,[73] and a diagnostic support system.[65]

Artificial intelligence (AI)-based tools, where programs learn from human cognition, will also play a more prominent role as it becomes integrated into healthcare.[118] Incorporating the intuitive learning that dermatologists spend many years building through experience, into AI-based tools is likely to be the path to improving diagnostic accuracy for skin diseases in the future.[118]

The limitations related to AI include the large amount of data needed, image quality, information governance, and ethical concerns regarding who is liable for any adverse outcomes.[118] The British Association of Dermatologists has recently expressed concerns that current AI studies overestimate diagnostic accuracy, by including highly selected groups and excluding atypical presentations.[119]

6.4 Conclusion

Approximately a third of suspected cellulitis presentations are misdiagnosed,[2,11] resulting in inappropriate hospital admissions and antibiotic prescribing.[2] Alongside highlighting the wide range of misdiagnoses, this thesis showed that the challenges in diagnosis centre around the clinical presentation, clinical reasoning, and the lack of learning/education opportunities.

There is a lack of good quality evidence on feasible and sustainable solutions to improve the diagnosis of cellulitis. However, this thesis has identified emerging diagnostic tools that warrant future investigation.

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Appendix A: Publications

REVIEW ARTICLE

BJD
British Journal of Dermatology

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

M. Patel [1,2] S.I. Lee [1] K.S. Thomas [2] and J. Kai [1]

[1]Division of Primary Care & National Institute for Health Research, University of Nottingham, Nottingham, U.K.
[2]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, U.K

Linked Comment: Raff. Br J Dermatol 2019; **180**:973.

Correspondence
Mitesh Patel.
E-mail: msamp9@email.nottingham.ac.uk

Accepted for publication
5 November 2018

Funding sources
M.P. is funded by a National Institute for Health Research (NIHR) academic clinical fellowship. The views expressed are those of the author and not necessarily those of the National Health Service, the NIHR or the Department of Health.

Conflicts of interest
None to declare.

*Plain language summary available online

DOI 10.1111/bjd.17415

Summary

Background Presentations of suspected lower-limb cellulitis 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 were summarized 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 minimize misdiagnosis. Future work should focus on gaining a greater qualitative understanding of the diagnostic challenges from the perspective of patients and clinicians.

What's already known about this topic?

- Lower-limb cellulitis is a common infection presenting in primary and secondary care.
- Almost one-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.

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 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 U.K., with a mean length of stay of 6 days.[5]

An important priority for cellulitis research, identified by both patients and healthcare professionals at the cellulitis Priority Setting Partnership, 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 the 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 criteria were all study designs; any language; misdiagnosis of lower-limb cellulitis, erysipelas or skin and soft-tissue infection; and all age groups, sexes, ethnicities and healthcare settings. Exclusion criteria were animal studies; laboratory *in vitro* studies; the terms 'cellulitis', 'erysipelas' or 'skin and soft tissue infection' not in the title or abstract; 'diagnosis' not discussed in the abstract; explicitly discussed non-lower-limb cellulitis only; conference abstracts; review articles; and not the views of patients, carers or healthcare professionals.

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 (1980–2017). 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 (D.G.; see Acknowledgments), using the concepts 'cellulitis', 'diagnosis' and 'challenges', with controlled vocabulary (MeSH terms and Emtree) and free-text headings (Table S1; see Supporting Information).

Study selection

Following the search, all identified citations were uploaded into EndNote X8 (Clarivate Analytics, Philadelphia, PA, U.S.A.) and duplicates were removed manually by one reviewer (M.P.). Titles and abstracts were screened by two reviewers independently (M.P. and S.I.L.) 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 (M.P.). These themes were reviewed with all other reviewers (S.I.L., K.S.T. and J.K.). Three themes were further explored, with full-text papers screened by M.P. and S.I.L. independently. Disagreements between the two reviewers were resolved through discussion with a third independent reviewer (K.S.T. or J.K.).

Data extraction and presentation

Data were extracted by two independent reviewers (M.P. and S.I.L.). A data extraction pilot using three papers was initially carried out by two reviewers (M.P. and S.I.L.). Non-English papers were translated by colleagues proficient in that language or Google Translate. Quantitative data are 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. Next, 533 full-text articles were assessed for eligibility and 71 were included for data extraction (Fig. 1).[9–79] 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 aetiology. *Clinical cases of misdiagnosis* were studies where lower-limb cellulitis was the incorrect initial diagnosis or was initially misdiagnosed as another pathology. *Service development* reports were studies looking at how service set-up may reduce misdiagnosis. *Diagnostic aids* included studies that developed or tested tools to help diagnosis. *Aetiology* included studies that discussed microbiological causes of cellulitis.

Three themes were deemed to be of particular relevance and were explored further: clinical cases of misdiagnosis, service development and diagnostic aids. The aetiology theme, identifying the microbiological cause of cellulitis, is also an important research topic from the cellulitis Priority Setting Partnership.[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

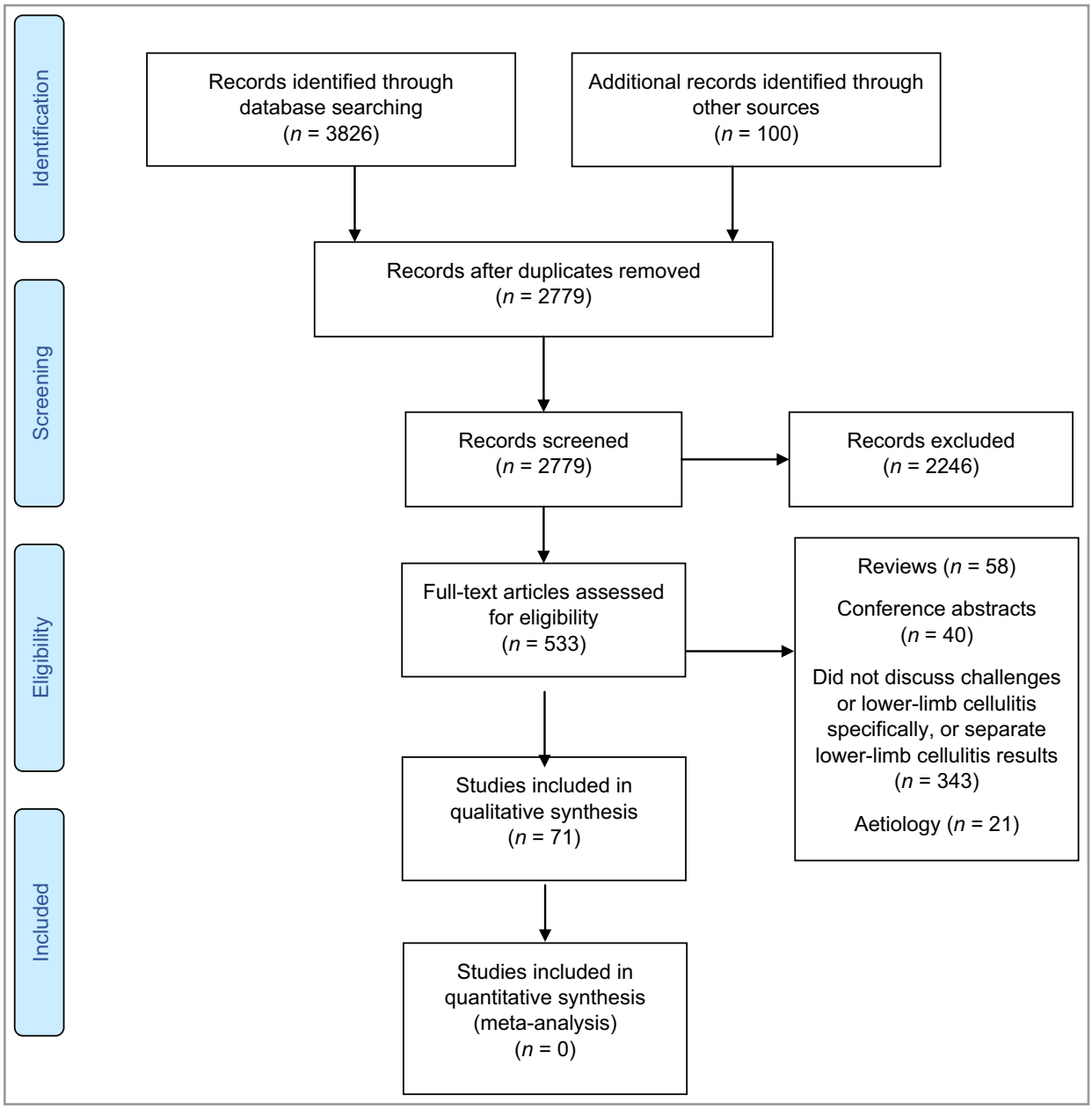

Fig 1. PRISMA flow diagram of the entire search.

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]

Clinical cases of misdiagnosis

For the misdiagnosis theme, 66 papers were included, with three observational studies[9–11] 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 were eczema (118 patients), lymphoedema (14 patients) and lipodermatosclerosis (nine patients).[9] Another prospective study of children aged under 15 years found that 19 of 50 patients with osteomyelitis were initially misdiagnosed as having 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

Overall 94 patients were included (43 male, mean age 41 years) (Table S2; see Supporting Information). 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] Necrotizing 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 or 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%) 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%). Prior antibiotics were given to 26 patients (28%).

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 haemangioendothelioma.[23]

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

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 U.K., operated by nurses and junior doctors from 09·00 to 17·00 h on weekdays, with faxed or telephone referrals from clinicians for patients diagnosed with suspected cellulitis.[9] In total 635 patients were treated through the specialist service, of whom 425 (67%) had cellulitis. Overall 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 were avoided in the patients without cellulitis.

Table 1 Key learning points from misdiagnosis of lower-limb cellulitis

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

Red legs service

In one hospital in the U.K., a retrospective audit of patients who were admitted with bilateral red legs found that 15 of 50 were misdiagnosed as having 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. Seventy-seven patients were seen by the service, of whom 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 patients (82%) were extremely satisfied with their level of care.

Diagnostic aids to help diagnosis

Four papers looked at developing or using an existing tool to help differentiate lower-limb cellulitis from alternative pathologies (Table 2).[76–79] Raff *et al.* explored cellulitis as the main pathology.[79] Three studies included patients with lower-limb cellulitis as a comparison group, where cellulitis and other diagnoses were compared. All four studies were observational studies conducted in different healthcare specialties.

Predictive test

An ALT-70 model was designed that involved assessment of asymmetry (unilateral involvement), leucocytosis (white blood cell count $\geq 10 \times 10^9$ cells L^{-1}), tachycardia (heart rate ≥ 90 b.p.m.) and age ≥ 70 years. A score below 3 had > 83·3% likelihood of indicating pseudocellulitis (an alternative diagnosis to cellulitis) and a score above 4 had > 82·2% likelihood of indicating cellulitis.[79]

Biochemical test

When cellulitis was compared with acute gout, delta neutrophil index > 1·7% was the only independent factor for predicting cellulitis ($P = 0·002$), compared with white blood cell count ($P = 0·41$), C-reactive protein ($P = 0·28$) and procalcitonin ($P = 0·12$).[78]

Imaging

In comparison with patients with Dercum disease, in cellulitis, attenuation was more linear, diffuse and nonmass-like on computed tomography and magnetic resonance imaging

Table 2 Key features of the four studies included using diagnostic tools or criteria, including the index and reference tests for lower-limb cellulitis

Study	Dominguez-Gadea 1993[76]	Petscavage-Thomas 2015[77]	Pyo 2017[78]	Raff 2017[79]
Country, setting	Spain, department of nuclear medicine and rheumatology (single centre)	U.S.A., department of radiology (single centre)	South Korea, division of rheumatology (single centre)	U.S.A., emergency department (single centre)
Years of study	1990–1991	Not stated	2010–2015	2010–2012
Study type	Cohort	Case series	Case–control	Cross-sectional
Funding source	None stated	None stated	Korean health industry development institute	None stated
Number of patients analysed	25 patients with 38 foot lesions. Nine patients had cellulitis	17: 10 with Dercum disease and seven with cellulitis	367: 184 with acute gout and 183 with cellulitis	259: 180 with cellulitis and 79 with pseudocellulitis
Mean age (years)	Not provided	52·3 in the cellulitis group	62	63
Male, n (%)	Not provided	4 (40) in a cellulitis group	285 (78)	118 (46)
Index test	$^{99}Tc^{m}$ AA scintigraphy	CT, MRI and ultrasound	Delta neutrophil index	ALT-70
Reference test for cellulitis	Clinical diagnosis of cellulitis by nuclear medicine physicians	Clinical diagnosis of cellulitis (unclear who made diagnosis)	Clinical diagnosis of cellulitis (unclear who made diagnosis) and ACR for gout	Clinical diagnosis by emergency department physician
Time frame for follow-up	No follow-up	No follow-up	No follow-up	30 days after discharge

AA, serum amyloid A; CT, computed tomography; MRI, magnetic resonance imaging; ACR, American College of Rheumatology; ALT-70, asymmetry, leucocytosis, tachycardia and age ≥ 70 years.

