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In patients presenting to the emergency department with skin and soft tissue infections what is the diagnostic accuracy of point-of-care ultrasonography for the diagnosis of abscess compared to the current standard of care? A systematic review an meta-analysis

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Keywords: cellulitis, abscess, ultrasound, emergency medicine, diagnosis

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Abstract

Objectives: The primary objective of this systematic review was to determine the accuracy of point-of-care ultrasonography (POCUS) in diagnosing abscess in emergency department (ED) patients with skin and soft tissue infections (SSTI). The secondary objective was the accuracy of POCUS in the paediatric population subgroup.

Setting: Prospective studies set in emergency departments.

Participants: Emergency department patients (adult and paediatric) presenting with SSTI and suspected abscess.

Primary and Secondary Outcome Measures: This systematic review was conducted according to Cochrane Handbook guidelines, and the following databases were searched: Pubmed, Medline, Embase, and the Cochrane database of systematic reviews. The authors included prospective cohort and case-control studies investigating ED patients with SSTI and abscess or cellulitis, a defined POCUS protocol, a clearly defined gold standard for abscess, and a contingency table describing sensitivity and specificity. Two reviewers independently ascertained all potentially relevant citations for methodologic quality according to QUADAS-2 criteria. The primary outcome measure was the sensitivity and specificity of POCUS for abscess. A preplanned subgroup (secondary) analysis examined the effects in paediatric populations, and changes in management was explored post-hoc.

Results: Of 3028 articles, 8 were identified meeting inclusion criteria; all were rated as good to excellent according to QUADAS-2 criteria. Combined test characteristics of POCUS on the ED diagnosis of abscess for patients with SSTI were as follows: sensitivity 96.2%, (95% CI 91.1-98.4)

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specificity 82.9%, (95% CI 60.4-93.9) positive likelihood ratio 5.63, (95% CI 2.2 to 14.6) and

negative likelihood ratio 0.05. (95% CI 0.01 to 0.11)

Conclusions: The use of POCUS helps differentiate abscess from cellulitis in ED patients with

SSTI.

Registration: The protocol for this study was registered *a priori* with the Prospero Registry

[CRD42015017115].

Data Sharing Statement

No additional data available

Strengths and limitations of this study

- Strengths of our study include the exhaustive search strategy, reproducible protocols, and strict adherence to systematic review methodology. The use of standardized and validated data collection and extraction tools limited bias and increased inter-rater reliability.
- Meta-analysis of the 8 studies included in our final review demonstrated a point estimate of 96.2% (95% CI 91.1-98.4) for the sensitivity of POCUS. The point estimate for specificity is 82.9% (95% CI 60.4-93.9).
- Point-of-care ultrasound resulted in management changes—to perform or not perform a drainage—in 14-56% of cases in the reviewed studies.
- Important limitations of our systematic review and meta-analysis include: i) owing to the small number of included studies, assessment of publication bias is difficult and ii) a patient

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<text> presenting with an SSTI may initially have cellulitis but develop an abscess; this is especially important if there was a time lag between the index test and the reference standard.

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Introduction

Skin and soft tissue infections (SSTIs) are a common presenting complaint to the emergency department, (ED) (1) The two most frequently encountered clinical entities are cellulitis and abscesses; the substantial degree of overlap ensures there will be difficulty differentiating the two, (2, 3) and physical examination may be noncontributory, particularly in paediatric populations. (4) Point-of-care ultrasound (POCUS) has been integrated into the training of emergency physicians, (5) and may help identify fluid collections suggestive of abscess to help guide appropriate therapy. To our knowledge, there is one prior systematic review, and no prior meta-analysis on this topic completed to assess the diagnostic accuracy of bedside ultrasound for the diagnosis of abscess in patients presenting with SSTI in the ED. (6) Since abscesses require incision and drainage or needle aspiration, and cellulitis is treated with systemic antibiotics, distinguishing the two is essential. (7) Blind needle aspiration for purulence can be undertaken, but this is a painful and unnecessary procedure in patients with cellulitis only. As a corollary, underappreciating an abscess can lead to inappropriate and ineffective treatment with antibiotics, leading to complications, additional ED visits, and increased cost. (4,7) As ED visits for SSTIs have doubled contemporaneously since the emergence of community acquired methicillin-resistant Staphylococcus aureus (MRSA) in the early 1990s, (1,8) the availability of an objective tool to differentiate an abscess from cellulitis is necessary to optimize patient care. (9)

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The primary objective of this systematic review was to determine the accuracy of POCUS in diagnosing abscess in ED patients with SSTI. The secondary objective was the accuracy of POCUS in the paediatric population subgroup.

Methods

Study Design

The investigators developed a systematic review protocol according to PRISMA guidelines and the Cochrane Handbook, (10) and this was recorded a priori with the Prospero registry. [CRD42015017115] (Data supplement S1) Both the Cochrane Handbook for Diagnostic Test Accuracy Reviews (10) and accepted guidelines were adhered to. (11)

Search Strategy

Investigators searched Ovid MEDLINE, Ovid Embase, and Cochrane Library for journal articles and conference proceedings prior to March 31, 2016. An experienced health sciences librarian assisted with the development of the preliminary search strategy in Ovid MEDLINE based on the research question: What is the accuracy of bedside of ultrasound for diagnosing abscess in the emergency department? The search strategy was independently reviewed by two librarians and validated against a sample result set of twenty-one studies identified by the primary investigator.

The strategy contained three concepts: location where the ultrasound was performed (i.e. in the emergency department), ultrasound of the skin and soft tissues, and the suspected condition (i.e. abscess, cellulitis). Available subject headings and keywords for each concept were combined with "OR;" and search results for each concept area were combined with

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"AND." Resulting references were limited to human studies in adults. No language restrictions were applied.

The librarian adapted the search as minimally as possible before executing it in Ovid Embase and Cochrane Library. Duplicate citations were removed and the final references were delivered to the primary investigator in a format compatible with EndNote citation management software. A search alert in Ovid MEDLINE was enabled to re-run the search on a monthly interval and send the investigator updates of any new publications. (The search strategy is available as Data Supplement S2.)

We used Science Citation Index to retrieve reports citing the relevant articles identified from our search in MEDLINE and EMBASE and then entered relevant studies identifies into PUBMED. We then used the "Related articles" feature as suggested by Sampson and colleagues. (12) We conducted online bibliographic searches of the table of contents for Critical Ultrasound Journal for each issue of the past 5 years. We manually searched the bibliographies of all potential articles (including review articles) to identify articles not identified by our primary search. Our grey literature search included scrutinizing reference lists of potential articles and searches of abstracts of major emergency medicine conferences. (Society of Academic Emergency Medicine, American College of Emergency Physicians, Canadian Association of Emergency Physicians) We contacted abstract authors for further information.

Study Selection

We included prospective cohort and case-control studies evaluating the diagnostic accuracy of POCUS in the diagnosis of abscess in ED patients. Only studies involving patients with SSTI and

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clinical uncertainty regarding abscess or cellulitis were included. The index test was the use of POCUS for the detection of abscess in ED patients with SSTI. We used a combined reference standard of: (1) purulent discharge from and incision and drainage, (2) abscess or cellulitis on computed tomography according to radiologist opinion, or (3) final diagnosis from clinical follow-up. No restriction was made on the protocol of ultrasonography used to diagnose abscess, and no restriction on the type of emergency physician was made. No restriction on the type of machine or transducer used was applied. We excluded case reports, retrospective studies, and other types of case-control studies. In addition, we excluded studies that did not report sensitivity or specificity, or if data could not be extracted to construct a 2x2 table. Finally, we excluded studies including patients in the primary care or inpatient setting.

Data Collection and Processing

Two review authors independently identified potential articles for inclusion by scanning the titles and abstracts of articles [DC, TJ]. Any disagreement was resolved by consensus. When this did not result in agreement, a third reviewer [JC] was involved to reach agreement. Two review authors [DB, FXS] independently extracted data from the selected articles using prepared data extraction sheets. Disagreement was resolved by consensus or by involvement of a third reviewer [JC]. No attempt was made to mask the author's name or the journal's name. A data extraction form was developed and pilot-tested for validity and accuracy. (Supplementary appendix S3) We extracted information on: author, title, journal name, year of publication, study design (prospective cohort, case-control), setting in which the study was conducted,

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protocol of ultrasonography used, reference standard chosen, QUADAS-2 items, (13) and data on sensitivity and specificity or data for 2x2 table if possible.

Outcome Measures

The primary outcome for this study was the sensitivity and specificity of POCUS for the diagnosis of abscess in the ED. Our secondary outcome was the sensitivity and specificity of POCUS in the paediatric population subgroup. A post-hoc secondary outcome was the reported change in management due to POCUS reported in the different studies. This was felt to be a clinically important outcome to include in the final review, which we had not initially included in our systematic review protocol.

Validity Assessments

Two review authors [DB, FXS] independently assessed the methodological quality of each selected article using the QUADAS-list (13) Disagreement was resolved by consensus or involvement of a third reviewer [JC]. The QUADAS-2 assesses 4 potential areas for bias and applicability to the research question. (1) Patient selection: The risk of bias was high if the study was a case-control design, enrolment was nonconsecutive, or the study had inappropriate exclusions. (2) Index test: If the results from incision and draining were incorporated into the US results, the risk of bias was high. (3) References standard: Risk of bias was high if the reference standard could misclassify the target condition, or the reference standard interpreted with knowledge of POCUS results. (4) Flow and timing: The risk of bias was high if not all patients

received the same POCUS protocol, (index test) not all patients received the same reference standard, or not all patients were included in the analysis.

Primary Data Analysis

We presented individual study results graphically by plotting sensitivity and specificity estimates on a forest plot to visually assess for heterogeneity, and on the hierarchical summary receiver-operating characteristic (HSROC) space to visually assess for the presence of a threshold effect. The HSROC may control for the lack of an ideal reference standard, and is recommended in the DTA guidelines. (10)

We explored possible sources of heterogeneity related to spectrum, design characteristics and method of ultrasound used. We combined data for meta-analysis using the HSROC model to obtain summary estimates of the pairs of sensitivity and specificity and a summary line. All data analyses were conducted using Stata (version 11.2, Stata Corp, College Station, TX) and REVMAN (version 5.2, the Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Characteristics of Retrieved Studies

Our search strategy returned a total of 3110 citations, which resulted in 3028 citations once duplicates were removed. After reviewing the abstracts of 70 articles and the full text of 25, we selected eight studies for inclusion in the final systematic review and meta-analysis. (Please see Figure 1 for the PRISMA diagram.)

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The 8 studies included in the final systematic review and meta-analysis contained 747 eligible patients. (14-21) This included 3 studies from the adult ED setting (14-16) and 5 studies from the paediatric ED setting. (17-21) All studies except one (17) were conducted in the United States of America. More detailed characteristics of the included studies are available in Table 1. Analysis of the data extraction process by two independent reviewers [DB, FXS] revealed a Kappa value of 0.8095 (SE 0.25).

Quality of Included Studies

Assessment of the methodologic quality of the 8 included studies using the QUADAS tool (13) revealed most of the studies to be of moderate to high quality [Figure 2].

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Main Results

The sensitivity of POCUS in the 8 included studies ranged from 65.0% to 100%, and the specificity from 30.0% to 100% (Figure 3). Meta-analysis of the 8 studies included in our final review demonstrated a point estimate of 96.2% (95% Cl 91.1-98.4) for the sensitivity of POCUS. The point estimate for specificity is 82.9% (95% Cl 60.4-93.9). (Figure 4) The positive likelihood ratio (LR) was 5.6 (95% Cl 2.2-14.6) and the negative LR was 0.05 (95% Cl .02-.11). The pre-planned, sub-group analysis of paediatric patients demonstrated similar point estimates for sensitivity 94.9% (95% Cl 88.0-97.8), and specificity 83.1% (95% Cl 46.6-96.5). The positive LR for paediatric patients was 5.6 (95% Cl 1.4-22.9) and the negative LR was 0.06 (95% Cl .03-.13).