(MRI). In addition, there was postcontrast enhancement in all three cases of contrast provided to patients with cellulitis.[77]

Three-phase immunoscintigraphy using $^{99}Tc^{m}$-labelled antigranulocyte monoclonal antibodies was used in patients with infectious diabetic foot, with six 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 U.S.A. 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 and 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] Pallin *et al.* looked at procalcitonin and *HLA-DQA1* gene expression among 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.* utilized a modified Laboratory Risk Indicator for Necrotizing Fasciitis score to differentiate cellulitis from necrotizing fasciitis,[88] Rahmouni *et al.* used MRI[89] and Sullivan *et al.* looked at nuclear scintigraphy.[90]

Discussion

This scoping review identified a lack of research on the challenges and facilitators in diagnosing lower-limb cellulitis. The existing literature on misdiagnoses is limited mainly to case reports and studies and was not always specific for lower-limb cellulitis. The 47 different misdiagnoses in case reports and series emphasize 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 U.K. to improve cellulitis diagnosis and care. One service showed that having cellulitis experts who are more likely to make a correct diagnosis 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 optimize correct diagnosis of red legs and merits further investigation.

Unfortunately, there is a lack of diagnostic aids for lower-limb cellulitis. Current aids have used biochemical tests or imaging, which may be unfeasible in some settings. All four

studies were conducted in secondary care and have not been repeated prospectively. They 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 useful only 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 it 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 computed tomography and MRI imaging would be used as a first-line investigation for cellulitis.

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 screening and data extraction. Studies were included only if they discussed lower-limb cellulitis, and 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 if the results were 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 have allowed inclusion all of 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 papers were translated, but it is possible that the information could still have been misinterpreted.

In 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.

Acknowledgments

We would like to thank Dr Douglas Grindlay (D.G.) for assisting with the search terms and Dr Yuki Maria Fakuda Andersen and Dr Hulya Guller Gledhill for translating foreign texts. We would also like to acknowledge Dr Nick Francis and Dr Nick Levell for their clinical advice in this review.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 The search terms used in the two databases.

Table S2 The 47 different pathologies misdiagnosed, with the initial and final diagnoses.

Powerpoint S1. Journal Club Slide Set.

SYSTEMATIC REVIEW

BJD
British Journal of Dermatology

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

M. Patel,[1] S.I. Lee,[1] R.K. Akyea,[1] D. Grindlay,[2] N. Francis,[3] N.J. Levell,[4] P. Smart,[5] J. Kai[1] and K.S. Thomas[2]

[1]Division of Primary Care & National Institute for Health Research, School of Medicine, [2]Centre of Evidence Based Dermatology, and [5]Patient representative, University of Nottingham, Nottingham, U.K.

[3]Division of Population Medicine, School of Medicine, Cardiff University, Cardiff, U.K.

[4]Dermatology Department, Norfolk and Norwich University Hospital NHS Trust, Norwich, U.K.

Linked Comment: George. Br J Dermatol 2019; **181**:1119.

Correspondence

M. Patel.

E-mail: msamp9@exmail.nottingham.ac.uk

Accepted for publication

2 March 2019

Funding sources

M.P. is funded by a National Institute for Health Research academic clinical fellowship. The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research or the Department of Health.

Conflicts of interest

None declared.

*Plain language summary available online

DOI 10.1111/bjd.17857

Summary

Background Cellulitis can be a difficult diagnosis to make. Furthermore, 31% of patients admitted from the emergency department with suspected lower-limb cellulitis have been misdiagnosed, with incorrect treatment potentially resulting in avoidable hospital admission and the prescription of unnecessary antibiotics.

Objectives 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 we assessed the quality of the studies identified using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. We included all types of study that described 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 considered to have a high risk for bias in at least one domain. The quantity and quality of available data was low and results could not be pooled owing to the heterogeneity of the findings.

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

What's 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. Consequently, this results in potentially avoidable hospital admissions and the prescription of unnecessary antibiotics.
- There are no diagnostic criteria available for lower-limb cellulitis in the U.K.

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.

Cellulitis is an acute bacterial infection of the dermis and associated subcutaneous tissue, with 60% of cases affecting the lower limb.[1] Erysipelas is a form of cellulitis that presents with more marked superficial inflammation.[2]

The diagnosis of cellulitis can be challenging, with 31% of patients who present with suspected lower-limb cellulitis in the emergency department (ED) subsequently being given a diagnosis other than cellulitis.[3] Routine biochemical and haematological blood tests and blood cultures are not specific for cellulitis.[4] This results in avoidable hospital admissions and unnecessary prescriptions of antibiotics.[5] Definitive diagnostic criteria could potentially improve clinical care and also improve the validity of clinical research on cellulitis by ensuring appropriate case definition.[6] However, there are currently no agreed diagnostic criteria for cellulitis.

Patients with cellulitis commonly present to primary care services or the ED.[7] A recent U.K. cellulitis research priority setting partnership ranked questions on 'diagnostic criteria' as important for future cellulitis research.[8]

The aim of this systematic review was to identify and conduct a critical appraisal of the quality of studies that have developed or validated diagnostic criteria or tools for lower-limb cellulitis.

We define diagnostic criteria or tools as the inclusion of a minimum of one variable that has been tested against at least one clinical feature. In this paper, 'cellulitis' 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 that investigated the development or validation of diagnostic criteria or tools for cellulitis.

Materials and 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,[9] with additional reference to the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[10] 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, which used diagnostic criteria or tools for diagnosis, were included.

Inclusion criteria

The following inclusion criteria were applied: any study type that used diagnostic criteria or tools, in any language, involving patients of any age, sex or ethnicity, who had lower-limb cellulitis or erysipelas.

Exclusion criteria

The following articles were excluded: animal studies; laboratory *in vitro* studies; literature and systematic review articles; expert opinions; conference abstracts; articles that included only patients with nonlower-limb cellulitis; articles where the site of cellulitis or erysipelas was not clear; articles where data from lower-limb cellulitis or erysipelas could not be separated; articles that used tools to determine ethology; case series with < 20 patients or those that included < 10 patients with lower-limb cellulitis or erysipelas.

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 (1980–2017), the Cochrane Library and Web of Science Core Collection. An updated search on 22 May 2018 was also undertaken in all the databases in order to ensure that the results were up-to-date.

Search strategies for these databases were developed with an information specialist (D.G.) and in consultation with a cellulitis expert (N.J.L.). Concepts were developed: 'cellulitis', 'diagnosis' and 'criteria', with controlled vocabulary (Medical Subject Headings terms and Emtree subject headings) and free-text headings (Table 1). National Institute for Health and Care Excellence Evidence was also searched using the term 'cellulitis'.

For grey literature, the first 100 articles (sorted by relevance) on Google Scholar retrieved using the search term 'diagnostic criteria for cellulitis' were included.

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

Study selection and data extraction

Following the searches, all citations were uploaded to Covidence (2018) online systematic review management software,[11] with duplicates removed by one reviewer (M.P.). Title and abstract screening, full-text screening and data extraction were conducted by independent reviewers (M.P. and S.L./R.K.A.) using predefined templates. Any disagreements between reviewers that arose were resolved through discussion, or with another independent reviewer (K.S.T., J.K. or N.J.L.). Data items sought at the data extraction stage included study aim, type, population, criteria, funding, sample size, index test, reference test and key findings.

Table 1 Search terms used in each database

Database	Search terms
Ovid MEDLINE	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/ 38. diagnostic feature.mp. 39. diagnostic features.mp. 40. exp biomarkers/ 41. biomarker$.mp. 42. marker$.mp. 43. or/37-42 44. or/36 or 43 45. exp cellulitis/ 46. cellulitis.mp. 47. exp erysipelas/ 48. erysipelas.mp. 49. or/45-48 50. and/44 and 49
Ovid EMBASE	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 $.mp. 23. exp assay/ 24. accura*.mp. 25. exp reproducibility/ 26. reproducibility.mp. 27. exp validation study/ 28. validation studies as topic.mp. 29. validat*.mp. 30. exp ''sensitivity and specificity''/ 31. sensitivity.mp. 32. specificity.mp. 33. exp predictive value/ 34. predictive.mp. 35. or/15-34 36. and/14 and 35 37. exp diagnostic test 38. diagnostic feature.mp. 39. diagnostic features.mp. 40. exp biological marker/ 41. biomarker$.mp. 42. exp marker/ 43. marker$.mp. 44. or/37-43 45. or/36 or 44 46. exp cellulitis/ 47. cellulitis.mp. 48. exp erysipelas/ 49. erysipelas.mp. 50. or/46-49 51. and/45 and 50
Cochrane Database of Systematic Reviews	1.diagnos* 2. differentiat* 3. discriminat* 4. determinin* 5. confirmat* 6. "ascertainment" 7. detect* 8. characteris* 9. characteriz* 10. "identification" 11. "identify" 12. MeSH descriptor: [Diagnosis] explode all trees 13. MeSH descriptor: [Diagnostic Imaging] explode all trees 14. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 15. "criteria" 16. "criterion" 17. MeSH descriptor: [Classification] explode all trees 18. "classification" 19. "clinical feature" 20. "clinical features" 21. test* 22. tool* 23. imag* 24. "assay" 25. accura* 26. MeSH descriptor: [Reproducibility of Results] explode all trees 27. "reproducibility" 28. MeSH descriptor: [Validation Studies as Topic] explode all trees 29. "validation studies" 30. valid* 31. MeSH descriptor: [Sensitivity and Specificity] explode all trees 32. "sensitivity" 33. "specificity" 34. "predictive" 35. #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 36. #14 and #35 37. MeSH descriptor: [Diagnostic Tests, Routine] explode all trees 38. "diagnostic feature" 39. "diagnostic features" 40. MeSH descriptor: [Biomarkers] explode all trees 41. biomarker* 42. marker* 43. #37 or #38 or #39 or #40 or #41 or#42 44. #36 or #43 45. MeSH descriptor: [Cellulitis] explode all trees 46. "cellulitis" 47. MeSH descriptor: [Erysipelas] explode all trees 48. "erysipelas" 49. #45 or #46 or #47 or #48 50. #44 and #49
Web of Science Core Collection	1.TS = diagnos* 2. TS = differentiat* 3. TS = discriminat* 4. TS = determinin* 5. TS = confirmat* 6. TS = ascertainment 7. TS = detect* 8. TS = characteris* 9. TS = characteriz* 10. TS = identification 11. TS = identify 12. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 13. TS = criterion 14. TS = classification 15. TS = "clinical feature" 16. TS = "clinical features" 17. TS = test* 18. TS = tool* 19. TS = imag* 20. TS = assay 21. TS = accura* 22. TS = reproducibility 23. TS = valid* 24. TS = "validation studies" 25. TS = sensitivity 26. TS = specificity 27. TS = predictive 28. #13 or #14 or #15 or #16 or#17 or#18 or#19 or #20 or #21 or #22 or#23 or #24 or #25 or #26 or #27 29. #12 and #28 30. TS = "diagnostic features" 31. TS = "diagnostic feature" 32. TS = biomarker* 33. TS = marker* 34. #30 or #31 or #32 or #33 35. #29 or #34 36. TS = cellulitis 37. TS = erysipelas 38. #36 or #37 39. #35 and #38

Evidence synthesis and risk of bias assessment

All included studies were described in a narrative synthesis. To evaluate the methodological quality, all studies were assessed by two reviewers (M.P. and R.K.A.) using signalling questions in the Quality Assessment of Diagnostic Accuracy Studies-2 tool,[12] with disagreements resolved by a third reviewer (S.I.L. or E.B.-T.). 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 answered 'yes', 'high risk' if the answer to at least one signalling question was 'no', or 'unclear' in all other cases.[12]

Results

Study selection

The PRISMA flowchart shows the results of the complete search (Fig. 1). A total of 98 papers were included for full-text screening.[5,13–109] Of these, 90 papers were subsequently excluded,[5,21–109] including 20 studies that did not specify the site of cellulitis[5,37,45,46,49,50,52,63,69,70,72,78,81,91,93,95,97,100,102,109] and

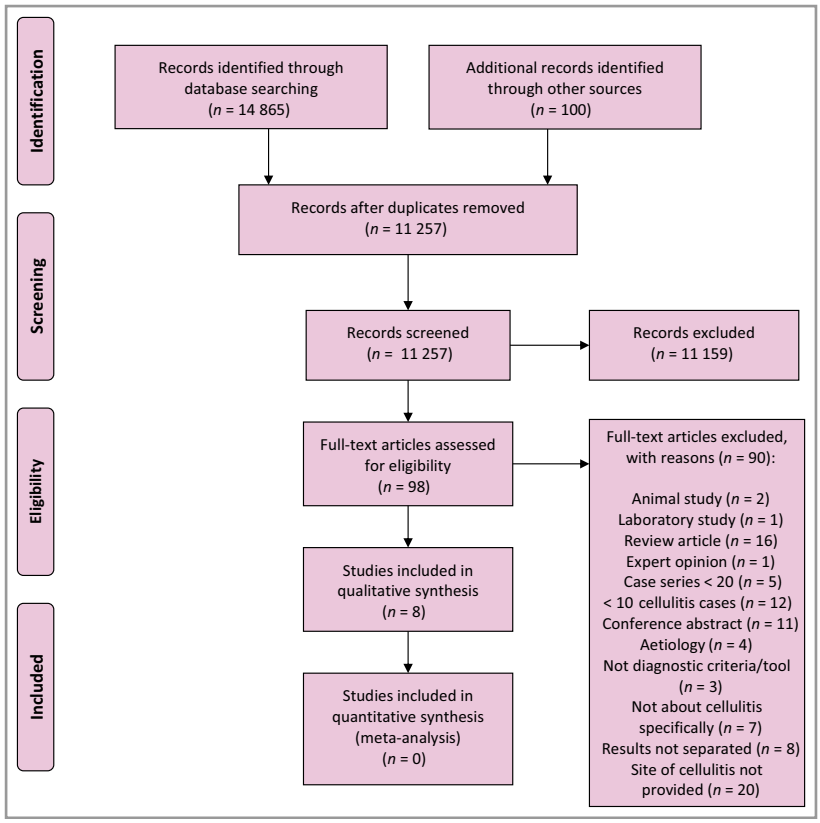

Fig 1. Preferred reporting items for systematic reviews and meta-analyses flowchart of literature search and study selection.

eight studies that did not separate the results of lower-limb cellulitis from other sites.[26,29,55,87,90,98,99,107] Eight studies were included for data extraction.[13–20]

Study characteristics

The characteristics of all eight included studies are summarized in Table 2. Raff *et al.* explored lower-limb cellulitis as the main pathology.[18] Seven studies included patients with lower-limb cellulitis as a comparison group, in which cellulitis and other diagnoses were compared.[13–17,19,20]

Six studies were case–control studies,[13–16,19,20] one study was a cohort study[17] and there was one cross-sectional study.[18] The most common setting was the ED (three studies).[17–20] The studies were conducted in six different countries. Kato *et al.* did not include exclusion criteria.[14]

Reference tests

The reference test for cellulitis was a clinical diagnosis in seven studies,[14–20] with a bone scan used by Fleischer *et al.*[13] However, only Rabuka *et al.* clearly stated the specialty of the physician who made the cellulitis diagnosis.[17] Two studies followed up patients for up to 30 days in order to determine the final diagnosis.[18,19]

Index tests

Studies where cellulitis was the main pathology

Predictive score In a study to compare cellulitis with pseudocellulitis, Raff *et al.* developed an ALT-70 score (7 points) that assessed the following: asymmetry (unilateral involvement, 3 points); leucocytosis (white blood cell count $\geq$ 10 000 μL^{-1}, 1 point); tachycardia (heart rate $\geq$ 90 beats per minute, 1 point); and age $\geq$ 70 years (2 points).[18] An ALT-70 score below 3 had a > 83·3% likelihood of pseudocellulitis – an alternative diagnosis to cellulitis, and a score above 4 had a > 82·2% likelihood of cellulitis.[18]

Studies where cellulitis was used as a comparator

Clinical features One study comparing cellulitis and osteomyelitis among patients with diabetes found that a temperature higher than 37·2 °C was predictive of osteomyelitis;[13] however, Malabu *et al.* found no significant differences in clinical parameters between these groups.[15]

Rabuka *et al.* showed that distinct margins of erythema were seen in six (8%) patients with cellulitis vs. 0 (0%) in patients with deep vein thrombosis (DVT) ($P = 0{\cdot}008$).[17] However, when comparing erysipelas with DVT, Rast *et al.*

Table 2 Characteristics of the eight included studies

Author, year	Country, setting	Years of study	Study type	Diagnoses explored in the study	Funding source	Number of patients analysed	Mean age of patients with cellulitis, years	Number of male patients with cellulitis patients, n (%)	Index test	Reference test for cellulitis	Timeframe for follow-up
Raff *et al.*, 2017[18]	U.S.A., emergency department (single centre)	2010–2012	Cross-sectional	Cellulitis and pseudocellulitis	None stated	259; 180 cellulitis and 79 with pseudocellulitis	63	78 (43)	ALT-70	Clinical diagnosis by ED physician or admitting team	30 days post-discharge
Fleischer *et al.*, 2009[13]	U.S.A., podiatric medicine (single centre)	2002–2006	Case–control	Osteomyelitis and cellulitis	None stated	54; 20 cellulitis and 34 osteomyelitis	62 (whole population)	44 (81) (whole population)	30 clinical and laboratory characteristics	Bone specimen and technetium scan (unclear who made the diagnosis)	No follow-up
Kato *et al.*, 2017[14]	Japan, department of dermatology (single centre)	2010–2014	Case–control	Necrotizing fasciitis and cellulitis	None stated	18; 16 cellulitis, 2 necrotizing fasciitis	Not available for cellulitis patients	Not available for cellulitis patients	LRINEC, CK, PCT	Clinical diagnosis (unclear who made the diagnosis)	No follow-up
Malabu *et al.*, 2007[15]	Saudi Arabia, department of medicine (single centre)	2005	Case–control	Osteomyelitis and cellulitis	None stated	43; 21 with cellulitis and 22 with osteomyelitis	56	12 (57)	ESR, haematocrit, haemoglobin, platelet count, red cell width, WBC	Clinical diagnosis (unclear who made the diagnosis)	No follow-up
Pyo *et al.*, 2017[16]	South Korea, division of rheumatology (single centre)	2010–2015	Case–control	Gout and cellulitis	Korean health industry development institute	367; 184 with acute gout and 183 with cellulitis	61	126 (69)	DNI	Clinical diagnosis (unclear who made the diagnosis)	No follow-up
Rabuka *et al.*, 2003[17]	Canada, emergency department (single centre)	1995–1998	Cohort	DVT and cellulitis	None stated	109; 19 DVT, 72 cellulitis, 18 other	71 (for cellulitis/patients with DVT)	37 (41)	Duplex ultrasound scan	Clinical diagnosis by ED physician	No follow-up
Rast *et al.*, 2015[19]	Switzerland, emergency department (single centre)	2013–2014	Case–control	DVT and erysipelas	Goldschmidt Jacobson Foundation, The Swiss National Science Foundation, The Kantonsspital Aarau	48; 31 erysipelas and 17 with DVT	31	18 (58)	PCT, CRP, WBC	Clinical diagnosis by treating physician	30-day telephone follow-up
Shin *et al.*, 2013[20]	South Korea, department of radiology (single centre)	2006–2010	Case–control	Lymphoedema, cellulitis and generalized oedema	None stated	44; 11 with cellulitis, 19 with lymphoedema and 14 with generalized oedema	63	5 (45)	CT scan	Clinical diagnosis (unclear who made the diagnosis)	No follow-up

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 years; CRP, C-reactive protein; DVT, deep vein thrombosis; ED, emergency department; CT, computed tomography.

found no significant differences between any physical signs.[19]

Biochemical and haematological tests In a study comparing cellulitis with acute gout, delta neutrophil index (immature granulocyte count) > 1·7% was the only independent factor for predicting cellulitis (P = 0·002), compared with white blood cell (WBC) count (P = 0·41), C-reactive protein (CRP) (P = 0·277) and procalcitonin (PCT) (P = 0·122).[16] Creatine kinase (CK) was significantly higher in all cases of necrotizing fasciitis (NF) compared with cellulitis.[14]

Malabu *et al.* found that in patients with diabetes, haemoglobin (P < 0·0001) and haematocrit (P < 0·0001) were higher in patients with cellulitis than in patients with osteomyelitis.[15] However, erythrocyte sedimentation rate (ESR) (P < 0·001),[13,15] CRP (P < 0·001),[13] platelet count (P < 0·01),[15] WBC (P < 0·05)[15] and red cell width (P < 0·05)[15] were higher in patients with osteomyelitis than in patients with cellulitis.[15]

In one study, PCT concentrations in patients with erysipelas were compared with PCT concentrations in patients with DVT.[19] Patients with erysipelas had significantly higher concentrations of PCT (P = 0·001). At a PCT threshold of > 0·25 μg L^{-1}, 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).[19]

In contrast, Rabuka *et al.* found a raised WBC in 21·3% of patients with cellulitis vs. 50% of patients with DVT (P = 0·038).[17] This study also found that CK was higher in the cellulitis group compared with the DVT group.[17]

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.[20] These features included 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.* examined ultrasound imaging in patients with a presentation suggestive of cellulitis, with 72 patients (80%) diagnosed with cellulitis after having a negative duplex scan.[17]

Methodological quality

Risk of bias

The risk of bias for patient selection was high for all eight studies; six used a case–control method[13–16,19,20] and the exclusion criteria were not deemed appropriate in two studies as they excluded patients who were more difficult to diagnose (Table 3 and Fig. 2).[17,18] The study by Shin *et al.* had a low risk of bias for the index test, as it included a prespecified threshold,[20] whereas the other seven studies did not.[13–19] The reference standard used in the study by Rabuka *et al.* was considered high risk as some patients received the reference test after the index test,[17] thereby increasing the risk of observer bias. The risk was unclear in the remaining seven studies as it was not possible to determine whether the diagnosis of cellulitis was accurate. The flow of timing was unclear in seven studies,[14–20] as it was not stated whether all the patients received the same reference standard test. The flow of timing described in the study by Fleischer *et al.* was considered high risk as not all the patients were analysed.[13]

Concerns regarding applicability

With regard to patient selection and reference standard applicability, all eight studies included patients who had already been diagnosed with cellulitis and we cannot definitively state that the correct diagnosis had been made. However, five studies were high risk for patient selection bias as they included either a rare differential diagnosis for cellulitis, i.e. osteomyelitis and NF,[13–15] or included only patients with initially suspected DVT.[17,20] The index test in four studies was judged to be high risk; two studies included only investigations for diabetic foot ulcers[13,15] and two studies included imaging for suspected DVT.[17,20]

Table 3 Risk of bias assessment using the Quality Assessment of Diagnostic Accuracy Studies-2 diagnostic accuracy critical appraisal tool showing risk of bias for each domain for individual studies

	Risk of bias				Concerns regarding applicability		
Study	Patient selection	Index test	Reference standard	Patient flow and timing	Patient selection	Index test	Reference standard
Fleischer *et al.*[13]	High	High	Unclear	High	High	High	Unclear
Kato *et al.*[14]	High	High	Unclear	Unclear	High	Low	Unclear
Malabu *et al.*[15]	High	High	Unclear	Unclear	High	High	Unclear
Pyo *et al.*[16]	High	High	Unclear	Unclear	Unclear	Low	Unclear
Rabuka *et al.*[17]	High	High	High	Unclear	High	High	Unclear
Raff *et al.*[18]	High	High	Unclear	Unclear	Unclear	Low	Unclear
Rast *et al.*[19]	High	High	Unclear	Unclear	Unclear	Low	Unclear
Shin *et al.*[20]	High	Low	Unclear	Unclear	High	High	Unclear

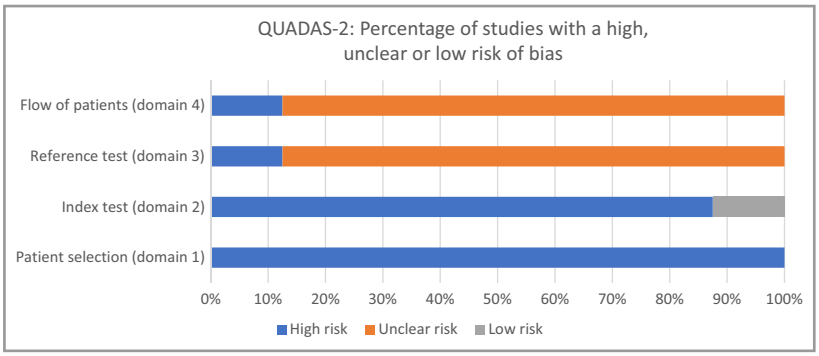

Fig 2. Graph showing the percentage of studies with a low, high or unclear risk of bias for each of the four domains. QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

Excluded studies

Of the excluded studies, 20 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.* studied PCT and HLA-DQA1 expression,[81] Kini *et al.* investigated ESR[52] and three other studies examined 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 examined magnetic resonance imaging (MRI)[49,50,91,95,97] and two considered ultrasound imaging in the paediatric setting.[46,72] Smirnova *et al.* investigated antibodies in erysipelas.[100]

Eight studies did not present the results of lower-limb cellulitis separately. Of these, Rahmouni *et al.* examined the use of MRI in cellulitis[90] and Chao *et al.* utilized ultrasound imaging for soft-tissue infections in the paediatric population.[29] Bonnetblanc *et al.* investigated 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] and Ko *et al.* examined the use of thermal imaging cameras.[54,55]

Discussion

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, including 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 was used as a comparator. Three studies compared cellulitis with rare differential diagnoses, such as osteomyelitis, which provide limited clinical applicability. This diversity in the tools explored emphasizes the difficulty in making a correct diagnosis on first presentation.