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Analysis of the Cooks distance for potential influence on the final HSROC point estimates was conducted. Two studies, Marin et al (15) and Tayal et al (19), demonstrated CooksD values greater than 1. (22)

Data supporting changed management (to perform or not perform a drainage) after POCUS was provided in five of seven studies. (14,15,18,20,21) In studies of paediatric patients, the rate of management change ranged from 14-27%. (18,20,21) The proportion of patients who were initially determined to need drainage based on clinical exam and who subsequently ended up not receiving a drainage based on POCUS findings ranged from 12-20%. (18,20) The proportion of patients who ended up receiving a drainage based on POCUS findings after initially being determined not to require drainage ranged from 13-18%. (18,20) Sivitz and colleagues found that management changes occurred most often in the quintiles representing equivocal pre-test probabilities (i.e. 2-3 out of 5) in 36% of cases.(18) Similarly, Adams et al. demonstrated that POCUS changed management most often in the context of an equivocal physical exam for the presence of abscess or when the pre-test probability of abscess was not high (<90%). (21) Studies in adults demonstrated a slightly higher rate of change in management ranging from 17-56%. (14,15) The proportion of patients who received unplanned drainage after POCUS ranged from 23-40%. (14,15) The proportion of patients who did not receive drainage despite being determined to require it after clinical exam ranged from 12-36%. Separating the pre-test probabilities of the presence of abscess into deciles, it was found that POCUS had an effect on management at every decile from 10 to 90%. (14) Since the study by Marin and colleagues blinded treating physicians to POCUS results, changes in management were unable to be determined. (19)

Discussion

The primary objective was to assess the test accuracy of POCUS to diagnose abscess in ED patients with SSTI. Although the 8 studies differed in terms of sensitivity and specificity, the pooled estimates of 96.2% (95% CI 91.1-98.4) sensitivity and 82.9% (95% CI 60.4-93.9) specificity are favorable. This assists clinicians by demonstrating that POCUS, a rapid, noninvasive, painless, easily repeatable test, can distinguish between abscess and cellulitis in the vast majority of cases. This could provide a greater degree of diagnostic certainty in SSTI patients presenting with equivocal signs and symptoms, thus leading to appropriate therapy more rapidly.

Our findings are particularly important in children, who may not tolerate physical examination, blood testing, and needle aspiration as readily as adults. In our planned subgroup analysis, paediatric patients demonstrated similar point estimates for sensitivity 94.9% (95% CI 88.0-97.8), and specificity 83.1% (95% CI 46.6-96.5). This may provide paediatricians and emergency physicians caring for children with an additional valuable to tool to discern between cellulitis and abscess in children with equivocal signs and symptoms.

A recent review by Alsaawi et al examined this same topic, however we feel that our study is stronger for several important reasons. (6) In our study, two independent reviewers screened all titles for inclusion, potentially minimizing selection bias. In our study, we included the same five studies as Alsaawi et al, and two additional studies, (17,21) one of which was unpublished at the time of the Alsaawi study. In addition, in our study we were able to conduct a

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quantitative synthesis (meta-analysis) of the available data to provide accurate point estimates of the sensitivity and specificity of POCUS in patients with SSTI in the ED.

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Point-of-care ultrasound resulted in management changes—to perform or not perform a drainage—in 14-56% of cases in the reviewed studies. (14,15,18,20,21) The Infectious Disease Society of America defines abscesess as "painful, tender, and fluctuant red nodules, often surmounted by a pustule and surrounded by a rim of erythematous swelling." (23) This simplistic definition is challenged by the high rates of management change born out of these studies. This implies that the clinical exam is neither sensitive nor specific for detecting abscesses. In the Tayal et al. study physicians had an error rate of 30-50% regardless of pre-test probability of abscess based on clinical assessment. (15) For instance, fluctuance is an imprecise indicator of abscess as only six out of 17 patients who underwent drainage of neck abscesses had fluctuance on exam. (17) We demonstrate that POCUS can accurately diagnose abscess in paediatric and adult populations and is likely superior to clinical examination. Adams et al. suggested that change in management occurred in one in four ultrasound studies performed. (21) The issue of whether or not patient outcomes are impacted by identifying the presence or absence of an abscess has received little study. Three studies stated that small

abscesses (e.g. <0.3 mL volume) were deemed too small to drain and only received medical therapy. (18-20) Only Sivitz et al. investigated longer term outcomes and found that there were no return visits to the emergency department in these patients. (18) It is unknown whether there is a size at which abscesses become clinically significant. Decisions to not drain small abscesses are based on clinical context and expert opinion. Cellulitis and abscess exist on a spectrum of disease in skin and soft tissue infections and can evolve over time. Seven patients Page 15 of 45

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with an initial diagnosis of cellulitis without abscess remained febrile despite antibiotic treatment 72 hours after initial treatment. Six of seven ended up receiving an incision and drainage after a repeat ultrasound demonstrated an abscess. (17) What remains unknown is what, if any, the clinical significance of these management changes are—it is possible that unrecognized abscesses treated medically with antibiotics will resolve with no sequelae. The utility of POCUS in preventing invasive procedures is more compelling, especially in paediatric populations where principles of reducing painful procedures and avoiding sedation and its associated risks are relevant. (24) A study of adults demonstrated that invasive drainage was prevented most often in those with high pre-test probabilities of abscess. (15) Thus, a clinical approach of performing POCUS on patients before proceeding with a drainage attempt is justifiable. Further study on the impact of more accurate abscess diagnosis because of POCUS on patient-oriented outcomes is needed.