All eight included studies identified in this review were observational studies.[16–19] The sample sizes were small, with only two studies including more than 100 patients with cellulitis.[16,18] No criteria or tools have been subsequently validated in a large prospective study.

Despite cellulitis being a common presentation in community settings, 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.[17]

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.[110] Blood tests need to be interpreted with caution, as ESR, CRP and WBC count are nondiscriminatory 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,[20] therefore findings cannot be applied to this under-researched population.

This is the first systematic review that aimed to identify diagnostic criteria or tools developed for lower-limb cellulitis. The key strength of this review is the comprehensive search strategy used, which was 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 the study was 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, 28 papers were excluded as the site of cellulitis was not specified or the results for lower-limb cellulitis were not separated. These papers did include diagnostic criteria or tools that need to be further evaluated. Owing to time constraints, only the first 100 results on Google Scholar were included.

In 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 should be validated in both primary and secondary care settings. To gain a better understanding of what ought to be included in diagnostic criteria or tools, qualitative research that includes input from a range of healthcare professionals and patients with experience of managing lower-limb cellulitis should be carried out.

Acknowledgments

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

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Video S1 Author video.

Mitesh Patel, Siang Ing Lee, Nick J Levell, Peter Smart, Joe Kai, Kim S Thomas and Paul Leighton

Confidence of recurrent cellulitis self-diagnosis among people with lymphoedema:

a qualitative interview study

Abstract

Background
Cellulitis can sometimes be challenging for healthcare professionals to diagnose, with no validated diagnostic criteria available. Supporting healthcare professionals to make a more accurate diagnosis of cellulitis in different groups, such as those with lymphoedema, is a cellulitis research priority. However, to the authors knowledge, no previous studies have looked at the involvement of non-healthcare professionals in the diagnostic process.

Aim
To explore the experience of people with lymphoedema and recurrent cellulitis in the diagnosis of lower-limb cellulitis.

Design and setting
Single, semi-structured, qualitative interviews carried out between 29 October and 19 December 2018.

Method
Adults with a suspected episode of cellulitis who had been diagnosed in the last 12 months or had a history of recurrent cellulitis were interviewed.

Results
Three key themes emerged: the recurrent nature of cellulitis symptoms, participants' experience of getting a cellulitis diagnosis, and participants' suggestions of how cellulitis diagnosis might be improved. Generally, people with lymphoedema experienced similar clinical features during each of their own recurrent cellulitis episodes and were confident that they could make a self-diagnosis of cellulitis. This is also reflected in the participants' perceived trust from the healthcare professional in being able to make a self-diagnosis. A diagnostic checklist and educational resources were suggested as methods to improve diagnosis.

Conclusion
Selected people with lymphoedema who have recurrent cellulitis are confident in self-diagnosing their own recurrent cellulitis episodes. There may be a role for greater involvement of people with lymphoedema in their cellulitis diagnosis.

Keywords
cellulitis; confidence; diagnosis; lower limb; lymphoedema; qualitative research; self-diagnosis.

INTRODUCTION

Cellulitis is a common presentation in primary care, with 60% of cases affecting the lower limbs.[1] Approximately one-third of people with cellulitis have recurrent episodes,[2] with lymphoedema shown to be the strongest risk factor for recurrent cellulitis.[3]

However, the diagnosis of cellulitis can be difficult, with approximately one-third of presentations of suspected lower-limb cellulitis subsequently found to be other diagnoses such as venous stasis dermatitis.[4] Currently, there are no agreed diagnostic criteria for cellulitis; a systematic review showed no robustly developed and validated diagnostic criteria or tools for lower-limb cellulitis.[5]

A UK cellulitis research priority setting partnership ranked questions on identifying early signs and symptoms in different groups of people with cellulitis, such as those with lymphoedema, as important for future cellulitis research.[6] A 2019 mixed-methods study found that people with cellulitis had a low awareness of cellulitis before their first episode,[7] but the views of people with recurrent cellulitis are not known. Also, despite lymphoedema being strongly associated with cellulitis, no previous studies have looked at the experience of cellulitis diagnosis in this group.

The aim of this interview study was to explore the experience of receiving a diagnosis of lower-limb cellulitis among people with lymphoedema and recurrent cellulitis.

METHOD

The study protocol was registered on the Centre of Evidence Based Dermatology website (https://www.nottingham.ac.uk/research/groups/cebd/documents/researchdocs/protocol-cellulitis-interview-study-with-patients.pdf) on 5 November 2018. For each participant, the interviewer obtained verbal consent before the start of the interview and written consent from each participant either before or after the interview.

The primary objective of the study was to explore the experience of people with lymphoedema and recurrent cellulitis in the diagnosis of lower-limb cellulitis.

Secondary objectives were to explore the key features of cellulitis that prompt participants to seek medical advice; to describe experiences where a diagnosis of cellulitis was correct, incorrect, or delayed; and to describe experiences of getting a diagnosis of cellulitis with different healthcare professionals.

Eligibility criteria

Inclusion criteria were age >18 years; all ethnicities; people with a suspected episode of lower-limb cellulitis in the last 12 months (or two or more episodes within the last

M Patel (ORCID: 0000-0003-3975-4689), BSc, PGcert, MRCGP, UKDCTN GP fellow; **SI Lee** (ORCID: 0000-0002-2332-5452), BSc, PGcert, MRCGP, GP academic clinical fellow; **P Smart**, patient representative; **J Kai** (ORCID: 0000-0001-9040-9384), MD, FRCGP, professor of primary care; **KS Thomas** (ORCID: 0000-0001-7785-7465), PhD, professor of applied dermatology research; **P Leighton** (ORCID: 0000-0001-5208-0274), PhD, associate professor of applied health research, School of Medicine, University of Nottingham, Nottingham. **NJ Levell** (ORCID: 0000-0003-3393-8305), MD, MBA, FRCP, consultant dermatologist, Dermatology Department, Norfolk and Norwich University Hospital NHS Trust, Norwich; honorary professor, University of East Anglia, Norwich.

Address for correspondence
Paul Leighton, Centre of Evidence Based Dermatology, School of Medicine, University of Nottingham, Room A103, King's Meadow Campus, Nottingham NG7 2NR, UK.

Email: mczpal1@exmail.nottingham.ac.uk

Submitted: 11 June 2019; **Editor's response:** 19 July 2019; **final acceptance:** 29 July 2019.

How this fits in

Diagnosing recurrent lower-limb cellulitis in people with lymphoedema can be challenging for healthcare professionals. People with lymphoedema and healthcare professionals want better support to make a more accurate diagnosis of cellulitis. Selected people with lymphoedema are confident about making a self-diagnosis when they experience an episode of recurrent cellulitis and can potentially be more involved in the early diagnosis of cellulitis. Healthcare professionals often trust these expert people in making the diagnosis of cellulitis.

2 years); ability to give informed consent; and ability to speak English.

Patients with non-lower-limb cellulitis were excluded from the study.

Participant selection

Participants were pragmatically recruited from a pre-existing cellulitis research database held at the Centre of Evidence Based Dermatology, including participants in previous cellulitis trials,[8,9] and James Lind Alliance cellulitis priority setting partnership,[6] and from the Lymphoedema Support Network (https://www.lymphoedema.org/).

Sampling strategy

Purposive sampling was used to ensure that participants included individuals >50 years as cellulitis prevalence increases with age and those managed by different types of healthcare professionals, so that different pathways to diagnosis might be captured. This was achieved by sending a short questionnaire to eligible participants to determine this information.

Data collection and analysis were undertaken concurrently, and sampling ceased when thematic saturation had been achieved, that is, new interviews generated no new insight.

Researcher characteristics

One researcher conducted the interviews, and two researchers coded and analysed the interviews (both GP trainees). The broader research group included experienced clinical academics, a patient representative, and research methodologists.

Interview setting

Each participant took part in a single, semi-structured, qualitative interview, with a mean duration of 30 minutes. These were either face to face or via telephone, according to participant preference. All participants received a 20 GBP reimbursement voucher.

Data collection

In anticipation of the interview, participants were invited to reflect on their experience of cellulitis diagnosis.

A topic guide, informed by a previous review,[10] was used to structure the interview (Box 1). Throughout the interview, participants were encouraged to introduce and/or develop topics that they felt were most pertinent to their experience of diagnosis.

Data processing and analysis

Interviews were audiorecorded and transcribed verbatim by two professional transcribers, who were independent of the study. Transcripts were checked and data handled using NVivo software (version 12).

Data analysis was inductive, finding themes in the data rather than predetermining concepts of interest. A structured, systematic, multistage approach to thematic analysis was followed.[11]

One researcher coded the data, and another researcher independently coded the first six transcripts. Disputes and uncertainties in coding and thematic organisation were resolved in consultation with the other authors. The final codebook was agreed by all authors and participants (Box 2).

RESULTS

Eighteen people with recurrent cellulitis were interviewed (Table 1); all except one had a history of lymphoedema. Interviews were conducted between 29 October and 19 December 2018. A summary of how the codes mapped to the overarching themes is presented in Box 3.

Three key themes were identified in the data: the recurrent nature of cellulitis symptoms; participants' experience of getting a cellulitis diagnosis; and participants' suggestions of how cellulitis diagnosis might be improved.

The recurrent nature of cellulitis symptoms

Participants described a red, warm, painful limb as being the core symptoms:

'I get a real bad bruise pain … It's the pain, bit like when you break a leg … Generally speaking, if I get that pain, I check my leg out to see where it's red, or raised or hot.' (Participant [P]2, 56-year-old female)

However, these features are also seen in other diseases and pose a diagnostic challenge. According to the interviewees,

Box 1. Topic guide used to structure the interview

Can you tell me about when you were last told you may have cellulitis?

Prompts:

- What did you notice?
- What made you go and seek medical advice?
- How long did you wait to seek help?
- Who did you see?
- Why did you see this person?
- What happened then?
- Were any tests done?
- What do you think went well?
- Was there anything that might have been more helpful?
- How was this similar to previous cases of cellulitis you have had?

Can you tell me about any occasion when diagnosing your cellulitis was a problem?

Prompts:

- What did you have on this occasion?
- At what point did you seek medical advice?
- What was diagnosed?
- Do you know why this was diagnosed?
- Did anything change from how you were?
- What did you do next?
- How long did you wait to seek advice again?
- What was done differently this time?
- Do you know what the final diagnosis was?