Strengths of our study include the exhaustive search strategy, reproducible protocols, and adherence to systematic review methodology. The use of standardized and validated data collection and extraction tools limited bias and increased inter-rater reliability. In summary, the evidence suggests that POCUS can accurately distinguish between cellulitis and abscess in the ED. The accuracy was similar between the adult and paediatric patient population. Further studies are needed to determine the impact of adding POCUS to the clinical assessment of patients presenting with SSTI.

Limitations

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> A number of issues warrant notice. Owing to the small number of included studies, assessment of publication bias is difficult. It is important to note that different protocols and different reference standards introduce heterogeneity.

A key element is timing: a patient presenting with an SSTI may initially have cellulitis but develop an abscess; this is especially important if there was a time lag between the index test and the reference standard. SSTI in different anatomic locations may predispose to abscess or cellulitis, as could pre-existing trauma or surgery, and there is no way to ascertain potential direction of bias.

Contributorship Statement

DB and DC conceived the study. DB, DC, JC and TJ developed the protocol, and DB built the search strategy with a health sciences librarian. DC and TJ screened citation titles, JC and FXS screened abstracts and full texts. DB and DC conducted the analysis, and all authors made significant contributions to the draft and final versions of the manuscript.

Competing Interests

The authors have no competing interests to declare.

Funding

The authors received no funding to conduct this study.

Data Sharing Statement

No additional data available

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141x291mm (72 x 72 DPI)

Table 1

	Quraishi	Squire	Tayal	Sivitz	Berger	lverson	Marin	Adams
Year of publication	1997	2005	2006	2010	2012	2012	2013	2016
Journal	Clinical Otolaryngology	Academic Emergency Medicine	Academic Emergency Medicine	Journal of Emergency Medicine	American Journal of Emergency Medicine	American Journal of Emergency Medicine	Academic Emergency Medicine	Journal of Pediatrics
Country of study	Ireland	USA	USA	USA	USA	USA	USA	USA
Patient population	Pediatric ED	ED	ED	Pediatric ED	ED	Pediatric ED	Pediatric ED	Pediatric ED
Number of patients (lesions)	23 (23)	107 (107)	126 (126)	50 (50)	40 (40)	65 (65)	755 (873)	148 (151)
Number and type of operators	Unknown	Unknown number of emergency physicians and residents	5 emergency physicians	1 pediatric emergency physician and 1 fellow	Unknown number of Emergency physicians and residents	Unknown number of pediatric emergency physicians and fellows	8 pediatric emergency physicians or fellows	8 pediatric emergency physicians, 2 pediatric emergency medicine fellows
Soft tissue ultrasound training or qualifications	Unknown	30 minutes of didactic and hands- on training	At least five supervised soft tissue scans	30 minute didactic, at least 5 soft tissue scans	15 minute didactic session	2 60-minute didactic and hands-on training sessions repeated quarterly	6-hour training including lecture and hands-on practice	1-2 day course, plus at least 25 abscess scans reviewed by ultrasound director
Quality assurance of scans	Unknown	Unknown	Unknown	Images recorded and inter- rater agreement	None	Interrater reliability checked throughout study	75% of scans reviewed by blinded sonologist	10% of scans repeated by second operator

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				measured				
Blinding	No	Unclear	Treating clinicians blinded, data collection unblinded	Intermittent	Yes	Intermittent	Yes	Treating clinicians unblinded; ultrasonographers blinded
US machine and probe	Unclear	BK Hawk 2102 8MHz linear; Sonosite Titan 10Mhz linear	Shimadzu model 400 & 450 7.5Mhz linear	Sonosite Micromaxx 8-13Mhz linear	Sonosite Turbo or Micromaxx 10Mhz linear	Siemen Sonoline G605 linear	Sonosite Micromaxx 6-13Mhz or 5-10 10Mhz linear, or 2- 5Mhz curved array	Sonosite Edge 6- 13Mhz linear
US protocol	unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reference standard	Positive I&D	Positive I&D and follow- up	Unclear	Positive I&D	Positive I&D	Positive I&D	Positive I&D and follow- up	I&D or follow-up
Industry sponsored	Unclear	No	No	No	No	No	Unclear	Unclear
Time to complete US study	Unclear	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded	Unclear	Not recorded
Prospective or retrospective	prospective	Prospective	Prospective	Prospective	Prospective	Prospective	Prospective	Prospective

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	Figure 2 - Forest plot of studies included in the final analysis
	261x63mm (72 x 72 DPI)



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Figure 3 - QUADAS-2 assessment of methodologic quality of studies included in the final analysis [part 1]

162x160mm (72 x 72 DPI)



Figure 3 - QUADAS-2 assessment of methodologic quality of studies included in the final analysis [part 2]

ant .





Figure 4 - HSROC curve of the studies included in the final analysis

229x246mm (72 x 72 DPI)

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PROSPERO International prospective register of systematic reviews

Review title and timescale

UNIVERSITY of Jork

Centre for Reviews and Dissemination

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review. Point-of-care ultrasonography for the diagnosis of abscess in patients presenting with skin and soft tissue infections to the emergency department.

2 Original language title

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

- 3 Anticipated or actual start date Give the date when the systematic review commenced, or is expected to commence. 01/02/2015
- 4 Anticipated completion date Give the date by which the review is expected to be completed. 01/02/2016
- 5 Stage of review at time of this submission

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact

The named contact acts as the guarantor for the accuracy of the information presented in the register record. David Barbic

- 7 Named contact email Enter the electronic mail address of the named contact. david.barbic@ubc.ca
- Named contact address
 Enter the full postal address for the named contact.
 Emergency Department St Paul's Hospital 1081 Burrard St Vancouver, BC CANADA V6Z 1Y6
- Named contact phone number
 Enter the telephone number for the named contact, including international dialing code.
 604-682-2344
- 10 Organisational affiliation of the review Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