We are interested in how different people diagnose cellulitis

Prompts:

- Who normally makes the diagnosis of your cellulitis?
- Are you confident that they will make the correct diagnosis?
- Would you see them again regarding cellulitis?
- Has your cellulitis ever been diagnosed by anybody else?
- If so, was there a difference in the approach that was used?
- What did they ask?
- What tests did they use?
- Has this changed who you would see in future?

examples of incorrect initial diagnoses included fungal infection (P1, 58-year-old female) and deep vein thrombosis (P4, 74-year-old male). In some cases, further investigations in secondary care including bloods tests and imaging with ultrasound were required:

'I woke up with my leg ... so swollen that the skin was tight, very red, very hot, and the doctor said he thought it might be a clot.' (P5, 69-year-old female)

Swelling was also described as a common symptom by some participants, although it was recognised that diagnosis rests in swelling being accompanied by other features such as erythema and pain:

'There is the heat in the leg, swelling in my leg and that swelling is of course, could be confused with the lymphoedema side of things. But it's the heat and the swelling, not just a swelling.' (P4)

Other symptoms including an 'itch in the skin', 'champagne bubbles popping underneath the skin' (P1), a 'burning oil [sensation]' (P2), and a smell 'like a bad piece of meat' (P3, 71-year-old female) were described.

Having a history of lymphoedema made identifying the features of cellulitis more difficult in the early stages, but, with recurrent episodes, participants felt more confident in identifying cellulitis themselves:

'There is a clear difference between every day if there's a swelling with cellulitis.' (P7, 47-year-old female)

Many participants described experiencing constitutional symptoms as marking the onset of cellulitis; these included feeling 'sort of flu-ey' (P14, 63-year-old female), generally 'feeling tired' (P4), and 'detached' (P18, 52-year-old female). This type of symptom prompted some participants 'to monitor my legs even [more] closely' (P5).

However, vague 'flu-like' symptoms would not always prompt a healthcare professional to make a diagnosis of cellulitis. They would require more typical features present on the leg to do this:

'Until the symptoms show themselves totally ... they [doctors] *are reluctant to make that* [diagnosis], *that it is cellulitis, but they are quite happy the day after when it's more apparent that this is it.'* (P4)

One patient sympathised with the healthcare practitioner:

'From your point of view as a doctor, it is quite difficult and then to start ramming antibiotics to a high level down someone's throat.' (P4)

Most interviewees felt that the clinical features of cellulitis during recurrent episodes were similar and that this helped them to recognise the diagnosis:

'Because this was my second episode ... symptoms I felt were very similar to the first time around but obviously I recognised them this time around.' (P9, 71-year-old male)

Box 2. Standardised codebook used by two independent coders

Codes used

- Symptoms and signs
- Recurrent episodes
- Tests
- Underlying cause
- Seeking medical advice
- Relative's involvement
- Approach by the healthcare professional
- Challenges for the healthcare professional
- Participants' confidence
- Participants' preferred healthcare professional to see
- Seeing different healthcare professional
- Pathways in different countries
- Participants' expert knowledge
- Healthcare professional's trust in the patient
- Participants not agreeing with the healthcare professional
- Solutions to help
- Participants' concern about a diagnosis
- Wanting an early diagnosis
- Delayed or incorrect diagnosis
- Lymphoedema as a challenge
- Other comorbidities as a challenge

This made participants more confident in seeking a medical review or starting emergency antibiotics that had been provided to them in advance by the GP.

The recurrent pattern of the clinical presentation of cellulitis also allowed family members to identify features to look out for:

'At that point that I think I might get cellulitis and then they watch for signals as well.' (P1)

Sometimes family members would also notice other changes that the participants were not aware of:

'My husband says I don't look well … I go much paler, glassy eyed, there we go, these are things I don't know 'cos I don't look at myself!' (P15, 62-year-old female)

The experience of the participant getting a cellulitis diagnosis

Learning from recurrent episodes of cellulitis allowed participants with lymphoedema to become more 'expert' in making a self-diagnosis before seeing a healthcare practitioner:

'As I've had it so many times, my [self] *diagnosis has got better. Simply because I know more about it myself.'* (P1)

Some were aware of looking to see any breaks in the skin where cellulitis could develop after undertaking activities such as gardening or walking barefoot (which might increase the risk).

Some participants felt positive that healthcare professionals in primary care and in the emergency department trusted their self-diagnosis:

'There are a lot of GPs who appreciate that I have had it so often and they know what is happening and they will go with my instinct.' (P1)

Table 1. Characteristics of the participants (*n* = 18)

Characteristic	Participants, *n* (%)
Sex	
Male	4 (22)
Female	14 (78)
Age, years	
18–24	0 (0)
25–34	1 (6)
35–44	1 (6)
45–54	2 (11)
55–64	8 (44)
65–74	6 (33)
≥75	0
Ethnicity	
White	18 (100)
Total number of cellulitis episodes in their lifetime	
1–5	6 (33)
6–10	2 (11)
>10	10 (56)
History of lymphoedema	
Yes	17 (94)
No	1 (6)

Box 3. Summary of how the codes map to the overarching themes

Theme	Code
The recurrent nature of cellulitis symptoms	Symptoms and signs Delayed or incorrect diagnosis Lymphoedema as a challenge Recurrent episodes Relative's involvement Challenges for the HCP
Participants' experience of getting a cellulitis diagnosis	Participants' expert knowledge Seeking medical advice HCP's trust in the patient Wanting an early diagnosis Seeing different HCP Approach by the HCP Participants' confidence in the HCP Participants' preferred HCP to see Participants not agreeing with the HCP
Participants' suggestions of how cellulitis diagnosis might be improved	Solutions to help Tests

HCP = healthcare professional.

Continuity in care was important for participants; some discussed how they had developed a strong relationship with healthcare professionals over a period of time, which built awareness of their recurrent history:

'I have a bond with my GP ... that I have known for a long time ... who know me well enough.' (P1)

Previous recorded episodes of cellulitis can also influence diagnosis in the out-of-hours setting and the emergency department:

'He looked at my records [in urgent care] *and he noticed that I had a record of cellulitis and he said "It certainly looks like it and I'm not going to take any chances".'* (P9)

Many participants wanted a diagnosis quickly and sought medical advice as soon as the first symptom appeared:

'Straight away [to be seen], *immediately when I notice it* [symptoms].*'* (P7)

This was not always easy, especially in primary care, leading some to rely on out-of-hours and the emergency department:

'The reason I do that is because if I go to my local surgery, the least I'm going to have to wait is next day and that's too long.' (P9)

Others were content to wait for changes in the limb before seeking help:

'I draw around it to see how quickly it is going.' (P11, 63-year-old female)

However, others started treatment at home first before seeking medical advice:

'I have antibiotics that I keep at home so that if this happens, I can start taking them but I started taking them and it hadn't gone away so I made an emergency appointment to see my GP.' (P8, 36-year-old female)

Participants consult a range of different healthcare professionals: GPs, emergency physicians, dermatologists, lymphoedema nurses, nurses in primary care, and pharmacists. Despite this variation, assessing for possible cellulitis was described as being similar across all professional groups:

'I don't actually think that they [emergency department] *asked anything particularly different* [to the GP].*'* (P8)

Later presentation, with development of clinical features in the emergency department, might provide a more straightforward diagnosis:

'I suppose by that point [in the emergency department], *basically everyone had already thought the day before that it was probably cellulitis ... I actually went there with the diagnosis whereas because I was sort of a bit further down the line.'* (P8)

Participants were generally confident that all healthcare professionals, irrespective of setting, would make the correct diagnosis of cellulitis:

'Well, yeah, I think so because I mean everyone seems to recognise it.' (P9)

Others pointed to confident self-diagnosis as a factor in this:

'[A correct diagnosis?] *I think so because of the fact that I tell them, I give them the background history.'* (P2)

One participant thought that the lymphoedema nurse and community nursing team were good at making a cellulitis diagnosis, as they are more familiar with its features:

'Funnily enough, the best person I have found for picking it up has been one of my district nurses. She's had previous experience of cellulitis ... I think that they see it more.' (P5)

As participants felt confident in making a self-diagnosis of cellulitis, they would become more determined for a healthcare professional to accept their judgement. If a professional did not concur, some would seek a second opinion:

'If I was sure it was cellulitis, and someone was saying "definitely not", then I would say "look, I know it is cellulitis, we need to get someone else to look at it because I know now what I am looking at".' (P11)

Some participants would push for a diagnosis even when a healthcare professional is unsure:
'I think I am a bit pushy maybe [getting a diagnosis] *and I push for it.'* (P2)

This often stemmed from the impact that cellulitis had on them and their urgency to get a quick diagnosis and treatment. Delays might impact on their role in the workplace, social activities, or as a carer; delays in

diagnosis might also lead to needing hospital admission for treatment.

Participants' suggestions of how cellulitis diagnosis can be improved

When asked about resources that may help a healthcare professional to make an accurate diagnosis more quickly, further education, with prompts and pictures, were suggested:

'Education — because I'm sure it's not something they come across every day so they'll just think, they need to be shown examples, pictures, anything, or even have somebody speak to them who suffers with it.' (P7)

However, among participants with lymphoedema, educating professionals on how cellulitis can present in lymphoedema was a specific area where more education might be beneficial. Other resources mentioned to assist diagnosis included a specific blood test:

'A specific blood test or antigen that they could test for and they can find out if that is what the problem was.' (P2)

When asked about being seen in a cellulitis clinic, participants thought this would be ideal:

'A dedicated clinic for me would be amazing. Because then you are dealing with people who know what cellulitis is on regular basis and familiar with it and everything.' (P1)

Some participants thought a symptom checklist could help, both for themselves and professionals:

'If I had a checklist that once I had completed it said yes, it is definitely cellulitis, this is how you treat it … I would certainly do it myself.' (P13, 55-year-old female)

However, regarding self-diagnosis, any self-diagnostic guide should have clear instructions about when to seek medical advice from the healthcare professional:

'I think you have to be very clear about if it reaches this stage, you need to get a health professional involved.' (P18)

DISCUSSION

Summary

This qualitative study found that people with lymphoedema experience similar clinical features during each of their own recurrent cellulitis episodes and generally feel confident in making their own clinical diagnosis. Participants often experience constitutional 'flu-like' symptoms and fatigue, typically before they noticed the inflammatory features of pain, warmth, and erythema. Relatives close to the patient could also detect some changes in the patient when cellulitis occurred.

However, swelling associated with cellulitis, particularly among people with lymphoedema, can be difficult to differentiate from pre-existing swelling. In addition, the typical features of cellulitis can also present in many differential diagnoses, making the diagnosis challenging.

Participants believed that the clinical diagnostic approach of various healthcare professionals that they consulted were comparable, with speed of being seen and being able to see a known healthcare professional as determining factors about who to consult. Participants were generally confident that a healthcare professional would make the correct diagnosis in recurrent episodes of cellulitis because of their previous history.

Participants consider themselves to have a great amount of knowledge in diagnosing their own cellulitis episodes and many perceive they have the trust of their healthcare professional in making a diagnosis and starting treatment. More education and a diagnostic checklist that both healthcare professionals and people with cellulitis could use were suggested as ways to improve diagnosis.

Strengths and limitations

The key strength of the qualitative approach used is that it allowed experiences to be gained in detail. Two independent coders used a standardised codebook to improve inter-coder reliability. Participants, as well as the authors, provided feedback on the final themes. Participants included are those at higher risk of experiencing recurrent cellulitis.[3]

The limitations stem from the pragmatic design and feasibility of the study. The authors initially wanted to explore the experiences in people with a single acute episode or recurrent episodes of cellulitis, and those with and without lymphoedema. However, all the people who contacted the study team had recurrent cellulitis and all except one had lymphoedema. Also, more females participated, which may reflect a higher incidence of lymphoedema in this group or that females are more likely to participate in research. Greater ethnic diversity in the present sample would also have enhanced the generalisability of findings.

In future, screening primary and secondary care health records with the appropriate ethical approval could improve the sample strategy.

People who are confident in making a self-diagnosis, more knowledgeable about their condition by being under the care of specialist lymphoedema services, and perhaps more willing to take responsibility of their health, are more likely to take part in this study. These participants, through their previous experiences, especially negative ones, are perhaps more likely to push for a diagnosis. Therefore, their views may not be generalisable. However, the wealth of experience that participants with recurrent cellulitis have gained over the years about their symptoms and when to seek treatment are invaluable. Also, this select group provided insight into distinguishing the early diagnosis of cellulitis in lymphoedema, a common diagnostic dilemma.

All participants were aware the interviewer was a doctor and this could influence their responses. Finally, the participants' overall confidence in self-diagnosis cellulitis limits the discussion of diagnostic uncertainty.

Comparison with existing literature

It is participants' knowledge and confidence in self-diagnosis that marks this study out from comparable research that has considered patients' understanding of cellulitis. Studies by Teasdale *et al*[7,13] and by Carter[14] show that many individuals demonstrate a degree of uncertainty about the cause and management of cellulitis, and that some feel ill-informed about the recurrent nature of cellulitis and are unprepared to manage such.[7] In contrast, interview data generated here, with patients who have both lymphoedema and recurrent cellulitis, presents a more confident and active patient population who are knowledgeable about how to manage their cellulitis. This is a population who know how to manage their cellulitis and who are confident in negotiating healthcare systems (and with healthcare professionals). Previous research has suggested that healthcare professionals' response to cellulitis can vary, and can be less than satisfactory for patients.[13]

This research shows that patients with both lymphoedema and recurrent cellulitis are (unsurprisingly) more knowledgeable than those experiencing their first incident of cellulitis. However, in line with previous research,[7,13,14] it suggests the importance of information, awareness, and education for people with cellulitis and the healthcare professionals who support them.

Implications for research and practice

The study findings can be applied to people with recurrent cellulitis and lymphoedema, a condition that predisposes to recurrent cellulitis. The key clinical features described, as well as the diagnostic overlap of these features with other pathologies, is well known in clinical practice and this study confirms this. The similarity of clinical features in recurrent cases is likely to be something healthcare professionals take into account when making a diagnosis, given that they seem to be more willing to diagnose cellulitis in a person with multiple previous episodes.

Constitutional features could be an indication of viral illness that does not require antibiotics, or an early feature of infection where the source of infection is not yet apparent. This poses great challenges to professionals in diagnosing cellulitis: it is a fine balance not to overdiagnose and to maintain antibiotic stewardship while not delaying cellulitis diagnosis.

With increasing pressures on health care in the UK and a growing cohort of 'expert groups', empowering individuals to self-diagnose and self-manage may become more common. However, this must be done cautiously by professionals who know the person with cellulitis well, with clear safety nets put in place. A shared validated diagnostic tool or set of criteria that both professionals and people with recurrent cellulitis can use may allow this to be done safely, similar to those available in asthma and chronic obstructive pulmonary disease. With reference to the interview findings that some participants find it difficult to access their primary care provider quickly during an acute episode, having a self-management plan becomes even more relevant. Other methods proposed to aid diagnosis include educational resources such as clinical images of cellulitis presentations made available to the healthcare professional or specialist cellulitis clinics, which have been shown to improve accurate diagnosis.[12]

Further research is also required to find a specific and validated biomarker for cellulitis, with no current single test available.

Funding

Mitesh Patel is funded by a National Institute for Health Research (NIHR) academic clinical fellowship (ACF-2016-12-502). This study was funded by the Claire Wand Fund (charity number 220008). The views are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Ethical approval

Ethical approval was granted by the Faculty of Medicine and Health Sciences Ethics Committee, University of Nottingham (5 October 2018) (Ref: 105-1809).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

Acknowledgements

The authors would also like to thank the 18 participants and the professional transcribers. Thanks also to the Lymphoedema Support Network and the Centre of Evidence Based Dermatology for help with recruitment.

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BMJ Open

An interview study to determine the experiences of cellulitis diagnosis amongst health care professionals in the UK

Mitesh Patel ,[1,2] Siang Ing Lee,[1] Nick J Levell,[3] Peter Smart,[2] Joe Kai,[1] Kim S Thomas,[2] Paul Leighton[2]

To cite: Patel M, Lee SI, Levell NJ, *et al*. An interview study to determine the experiences of cellulitis diagnosis amongst health care professionals in the UK. *BMJ Open* 2020;**10**:e034692. doi:10.1136/bmjopen-2019-034692

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-034692).

Received 02 October 2019
Revised 30 July 2020
Accepted 07 September 2020

[1]Division of Primary Care & National Institute for Health Research, School of Medicine, University of Nottingham, Nottingham, UK
[2]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK
[3]Dermatology, Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, UK

Correspondence to
Dr Mitesh Patel;
mpatel59@doctors.org.uk

ABSTRACT

Objectives To explore healthcare professionals (HCPs) experiences and challenges in diagnosing suspected lower limb cellulitis.

Setting UK nationwide.

Participants 20 qualified HCPs, who had a minimum of 2 years clinical experience as an HCP in the national health service and had managed a clinical case of suspected cellulitis of the lower limb in the UK. HCPs were recruited from departments of dermatology (including a specialist cellulitis clinic), general practice, tissue viability, lymphoedema services, general surgery, emergency care and acute medicine. Purposive sampling was employed to ensure that participants included consultant doctors, trainee doctors and nurses across the specialties listed above. Participants were recruited through national networks, HCPs who contributed to the cellulitis priority setting partnership, UK Dermatology Clinical Trials Network, snowball sampling where participants helped recruit other participants and personal networks of the authors.

Primary and secondary outcomes Primary outcome was to describe the key clinical features which inform the diagnosis of lower limb cellulitis. Secondary outcome was to explore the difficulties in making a diagnosis of lower limb cellulitis.

Results The presentation of lower limb cellulitis changes as the episode runs its course. Therefore, different specialties see clinical features at varying stages of cellulitis. Clinical experience is essential to being confident in making a diagnosis, but even among experienced HCPs, there were differences in the clinical rationale of diagnosis. A group of core clinical features were suggested, many of which overlapped with alternative diagnoses. This emphasises how the diagnosis is challenging, with objective aids and a greater understanding of the mimics of cellulitis required.

Conclusion Cellulitis is a complex diagnosis and has a variable clinical presentation at different stages. Although cellulitis is a common diagnosis to make, HCPs need to be mindful of alternative diagnoses.

Strengths and limitations of this study

- The research question was developed from research priorities in the cellulitis priority setting partnership, involving patients.
- Participants were included nationally around the UK.
- Participants from various specialties that commonly diagnose cellulitis were recruited.
- Our recruitment strategy is most likely to have targeted healthcare professionals with an interest in dermatology.
- The size and scope of the sample population is a limitation.

INTRODUCTION

Cellulitis is a frequent presentation in both the community and secondary care, with 60% of presentations affecting the lower limbs.[1] However, the diagnosis of cellulitis can be challenging, with up to a third of suspected lower limb cellulitis cases being later diagnosed as other diagnoses.[2] This results in avoidable hospital admissions and unnecessary antibiotic prescribing[3] and is further compounded by the lack of validated diagnostic criteria or tools for cellulitis.[4]

A UK cellulitis research priority setting partnership (PSP) determined that improving healthcare professionals' (HCPs) diagnostic accuracy is a key priority for future cellulitis research.[5] An interview study of people with recurrent cellulitis and lymphoedema suggested that patients often experience difficulties in obtaining a speedy and accurate diagnosis.[6]

The aims of this interview study were to explore the HCP experiences and challenges faced in diagnosing suspected lower limb cellulitis.

METHODS

Protocol registration and ethics

The final protocol was registered on the Centre of Evidence Based Dermatology

(CEBD) website (9 May 2019). Ethical approval was granted by the Health Research Authority and Health and Care Research Wales (19/HRA/0485, 30 November 2018). Verbal and written consent was obtained from each participant.

Patient and public involvement

The research question was developed from research priorities in the cellulitis PSP, involving patients. A patient representative helped design this study and is a coauthor. On publication, participants will be sent the final manuscript.

Eligibility criteria

Selection of participants

Participants were qualified HCPs, who had a minimum of 2 years clinical experience as an HCP in the national health service and had managed a clinical case of suspected cellulitis of the lower limb in the UK. Two years' experience was the minimum requirement as then HCPs will have gained adequate exposure to cellulitis cases. HCPs were recruited from departments of dermatology (including a specialist cellulitis clinic), general practice, tissue viability, lymphoedema services, general surgery, emergency care and acute medicine.

Purposive sampling was employed to ensure that participants included consultant doctors, trainee doctors and nurses across the specialties listed above. Participants were recruited through:

1. National networks.
2. HCPs who contributed to the cellulitis PSP.
3. UK Dermatology Clinical Trials Network.
4. Snowball sampling where participants helped recruit other participants.
5. Personal networks of the authors.

Potential participants were approached and recruited by email. Data collection and analysis were undertaken concurrently and sampling ceased when thematic saturation had been achieved (ie, new interviews generated no new insights).[7]

Researcher characteristics

Interviews were conducted by MP (male), and coded and analysed by MP and SIL (female, both general practitioner (GP) trainees who had managed clinical cases of cellulitis previously). Both MP and SIL attended qualitative methodology training courses. The broader research group included experienced clinical academics (JK (academic GP) and NL (clinical professor of dermatology), a patient representative (PS) and senior qualitative experts (JK and PL)). Three participants had clinical interactions with the interviewer in the past, but not regarding cellulitis.

Interview setting

Each participant took part in a single, semistructured, qualitative interview. Two interviews were face to face, with the remaining via telephone. Written consent was gained from participants, with additional verbal consent gained before the interview. All participants received a £20 reimbursement voucher or donated this fee to the British Skin Foundation charity.

Data collection

Prior to the interview, participants were asked to reflect on their most recent experiences of making a cellulitis diagnosis, focusing on the typical presentations, challenging cases and differential diagnoses.

A topic guide, informed by a prior systematic review and interview study,[8] was used to structure the interview (see online supplemental material). However, participants were urged to propose and/or expand on topics which they felt were relevant to their experience of diagnosis. New topics were then added to the topic guide for subsequent interviews.

Data processing

Interviews were audiorecorded and transcribed. Transcripts were checked (by MP) and data managed using QSR NVivo 12 software.

Data analysis

Analysis was inductive, searching for themes in the data. A structured, systematic, multistage approach to thematic analysis was followed.[9] Coders immersed themselves in the data, by reading the dataset before coding. Data were coded manually by MP, with SIL also independently coding a third of the transcripts. A list of each code, with a brief description was then used to group the codes into theme piles. Themes were defined and refined, with subthemes also developed.

Uncertainties in coding and thematic organisation were resolved in discussion with the other authors. Data collection and analysis was concurrent. The final codebook was agreed by all authors and is presented in figure 1. The interviewer kept a reflexive research diary, logging intuitive thoughts and immediate reflections after each interview. These reflections, as well as queries around data collection, handling and interpretation were then discussed at regular research meetings.

RESULTS

Twenty HCPs were interviewed (table 1). The age range was 29–67 years; 15 were female; 6 had <10 years of clinical experience, 9 had 11–20 years and 5 had >20 years. Interviews were conducted between 19 March and 11 June 2019, with a mean duration of 29 min.

Main findings

Four key themes were identified: (1) the patient presentation; (2) challenges leading to diagnostic uncertainty; (3) strategies to improve diagnosis; and (4) the need for an objective diagnostic aid, with further classification into subthemes. How the codes mapped onto the overarching themes are shown in table 2.

Diagnosis of cellulitis

The typical patient and risk factors

In general practice, the typical patient described by participants included older adults with comorbidities; concerns

Codes used

- Trial of treatment guides diagnosis
- Discussing diagnosis with colleagues
- Time and safety netting approach
- Patients who self-diagnose and treat
- Approach when HCPs do not agree with patient self-diagnosis
- Patients involved with diagnosis with the HCP
- Typical cellulitis presentations
- Clinical features of cellulitis
- Factors that decrease the likelihood of cellulitis diagnosis
- Factors that increase the likelihood of cellulitis diagnosis
- Investigations to aid diagnosis
- Missed/delayed diagnosis of cellulitis (final diagnosis)
- Missed/delayed diagnosis of cellulitis (initial diagnosis)
- Patient finds it difficult to accept it is not cellulitis
- Reasons why cellulitis diagnosis is challenging
- Suggestions on what may improve diagnosis
- Views on diagnostic aids for HCP
- Views on diagnostic aids for patients
- Views on how well HCP make diagnosis
- Experience guides diagnosis
- Seeing patients part way through assessment and management
- Differential diagnoses
- Sepsis as a concern
- Medico legal issues as a factor
- Follow up of patients
- Most suitable HCP to diagnose cellulitis
- Fear of missing more serious differentials
- Clinical features to include in diagnostic algorithm
- Other factors influencing diagnosis

Figure 1 Standardised codebook used by two independent coders. HCP, healthcare professional

of possible cellulitis cases were often raised by district nursing colleagues. Emergency care and acute services described people who presented with features of systemic compromise. Both infectious disease and general surgery services often managed intravenous drug users who were at risk of deeper infection.