UN Cer	IVERSI Intre for R	TY of York eviews and Dis	semination	NHS National Institute for Health Research			
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11	Review te Give the ti organisatio	eam members and tle, first name and la onal affiliations of ea	their organisational st name of all member ch member of the revie	affiliations s of the team working directly on the review. Give the ew team.			
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12	Funding s Give detai managing individuals No funding	sources/sponsors Is of the individuals, , sponsoring and/or f s or bodies listed sho g	organizations, groups inancing the review. Al uld be included.	or other legal entities who take responsibility for initiating, ny unique identification numbers assigned to the review by the			
13	Conflicts List any co investigate Are there a None know	of interest onditions that could le ed in the review. any actual or potenti wn	ead to actual or perceiv al conflicts of interest?	ved undue influence on judgements concerning the main topic			
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15	Review q State the o To investion presenting	uestion(s) question(s) to be add gate the sensitivity a g with skin and soft ti	Iressed / review object nd specificity of bedsid ssue infections in patie	ives. Please complete a separate box for each question. e ultrasonography for the diagnosis of abscess in patients ents presenting to the emergency department.			
16	Searches Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment. Investigators will search Ovid MEDLINE, Ovid Embase, and Cochrane Library for journal articles and conference proceedings. An experienced health sciences librarian will develop a preliminary search strategy in Ovid MEDLINE based on the research question: What is the accuracy of bedside of ultrasound for diagnosing abscess in the emergency department? The search strategy will be independently reviewed by two librarians and validated against a sample result set of twenty-one studies identified by the primary investigator. We will use Science Citation Index to retrieve reports citing the relevant articles identified from our search in MEDLINE and EMBASE and then we will enter relevant studies identifies into PUBMED and then use the Related articles feature as suggested by Sampson and colleagues [13]. We will conduct online bibliographic searches of the table of contents for Critical Ultrasound Journal, done in the past 5 years. We will search manually the bibliographies of all potential articles (including review articles) to identify articles not identified by our primary search.						
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NHS National Institute for Health Research

Yes

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18 Condition or domain being studied Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes. Skin and soft tissue infections 19 Participants/population Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria. Patients presenting to the emergency department 20 Intervention(s), exposure(s) Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed Point-of-care ultrasonography for the differentiation of cellulitis and abscess 21 Comparator(s)/control Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). Computed tomography, results from incision and drainage, or final diagnosis from clinical follow-up will be accepted as reference standards. Types of study to be included initially 22 Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated. Prospective cohorts, case controls, and randomized controlled trials 23 Context Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria. All patients presenting to the emergency department with suspected skin and soft tissue infections 24 Primary outcome(s) Give the most important outcomes. Diagnosis of abscess vs cellulitis Give information on timing and effect measures, as appropriate. 25 Secondary outcomes List any additional outcomes that will be addressed. If there are no secondary outcomes enter None. Time to conduct point-of-care ultrasonography Give information on timing and effect measures, as appropriate. 26 Data extraction, (selection and coding) Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted. Two review authors will independently identify potential articles for inclusion by scanning the titles and abstracts of articles. Any disagreement will be resolved by consensus or by involvement of a third reviewer. Two review authors will independently extract data from the selected articles using prepared data extraction sheets. Any disagreement will be resolved by consensus or by involvement of a third reviewer. No attempt will be made to mask the author's name or the journal's name during data extraction and management. We will extract information on: author, title, journal name, year of publication, study design (prospective cohort, case-control), setting in which the study was conducted, protocol of ultrasonography used, reference standard chosen, QUADAS-2 items{Whiting:2011hx}, and data on sensitivity and specificity or data for 2x2 table if possible. We will also adhere to guidelines for systematic reviews and meta-analyses of DTA set forth previously. 27 Risk of bias (quality) assessment State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis. Two review authors will independently assess the methodological quality of each selected article using the QUADAS-

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	list{Whiting:2011hx}. Any disagreement will be resolved by consensus or involvement of a	third reviewer.
28	Strategy for data synthesis Give the planned general approach to be used, for example whether the data to be used w level of individual participants, and whether a quantitative or narrative (descriptive) synthes appropriate a brief outline of analytic approach should be given. We will present individual study results graphically by plotting sensitivity and specificity esti- visually assess for heterogeneity, and on the ROC space to visually assess for the present will meta-analyze, if appropriate using the HSROC model to obtain summary estimates of to specificity and a summary line.	ill be aggregate or at the sis is planned. Where mates on a forest plot, to be of a threshold effect. We she pairs of sensitivity and
29	Analysis of subgroups or subsets Give any planned exploration of subgroups or subsets within the review. 'None planned' is subgroup analyses are planned. We will explore possible sources of heterogeneity related to spectrum, design characteristic ultrasound used, specifically: Patient population: We hypothesize that no difference in test ultrasound studies performed in adult and child patients. We will formally explore sources of model, by adding covariates indicating patient, method of ultrasound used or design feature explore whether, on average, studies that differ with respect to these features result in differ diagnostic accuracy.	a valid response if no cs and method of accuracy will exist between of variation in the HSROC es. This will enable us to erent estimates of
Rev	view general information	
30	Type of review Select the type of review from the drop down list. Diagnostic	
31	Language Select the language(s) in which the review is being written and will be made available, from the control key to select more than one language. English	n the drop down list. Use
	Will a summary/abstract be made available in English? Yes	
32	Country Select the country in which the review is being carried out from the drop down list. For mult select all the countries involved. Use the control key to select more than one country. Canada	ti-national collaborations
33	Other registration details List places where the systematic review title or protocol is registered (such as with he Cam Joanna Briggs Institute). The name of the organisation and any unique identification number by that organization should be included.	pbell Collaboration, or The er assigned to the review
34	Reference and/or URL for published protocol Give the citation for the published protocol, if there is one. Give the link to the published protocol, if there is one. This may be to an external site or to CRD in pdf format.	a protocol deposited with
	l give permission for this file to be made publicly available Yes	
35	Dissemination plans Give brief details of plans for communicating essential messages from the review to the ap Presentation at scientific meetings for emergency medicine and publication in emergency r	propriate audiences. nedicine journal(s)
	Do you intend to publish the review on completion? Yes	

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Centre for Reviews and Dissemination Keywords Give words or phrases that best describe the review. (One word per box, create a new box for each term) ultrasound skin and soft tissue infection cellulitis abscess emergency medicine Details of any existing review of the same topic by the same authors Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. Current review status Review status should be updated when the review is completed and when it is published. Ongoing Any additional information Provide any further information the review team consider relevant to the registration of the review. Details of final report/publication(s) This field should be left empty until details of the completed review are available. Give the full citation for the final report or publication of the systematic review. Give the URL where available.