Factors that HCPs stated increased the likelihood of cellulitis were features of systemic upset including fever, malaise, rigours; coexisting injury or infection such as tinea, superficial ulceration, previous history of cellulitis, previous history of dermatological conditions such as eczema, diabetes, immunosuppressive medications and those with no fixed abode with social and health risks. Bilateral symptoms were commonly described by participants as a factor increasing the likelihood of chronic, systemic pathologies rather than cellulitis.

Confidence in diagnosis

One dermatologist explained how being more aware of the differential diagnoses made them more likely to accurately diagnose cellulitis, especially compared with junior colleagues. Generally, HCPs with more clinical experience felt more confident with diagnosis, as they appreciated the presentation with more observed cases 'I would say it is just experience [helping diagnosis], a lot of the juniors that come into A&E have not seen that many cellulitis [cases]' (P19, emergency care consultant, 10 years clinical experience).

Table 1 Characteristics of the participants

Participant	Ethnicity	Clinical role	Number of times they have diagnosed cellulitis	Time since they last diagnosed cellulitis
1	Asian British	GP	>50	One week ago
2	White British	Acute medicine/infectious disease consultant	>50	One week ago
3	White Irish	GP	>50	Three weeks ago
4	White British	Acute medicine consultant	>50	Last 4 weeks
5	White British	Acute medicine consultant	>50	One week ago
6	White British	Tissue viability nurse	10–50	Less than 1 week
7	White British	Lymphoedema specialist nurse	>50	One week ago
8	Asian British	Emergency medicine consultant	>50	Less than 1 week
9	Asian British	Dermatology consultant	10–50	Four weeks ago
10	White British	District nurse	>50	Last 3 months
11	Black	GP trainee	10–50	Less than 1 week
12	White British	GP locum	10–50	Two weeks ago
13	White British	GP out of hours	>50	Two weeks ago
14	White British	Dermatology specialist nurse	>50	Last 3 months
15	White British	Dermatology consultant	10–50	Last 12 months
16	Mixed	Surgical trainee	10–50	Last 4 weeks
17	White British	Community advanced nurse practitioner	>50	Less than 1 week
18	White British	Dermatology trainee	>50	Four weeks ago
19	White British	Emergency medicine consultant	>50	Last 3 months
20	White British	Dermatology consultant	>50	Less than 1 week

GP, general practitioner.

Table 2 How the codes mapped onto themes

Themes	Subthemes	Codes
The patient presentation	The typical patient and risk factors	► Typical cellulitis presentations
		► Factors that increase the likelihood of cellulitis diagnosis
	Confidence in diagnosis	► Most suitable HCP to diagnose cellulitis
		► Experience guides diagnosis
	Cases of misdiagnoses	► Missed/delayed diagnosis of cellulitis (final diagnosis)
		► Missed/delayed diagnosis of cellulitis (initial diagnosis)
	Differential diagnoses	► List of alternative diagnosis
Challenges leading to diagnostic uncertainty	Continuum of clinical features	► Changes in clinical presentation
	A subjective diagnosis	► Reasons why cellulitis diagnosis is challenging
	Community challenges	► Seeing patients part way through assessment and management
		► Follow-up of patients
	The role of 'defensive' medicine	► Sepsis as a concern
		► Medico legal issues as a factor
		► Fear of missing more serious differentials
	Patient-specific factors	► Other factors influencing diagnosis
Strategies to improve diagnosis	Using time as a guide	► Time and safety netting approach
	Trial of treatment	► Trial of treatment guides diagnosis
	Biochemical investigations	► Investigations to aid diagnosis
	Seeking advice	► Discussing diagnosis with colleagues
	Further education	► Suggestions on what may improve diagnosis
The need for an objective diagnostic aid	A diagnostic algorithm	► Views on diagnostic aids for HCP
	Indices for an algorithm	► Clinical features to include in diagnostic algorithm

HCP, health care professional.

A dermatology trainee felt seeing less cellulitis cases during their training compared with their senior colleagues historically, and therefore not getting as much exposure, hindered accurate diagnosis.

Cases of misdiagnoses

Trauma-related skin changes were frequently an initial misdiagnosis in the emergency department. When discussing cases of uncertainty, where cellulitis was the initial suspected diagnosis, one GP described a case of venous eczema which was managed with repeated antibiotics 'Generally anything that is red and hot on the legs is treated with antibiotics' (P1, GP,>13 years clinical experience). Chronic rashes were frequently seen by dermatology and infectious disease discussed lymphoma cases initially referred as cellulitis 'We did see [patients] coming in with 'Oh this must be a resistant cellulitis', have got a swollen limb that might be a little bit red and it turns out to be some horrible form of lymphoma' (P2, infectious disease consultant, 25 years clinical experience).

The importance of a correct diagnosis is key, as two participants discussed the possibility of prophylactic antibiotics for patients with recurrent cellulitis. A dermatology consultant explained how misdiagnosis can result in inappropriate and costly admissions to the ward.

Differential diagnoses

A frequent diagnosis of uncertainty for primary and emergency care was deep vein thrombosis (DVT), as the clinical features of cellulitis can overlap 'One thing that is always a problem is leg swelling…it is difficult to ascertain between DVT and cellulitis' (P8, emergency care consultant, 20 years clinical experience). Common differential diagnoses discussed by participants, which they observed in their clinical practice, with discriminating features from cellulitis that they described, are shown in table 3.

Challenges leading to diagnostic uncertainty

The continuum of clinical features

Participants described how the presentation of lower limb cellulitis changed as the episode ran its course. This was influenced by when patients seek clinical review and

Table 3 Differential diagnoses of lower limb cellulitis discussed by participants

Differential diagnoses	Key differentiating factors from cellulitis
Chronic heart failure causing oedema	Chronic, bilateral, lack of mobility, breathless, cardiac history (P1, GP; P14, dermatology specialist nurse)
Venous eczema	Usually chronic with haemosiderin scaling, itching, crusting, likely bilateral, possibly eczema elsewhere on body, less well defined, (P3, GP; P15, dermatology consultant)
Thrombophlebitis	Tender, localised, hard, lumpy rash around an often-thickened vein (P3, GP; P5, acute medicine consultant; P12, GP locum)
Erythema nodosum	Multiple, discrete swellings (P13, GP out of hours)
DVT	Pain is usually deep in calf rather than superficial, less sharply demarcated and less intense erythema, diffuse swelling of limb, can be young, can be intravenous drug users, high DVT wells score, fewer systemic features (P2, infectious disease consultant; P12, GP locum; P13, GP out of hours)
Lymphoedema	Chronic, bilateral, usually less painful, thickened warty skin in the long-term, normal inflammatory markers (P9, dermatology consultant; P18, dermatology trainee)
Allergic reaction to insect bites	Central puncture mark, itch, when acute, developing lichenified erythema when chronic (P2, infectious disease consultant)
Lipodermatosclerosis	Often bilateral, systemically well, tight non-tender skin with inverted champagne bottle appearance (P4, acute medicine consultant; P20, dermatology consultant)
Necrotising fasciitis	Crepitus, rapidly spreading, septic, very tender (P5, acute medicine consultant; P16, surgical trainee)
Wound infection	Local to the wound, covers small area, yellow exudate, strong odour (P10, district nurse; P16, surgical trainee)
Baker's cyst	Unilateral popliteal swelling, suddenly more tender on rupture (P15, dermatology consultant)

DVT, deep vein thrombosis; GP, general practitioner.

meant that different specialties observed clinical features at varying stages of cellulitis.

In dermatology services, presentations were seen later in the episode. However, partial treatment and response did make the diagnosis challenging as the initial typical features of cellulitis may then vary. However, seeing patients later in the journey allowed dermatologists to appreciate the progression of clinical features 'I learnt to appreciate much more that [cellulitis] is coming up, it is happening and that it is fading away…When I was [junior], I was seeing [cellulitis] at the beginning and middle stages, trying to diagnose it, but in dermatology you're seeing it more at that other end of the spectrum…so I think there is a lot [to be] learnt about seeing that pattern developing and progressing and then resolving' (P18, dermatology trainee, 8 years clinical experience).

Importantly for dermatologists, other more serious pathologies such as a DVT had often been ruled out.

A subjective diagnosis

One GP explained how there is no specific test that can aid diagnosis, thus subjective assessment can lead to different diagnoses 'I think the fact that there is no specific diagnostic test…and two different people can look at [possible cellulitis) and come up with two different answers' (P1, GP, >13 years clinical experience). She added how this is further influenced by previous experiences, including how long and where HCPs have trained.

Community challenges

In the community, additional challenges for GPs were not being familiar with the patient's background history, seeing a patient for the first time or taking over care part way through the patient journey. Working as a locum doctor with a lack of follow-up available, often led to treatment when unsure of the diagnosis 'You've not met the patient before and sometimes you're not going to be able to follow them up so you probably are more likely to give antibiotics' (P12, GP locum, 7 years clinical experience). Limited resources to see patients, such as not being able to conduct an urgent home visit, also influenced diagnosis and subsequent management by GPs.

The role of 'defensive' medicine

HCPs in the community, emergency care and surgery were particularly wary of missing a more serious diagnosis, which needed to be ruled out first, such as DVT and necrotising fasciitis 'I think you would want to rule out DVT first because if you miss that then that is…a problem' (P1, GP, >13 years clinical experience; P16, female, surgical trainee, 5 years clinical experience). Many HCPs also mentioned '*sepsis*' when discussing clinical features and diagnosis. This may be leading to an over diagnosis of cellulitis due to concerns of medicolegal complaints of missing an infection which could then get worse 'We're all risk adverse aren't we? We would rather make sure we weren't sued because we had missed someone with an infection' (P2, infectious disease consultant, 25 years clinical experience).

Patient-specific factors

Participants found people with pigmented skin, lymphoedema and with non-specific symptoms particularly difficult to diagnose in the acute setting 'One of these classical patients that comes in hasn't got a rash…[or] the features of swelling, redness, rash and pain in the leg but they come in none specifically unwell…I think those patients are much trickier [to diagnose cellulitis]' (P5, acute medicine consultant, 16 years clinical experience). One nurse described another diagnostic challenge was when a patient presents with chronic skin changes or a recent episode of cellulitis with continuing signs 'People with chronic red [legs], their legs are red most of the time… the skin takes so long to settle, so they could have had cellulitis four weeks ago and it is still red' (P17, advanced nurse practitioner, 20 years clinical experience).

Strategies used to reduce uncertainty

Using time as a guide

In cases where the HCP was not sure of the diagnosis, different strategies were employed. Using time to allow further clinical features to develop, with appropriate safety netting was a commonly used approach. This was easier when follow-up appointments were available in the community, but was also done in the acute setting 'So if they were well…then I would bring them back to clinic the next day or two' (P4, acute medicine consultant, 17 years clinical experience). But follow-up in secondary care was difficult, often not done and can be a missed opportunity to learn from incorrect diagnoses previously.

Trial of treatment

Some HCPs started antibiotics for a suspected cellulitis and reviewed the response to help provide the diagnosis retrospectively 'Cellulitis…was the easiest thing to try and treat so I think that definitely pushed [me] to try some antibiotics and see if this is an infection' (P11, GP trainee, 6 years clinical experience). A major concern highlighted by one GP with this approach was antibiotic resistance and side effects. However, overall, there was a common understanding in primary care why this approach was taken in some instances.

Biochemical investigations

In primary care, one doctor described how blood tests and cultures were rarely done to diagnose cellulitis, as such patients would need to be seen in secondary care. Blood cultures were requested by the infectious disease physician if it was an atypical infection, but a challenge described by one dermatology consultant was that organisms are not isolated in the majority of patients. Swabs were done for discharging wound infections, mainly by district nurses or prior to discussion with microbiology, when see by dermatologists.

An emergency physician and surgical trainee explained how blood tests and imaging such as X-rays are important to check for osteomyelitis. The blood tests commonly requested by secondary care HCPs were white cell count (WCC) and C-reactive protein (CRP) for infection with one dermatologist stating how changes in blood test results were important when taking referrals for suspected cellulitis '[With cellulitis]…you expect a) it is unilateral, b) you want some inflammatory markers which are raised, at least a reasonable WCC and CRP and if it is normal it is not going to be cellulitis' (P9, dermatology consultant, 10 years clinical experience). However, one challenge with interpreting blood tests was in the group partially treated with antibiotics, who have improving blood tests but limited clinical response. A biomarker or point of care test for cellulitis was suggested as investigations to aid diagnosis by one dermatology consultant and one GP, respectively.