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PROTOCOL

Point-of-care ultrasonography for the diagnosis of abscess in patients presenting with skin and soft tissue infections to the emergency department.

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Abstract:

This is a protocol for a review and there is no abstract. The objectives are as follows:

To investigate the sensitivity and specificity of bedside ultrasonography for the diagnosis of abscess in patients presenting with skin and soft tissue infections in patients presenting to the emergency department.

We will also investigate how test accuracy varies with the patient population (adult vs paediatric).

Background:

Skin and soft tissue infections (SSTIs) are a common presenting complaint to the emergency department (ED) (1). Cellulitis and abscess represent the most commonly encountered entities along the spectrum of SSTIs in the ED. Even the most seasoned emergency physician may have difficulty differentiating between these two because they share similar clinical features and often co-exist(2, 3). Physical examination is not always helpful because the presence of edema, induration and/or pain can make palpation of an abscess difficult, particularly in the pediatric populations (4).

Differentiation between cellulitis and abscess is essential to choose the appropriate therapy. Abscesses require incision and drainage or needle aspiration, while cellulitis is treated with systemic antibiotics(5). Classical teaching suggests that blind, needle-aspiration for purulent material should be undertaken in cases of diagnostic uncertainty. In patients with cellulitis but no abscess, this represents an unnecessary and uncomfortable procedure. This is of particular concern in pediatric populations who may be subjected to unnecessary sedation(4). On the other hand, misdiagnosis of an abscess can lead to inappropriate and ineffective treatment with antibiotics, medical complications, additional ED visits and increased cost(4, 5).

Emergency department visits for SSTIs have doubled contemporaneously since the emergence of community acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in the early 1990s(1,6). This organism has been implicated in the increasing incidence of purulent abscesses in many centres (1). The increasing skin prevalence of abscess-forming organisms such as MRSA makes the availability of an objective tool to differentiate an abscess from cellulitis even more appealing and necessary to provide optimal patient care (7).

Bedside ultrasound (US) has been integrated into the training of emergency physicians (8). Bedside US may provide the ability to identify fluid collections suggestive of abscess and can help guide appropriate therapy. To our knowledge, no systematic review has been completed to assess the diagnostic accuracy of bedside ultrasound for the diagnosis of abscess in patients presenting with skin and soft tissue infections in the ED.

Objectives:

Primary objective:

To investigate the sensitivity and specificity of bedside ultrasonography for the diagnosis of abscess in patients presenting with skin and soft tissue infections in patients presenting to the emergency department.

Secondary objective (see investigation of sources of heterogeneity section for details):

We will also investigate how test accuracy varies with the patient population (adult vs paediatric) if possible.

Methods:

Criteria for considering studies for this review:

Type of studies:

Studies evaluating the diagnostic accuracy of bedside ultrasonography in the diagnosis of abscess in the emergency department will be included. Prospective cohort and case-control studies will be included. Case reports, retrospective studies and other types of case-control studies will be excluded. Studies that do not report sensitivity and specificity, or studies in which data could not be extracted to construct a 2x2 table for true positives, true negatives, false positives, and false negatives, after contacting the authors, will be excluded.

Participants:

Studies including patients in the primary care setting or inpatients with skin and soft tissue infections will not be included.

Index test:

Bedside ultrasonography for detection of abscess in patients presenting with skin and soft tissue infections in patients presenting to the emergency
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data mining, AI training, and similar technologies

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department. No restriction will be made on the protocol of ultrasonography used to diagnose abscess. No restriction on the type of machine or transducer used will be applied.

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Comparator test:

None

Target condition:

The target condition for this review will be abscess in patients presenting with skin and soft tissue infections in patients presenting to the emergency department.

Reference standards:

Computed tomography, results from incision and drainage, or final diagnosis from clinical follow-up will be accepted as reference standards.

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Search methods:

Electronic search:

Investigators will search Ovid MEDLINE, Ovid Embase, and Cochrane Library for journal articles and conference proceedings. An experienced health sciences librarian will develop a preliminary search strategy in Ovid MEDLINE based on the research question: *What is the accuracy of bedside of ultrasound for diagnosing abscess in the emergency department?* The search strategy will be independently reviewed by two librarians and validated against a sample result set of twenty-one studies identified by the primary investigator.

The strategy will contain three concepts: location where the ultrasound was performed (i.e. in the emergency department), ultrasound of the skin and soft tissues, and the suspected condition (i.e. abscess, cellulitis). Available subject headings and keywords for each concept will be combined with "OR;" and search results for each concept area will be combined with "AND." Resulting references will be limited to human studies in adults. No language restrictions will be applied.

The librarian will adapt the search as minimally as possible before executing it in Ovid Embase and Cochrane Library. Duplicate citations will be removed and final references delivered to the primary investigator in a format compatible with EndNote citation management software. A search alert in Ovid MEDLINE will be enabled to re-run the search on a monthly interval and send the investigator updates of any new publications.

Searching other sources:

We will use Science Citation Index to retrieve reports citing the relevant articles identified from our search in MEDLINE and EMBASE and then we will enter relevant studies identifies into PUBMED and then use the Related articles feature as suggested by Sampson and colleagues [13].

We will conduct online bibliographic searches of the table of contents for *Critical Ultrasound Journal*, done in the past 5 years.

We will search manually the bibliographies of all potential articles (including review articles) to identify articles not identified by our primary search.

Data collection and analysis:

Selection of studies:

Two review authors will independently identify potential articles for inclusion by scanning the titles and abstracts of articles. Any disagreement will be resolved by consensus or by involvement of a third reviewer.