Seeking advice

Another approach during uncertainty was to discuss with colleagues. In the community the nurse may ask the GP to review and vice versa. In hospital, specialists in infectious disease, dermatology, microbiology and general/plastic surgeons are most often contacted for review.

Further education

Many HCPs mentioned teaching sessions to improve diagnosis, both at the undergraduate and postgraduate level. One GP stated that real-life clinical cases were felt to be important for teaching, rather than focusing on pictures 'It is all very well seeing pictures but pictures aren't that helpful sometimes, it is how it feels sometimes that makes a difference and actually seeing it in the flesh is very different to seeing even good quality pictures, so I do think that clinical exposure [is important]' (P13, GP, 20 years clinical experience).

A dermatology consultant suggested that a key area of education among HCPs was being aware of differential diagnoses for frontline services 'It is not something people will have put a lot of thought into, the differentials, and I think the focus needs to be on teaching the frontline staff' (P15, dermatology consultant, 18 years clinical experience).

One trainee who worked in a specialist cellulitis clinic found that seeing many cases helped improve her recognition of cellulitis.

The need for an objective diagnostic aid

A diagnostic algorithm

Many participants mentioned developing a diagnostic algorithm, similar to the Wells score for DVT. A GP explained how this may also help GPs make a validated clinical decision when colleagues such as district nurses are suspecting cellulitis and the patient cannot be seen quickly. A dermatology nurse described how she often used checklists and how an algorithm would help HCPs not to miss any clinical features '[A checklist] could help people that weren't experienced or confident enough… it just gives you something to think about like *"oh I hadn't thought about the heat"*' (P14, dermatology nurse, 9 years clinical experience).

One dermatology consultant suggested that a diagnostic checklist should be more of an educational tool to help rule out other differential diagnoses 'For a diagnostic checklist you almost want it to be provided as an education tool with photographs and descriptions…so that people can put these differential diagnoses into their head' (P15, dermatology consultant, 18 years clinical experience).

A dermatology trainee felt that the indices of a checklist would have to reflect how cellulitis changes through the course of the episode. Other challenges described by participants, regarding developing an algorithm were the number of alternative diagnoses, with features that often overlapped with cellulitis and vague initial features. Another concern highlighted by a dermatology consultant was that algorithms will miss patients who may present with atypical features 'Sometimes the trouble with guidelines, algorithms…you could probably cover 95% but does it mean that actually the atypical 5% then [do not] get diagnosed?' (P20, dermatology consultant, 42 years clinical experience).

Indices for an algorithm

The key clinical features that HCPs suggested to include in a diagnostic algorithm for lower limb cellulitis were unilateral, pain, erythema, warmth of limb, fever, swelling, acute onset, trauma to the limb, break in the skin, single area affected, clear demarcation, exudate, influenza like malaise, tracking rash, shiny, tenser skin, previous cellulitis, coexisting immunosuppression, coexisting skin conditions, clinical observations for sepsis, negative Wells score and patient concern. No HCP suggested blood tests were a priority in the algorithm, but a GP trainee suggested it could be included in a modified algorithm in secondary care, similar to the CURB-65 score used for pneumonia.

Additional quotes from participants are shown in table 4.

DISCUSSION

Summary

This study found that the presentation of lower limb cellulitis changes as the episode progresses, leading to variation in the clinical features, seen in different clinical settings. This may be reflected in the range of typical differential diagnoses that specialties discussed and has been described in literature.[10]

Clinical experience was described as an important factor in making a more accurate diagnosis. Dermatologists have previously been suggested as the ideal HCP to diagnose cellulitis.[11] However, the clinical reasoning behind a diagnosis was contradictory between some HCPs.

A core group of clinical features to diagnose cellulitis were suggested. But the challenge is that these features can overlap with other pathologies, irrespective of how likely these are.[12] More serious pathologies then need to be ruled out first, both for the safety of the patient and to avoid medico-legal consequences.

Suggestions to improve the accuracy of diagnoses included developing a diagnostic algorithm which could objectively help HCPs with different levels of experience.[13] The challenge with a diagnostic algorithm is that it would need to incorporate the various stages of a cellulitis episode and therefore various versions of an algorithm might be required.

Importantly, having a greater understanding of the alternative diagnoses is required, especially when the features are vague, atypical or not responding to antibiotic treatment. Educating both doctors and nurses, using real-life clinical scenarios and a focus on differential diagnoses, was also discussed and may be an initial feasible approach to improve diagnostic accuracy. A visually based computerised diagnostic decision support system, focusing on differential diagnoses, has been shown to improve the diagnostic accuracy of cellulitis.[3]

Strengths and limitations

A key strength of this study is that participants were included nationally around the UK, across various specialties that commonly diagnose cellulitis, with both nurses and doctors of varying clinical experience.

Like similar studies, the size and scope of the sample population is a limitation of this work. While we argue that our findings are transferable to other settings, we acknowledge that those interviewed were perhaps more interested and better informed about dermatology than many HCPs. This was a function of our purposive sampling, and the likelihood that those interested in cellulitis were more likely to consent to an interview. Furthermore, the participants in this study were mainly female doctors. This may not be representative of the workforce in non-UK countries; therefore the transferability of our findings may be limited.

Some participants were unable to fully describe their clinical rationale behind diagnostic decisions during the interview. This may be because they have developed an intuitive, pattern-recognition, approach in decision-making with experience. Such heuristic diagnostic processes in dermatology are well documented.[14]

As the interviewer was a fellow clinician, interviewees may not have fully shared the details of cases that were misdiagnosed or where diagnoses were delayed due to social desirability bias or fear of litigation. Clinical researcher bias was unavoidable, as the interviewer had clinical insight into cellulitis. However, non-clinicians within the broader authorship group were also involved with coding and analysis of the interviews.

Three participants were known to the interviewer, which can lead to response bias, however the interviewer felt this also allowed an honest, open discussion.

Comparison with existing literature

To our knowledge, this is the first interview study undertaken with HCPs, discussing their experiences of cellulitis diagnosis. Our findings on the clinical features of cellulitis, differential diagnoses and also the need to be

Table 4 Additional quotes from participants, grouped into themes and subthemes

Themes	Subthemes	Participant quotes
The patient presentation	Confidence in diagnosis	'*I probably thought more presentations were [cellulitis] as a junior doctor…I probably didn't really recognise that sort of stretched skin appearance. I think that has come along as part of just experience over the years, so I probably diagnosed more cellulitis inappropriately as a more junior doctor*' (P13, GP out of hours, 20 years clinical experience)
	Cases of misdiagnoses	'*One of the nurse practitioners had seen ankle swelling and the patient thought it…he played some cricket two or three days ago and after one or two days the swelling appeared and she thought that it was just a sprain but next day he represented, I saw him and it looked more like cellulitis because it was quite red, localised area…on close examination I could see a couple of scratches around the ankle so that was maybe the source of cellulitis spreading on the leg'* (P8, emergency care consultant, 20 years clinical experience)
		'*There are too many chronic rashes that get referred [to dermatology] as cellulitis*' (P18, dermatology trainee, 8 years clinical experience)
Challenges leading to diagnostic uncertainty	Continuum of clinical features	'*Usually the patient is already admitted…[the referring team] have tried [multiple antibiotics], but nothing is happening, "please can you come and tell us what is going on?"*' (P9, dermatology consultant, 10 years clinical experience)
		'*There are varying ranges of erythema, from a little bit of light pinkness to rip roaring hot red, tender, well demarcated, unilateral; the classic sort of textbook stuff*' (P18, dermatology trainee, 8 years clinical experience)
		'*Virtually every patient that I see…they have had their d-dimer and their duplex done so [DVT] is usually a diagnosis that has been excluded*' (P20, dermatology consultant, 42 years clinical experience)
	Community challenges	'*If you know the patient and you know that they have recurrent cellulitis, someone had seen it like a district nurse and it is Friday afternoon and you can't get out [for a visit]. you would make a judgement call*' (P1, GP, >13 years clinical experience)
	The role of 'defensive' medicine	'*We're so much more aware of things like sepsis…looking at any kind of signs of infection*' (P10, district nurse, 25 years clinical experience)
Strategies to improve diagnosis	Using time as a guide	'*All you can really do is reassure the patient and say…I don't see any clear evidence of cellulitis but we will keep an eye on it…you give safety net advice to the patients'* (P18, dermatology trainee, 8 years clinical experience)
	Trial of treatment	'*(My concerns with this approach) are antibiotic resistance and side effects…especially in older groups…I would say probably that is not the best approach'* (P3, GP, 18 years clinical experience)
	Biochemical investigations	'*If I am thinking about doing blood tests…it is unlikely that I am going to continue managing them in the community*' (P11, GP trainee, 6 years clinical experience)
		'*I would never not diagnose somebody (with cellulitis) just because their inflammatory markers are normal*' (P5, acute medicine consultant, 16 years clinical experience)
	Further education	'*You very quickly just get entrenched in…your preferences for diagnoses and it is often good to refresh*' (P11, GP trainee, 6 years clinical experience)
		'*I only did 2 weeks (of dermatology) as a medical student…but certainly increasing dermatology teaching at an earlier stage would make a massive difference'* (P13, GP, 20 years clinical experience).
		'*Pattern recognition and (seeing) variation in the progression of the rash (are important)*', thereby appreciating the '*life of rashes*' (P18, dermatology trainee, 8 years clinical experience).
The need for an objective diagnostic aid	A diagnostic algorithm	'*I think it can be helpful to have those objective measures (of an algorithm), if it was accepted and validated as a reasonable measure of cellulitis, I think I would actually use that*' (P11, GP trainee, 6 years clinical experience).
		'*You would have to develop a criteria that can pick up the beginning, it is in the middle and it is resolving at the end*' (P18, dermatology trainee, 8 years clinical experience).
		'*Because there is such a wide differential…how would you exclude all of those and also it can be quite nonspecific sometimes in the early stages*' (P12, GP locum, 7 years clinical experience).

GP, general practitioner.

aware of mimics have been described in previous review articles.[10] A previous review also described cases of misdiagnosis and emerging approaches to improve diagnoses,[8 15] which were echoed in this study. The diagnostic challenges of infection in primary care, due to atypical presentations and lack of diagnostic tests, have previously been described.[16] Using treatments such as antibiotics as diagnostic aids and discussing with colleagues when uncertain about a diagnosis are common strategies.[17 18] Litigation and fear missing a diagnosis has also been well documented in literature.[19]

Implications for research and practice

This study has highlighted that HCPs need to be aware that cellulitis can present with different features at various stages of the acute episode and need to consider the cellulitis mimics. With a current shift in healthcare resulting in trained nurses now managing more acute presentations,[20] upskilling nurses in cellulitis could be part of the solution.

Many HCPs felt confident in making an accurate diagnosis, often guided by experience and intuition, but found it difficult to verbalise the key distinguishing features.

This makes it difficult for the clinical experience to be shared among other colleagues, especially less experienced or junior HCPs. Acquiring this insight is important to improve diagnostic accuracy, which can prevent avoidable antibiotic prescribing and hospital admissions. To overcome this, further qualitative research is required to identify the clinical reasoning behind the expert process of making a diagnosis, perhaps using clinical cases and pictures. This will form the basis of the proposed solution of focused education and clinical features to be included in a diagnostic aid. The challenge with further education for HCPs is that information needs to be accessible for everyone, while information overload can lead to a reduction in the quality of decisions.[21]

Some indices and risk factors for a diagnostic algorithm have been identified in this study and previous studies,[22] as well as key distinguishing features from differential diagnosis, but these need validating with larger studies and an expert consensus setting exercise.

CONCLUSION

This interview study has shown that cellulitis is a complex diagnosis. Not only does the core features overlap with other diagnoses, the presentation of cellulitis changes as the episode progresses. Although cellulitis is a common diagnosis to make, and while further research in developing diagnostic aids needs to be undertaken, simply being aware of the cellulitis mimics may help improve diagnostic accuracy.

Acknowledgements The authors would like to thank the participants who were interviewed and the professional transcriber Claire Poxon. We also want to thank the Royal College of General Practitioners for supporting this study. The views expressed in this paper are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research or the Department of Health.

Contributors MP was involved with the design of the study, collection and analysis of data, drafting the manuscript and final approval of the manuscript. SIL, NJL, PS, JK, KST and PL were involved with the design of the study, analysis of data, drafting the manuscript and final approval of the manuscript.

Funding This study was supported by the Scientific Foundation Board of the Royal College of General Practitioners (grant SFB 2018-31).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD

Mitesh Patel http://orcid.org/0000-0003-3975-4689

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