Data extraction and management:

Two review authors will independently extract data from the selected articles using prepared data extraction sheets. Any disagreement will be resolved by consensus or by involvement of a third reviewer. No attempt will be made to mask the author's name or the journal's name during data extraction and management. We will extract information on: author, title, journal name, year of publication, study design (prospective cohort, case-control), setting in which the study was conducted, protocol of ultrasonography used, reference standard chosen, QUADAS-2 items{Whiting:2011hx}, and data on sensitivity and specificity or data for 2x2 table if possible. We will also adhere to guidelines for systematic reviews and meta-analyses of DTA set forth previously.{JB:2009wc, Leeflang:2008vn}

Assessment of methodological quality:

Two review authors will independently assess the methodological quality of each selected article using the QUADAS-list{Whiting:2011hx}. Any disagreement will be resolved by consensus or involvement of a third reviewer.

Statistical analysis and data synthesis:

We will present individual study results graphically by plotting sensitivity and specificity estimates on a forest plot, to visually assess for heterogeneity, and on the ROC space to visually assess for the presence of a threshold effect. We will meta-analyze, if appropriate using the HSROC model to obtain summary estimates of the pairs of sensitivity and specificity and a summary line.

Investigation of heterogeneity:

We will explore possible sources of heterogeneity related to spectrum, design characteristics and method of ultrasound used, specifically:

1. Patient population: We hypothesize that no difference in test accuracy will exist between ultrasound studies performed in adult and child patients.

We will formally explore sources of variation in the HSROC model, by adding covariates indicating patient, method of ultrasound used or design features. This will enable us to explore whether, on average, studies that differ with respect to these features result in different estimates of diagnostic accuracy.

References:

- 1. Sampson M, Shojania, KG., McGowan, J. et al. Surveillance search techniques identified the need to update systematic reviews. *Journal of Clinical Epidemiology*, 2008. *61*(8), 755–762.
- 2. Whiting, P, Rutjes, AW, Reitsma, JB, et al. *BMC Medical Research Methodology*, 2003. *3*(1), 25.

Intro References

- 1. Hersh AL, Chambers HF, Maselli JH, Gonzales R. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. Arch Intern Med. 2008 Jul 28;168(14):1585–91.
- 2. Swartz MN. Clinical practice. Cellulitis. N Engl J Med. 2004 Feb 26;350(9):904–12.
- Holtzman LC, Hitti E, Harrow J. Chapter 37 Incision and Drainage. Roberts & Hedges Clinical Procedures in Emergency Medicine, 6th Edition, 2014.
- 4. Iverson K, Haritos D, Thomas R, Kannikeswaran N. The effect of bedside ultrasound on diagnosis and management of soft tissue infections in a pediatric ED. Am J Emerg Med. Elsevier Inc; 2012 Oct 1;30(8):1347–51.
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- 8. Counselman FL, Sanders A, Slovis CM, Danzl D, Binder LS, Perina DG. The status of bedside ultrasonography training in emergency medicine residency programs. Acad Emerg Med. 2003 Jan;10(1):37–42.

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Data Supplement S2

MEDLINE Search strategy

- 1. exp Soft Tissue Infections/
- 2. exp cellulitis/ or exp skin diseases/
- 3. soft tissue*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
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- 5. exp Suppuration/
- 6. abscess*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 7. suppurat*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 8. cutaneous.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 9. or/1-8
- 10. exp Ultrasonography/
- 11. ultrasound.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 12. us.fs.
- 13. 10 or 11 or 12
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- 15. exp Emergency Medicine/
- 16. exp Emergency Service, Hospital/
- 17. emergenc*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 18. 15 or 16 or 17
- 19. 14 and 18
- 20. 5 or 6 or 7
- 21. 1 or 2 or 3 or 4 or 8
- 22. 13 and 20 and 21
- 23. 22 not19.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 24. 22 not 19
- 25. 9 and 13
- 26. 25 and 20
- 27. 19 or 24

EMBASE

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PRISMA 2009 Checklist

4 5 Section/topic 6	#	Checklist item	Reported on page #			
g Title	1	Identify the report as a systematic review, meta-analysis, or both.	1			
2 Structured summary 3 Structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, 4 participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and 5 implications of key findings; systematic review registration number.						
17 Rationale	3	Describe the rationale for the review in the context of what is already known.	3			
16 19 Objectives 20	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3			
22 23 Protocol and registration 24	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5			
2 ⁵ Eligibility criteria 26 27	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7			
28 28 Information sources 29	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6			
30 Search 31	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6			
32 33 Study selection 34	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7			
35 Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7			
38 Data items 39	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7			
40 Risk of bias in individual 41 studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8			
43 Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9			
44 45 46	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	9			
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PRISMA 2009 Checklist

		Page 1 of 2						
Section/topic	#	Checklist item	Reported on page #					
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8					
Additional analyses	16	scribe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating ich were pre-specified.						
³ RESULTS								
5 Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9,10					
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9,10					
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10					
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.						
4 Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.						
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10					
7 Additional analysis	dditional analysis 23 Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).		11					
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12					
3 Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15					
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.						
Ծ Գ Funding Փ	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15					

42 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. 43 doi:10.1371/journal.pmed1000097

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In patients presenting to the emergency department with skin and soft tissue infections what is the diagnostic accuracy of point-of-care ultrasonography for the diagnosis of abscess compared to the current standard of care? A systematic review and meta-analysis.

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Keywords:	Ultrasound < RADIOLOGY & IMAGING, ACCIDENT & EMERGENCY MEDICINE, INFECTIOUS DISEASES

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In patients presenting to the emergency department with skin and soft tissue infections what is the diagnostic accuracy of point-of-care ultrasonography for the diagnosis of abscess compared to the current standard of care? A systematic review and metaanalysis

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Keywords: cellulitis, abscess, ultrasound, emergency medicine, diagnosis

Word Count: 2973 [excluding Abstract, Strengths and Limitations, References]

Abstract

Objectives: The primary objective of this systematic review was to determine the accuracy of point-of-care ultrasonography (POCUS) in diagnosing abscess in emergency department (ED) patients with skin and soft tissue infections (SSTI). The secondary objective was the accuracy of POCUS in the paediatric population subgroup.

Setting: Prospective studies set in emergency departments.

Participants: Emergency department patients (adult and paediatric) presenting with SSTI and suspected abscess.

Primary and Secondary Outcome Measures: This systematic review was conducted according to Cochrane Handbook guidelines, and the following databases were searched: Pubmed, MEDLINE, EMBASE, and the Cochrane database of systematic reviews (1946-2015). We included prospective cohort and case-control studies investigating ED patients with SSTI and abscess or cellulitis, a defined POCUS protocol, a clearly defined gold standard for abscess, and a contingency table describing sensitivity and specificity. Two reviewers independently ascertained all potentially relevant citations for methodologic quality according to QUADAS-2 criteria. The primary outcome measure was the sensitivity and specificity of POCUS for abscess. A preplanned subgroup (secondary) analysis examined the effects in paediatric populations, and changes in management were explored post-hoc.

Results: Of 3028 articles, 8 were identified meeting inclusion criteria; all were rated as good to excellent according to QUADAS-2 criteria. Combined test characteristics of POCUS on the ED diagnosis of abscess for patients with SSTI were as follows: sensitivity 96.2%, (95% CI 91.1-98.4)

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specificity 82.9%, (95% CI 60.4-93.9) positive likelihood ratio 5.63, (95% CI 2.2 to 14.6) and negative likelihood ratio 0.05. (95% CI 0.01 to 0.11)

Conclusions: A total of 8 studies of good to excellent quality were included in this review. The

use of POCUS helps differentiate abscess from cellulitis in ED patients with SSTI.

Registration: The protocol for this study was registered *a priori* with the Prospero Registry

[CRD42015017115].

Data Sharing Statement

No additional data available

Strengths and limitations of this study

- Strengths of our study include the exhaustive search strategy, reproducible protocols, and strict adherence to systematic review methodology. The use of standardized and validated data collection and extraction tools limited bias and increased inter-rater reliability.
- Important limitations of our systematic review and meta-analysis include: i) owing to the small number of included studies, assessment of publication bias is difficult and ii) a patient presenting with an SSTI may initially have cellulitis but develop an abscess; this is especially important if there was a time lag between the index test and the reference standard.

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Introduction

Skin and soft tissue infections (SSTIs) are a common presenting complaint to the emergency department(ED). (1) The two most frequently encountered clinical entities are cellulitis and abscesses. Substantial degrees of overlap between the clinical presentation of cellulitis and abscesses frequently creates clinical uncertainty in differentiating the two conditions., (2, 3) This is notably true for specific populations including pediatrics, where physical examination may be noncontributory (4) Since abscesses require incision and drainage or needle aspiration, and cellulitis is treated with systemic antibiotics, distinguishing the two is essential. (5) Blind needle aspiration for purulence can be undertaken, but this is a painful and unnecessary procedure in patients with cellulitis only. As a corollary, underappreciating an abscess can lead to inappropriate and ineffective treatment with antibiotics, leading to complications, additional ED visits, and increased cost. (4,5) As ED visits for SSTIs have doubled contemporaneously since the emergence of community acquired methicillin-resistant Staphylococcus aureus (MRSA) in the early 1990s, (1,6) the availability of an objective tool to differentiate an abscess from cellulitis is necessary to optimize patient care. (7)

In patients presenting with SSTI, the treatment of cellulitis and abscess differs substantially. As a result, a high level of diagnostic accuracy is important to inform correct treatment for patients presenting with each condition. Point-of-care ultrasound (POCUS) has been integrated into the training of emergency physicians (8). POCUS has been hypothesized to help identify fluid collections suggestive of abscess to help guide appropriate therapy.(9) To our knowledge, there is one prior systematic review from 2015,(10) and no prior meta-analysis on this topic

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completed to assess the diagnostic accuracy of bedside ultrasound for the diagnosis of abscess in patients presenting with SSTI in the ED. (10)

The primary objective of this systematic review was to determine the accuracy of POCUS in diagnosing abscess in ED patients with SSTI. The secondary objective was the accuracy of POCUS in the paediatric population subgroup.

Methods

Study Design

The investigators developed a systematic review protocol according to PRISMA guidelines (11) and the Cochrane Handbook, (12) and this was recorded *a priori* with the Prospero registry. [CRD42015017115] (Data supplement S1) Both the Cochrane Handbook for Diagnostic Test Accuracy Reviews (12) and accepted guidelines were adhered to. (13)

Search Strategy

Investigators searched Ovid MEDLINE, Ovid EMBASE, and Cochrane Library for journal articles and conference proceedings prior to March 31, 2016. An experienced health sciences librarian assisted with the development of the preliminary search strategy in Ovid MEDLINE based on the research question: *What is the accuracy of bedside of ultrasound for diagnosing abscess in the emergency department?* The search strategy was independently reviewed by two medical librarians and validated against a sample result set of twenty-one studies identified by the primary investigator.

The librarian adapted the search as minimally as possible before executing it in Ovid Embase and Cochrane Library. Duplicate citations were removed and the final references were

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delivered to the primary investigator in a format compatible with EndNote[®] citation management software. A search alert in Ovid MEDLINE was enabled to re-run the search on a monthly interval and send the investigator updates of any new publications. (The search strategy is available as Data Supplement S2.)

We used Science Citation Index to retrieve reports citing the relevant articles identified from our search in MEDLINE and EMBASE and then entered relevant studies identifies into Pubmed. We then used the "Related articles" feature as suggested by Sampson and colleagues. (14) We conducted online bibliographic searches of the table of contents for Critical Ultrasound Journal for each issue of the past 5 years. We manually searched the bibliographies of all potential articles (including review articles) to identify articles not identified by our primary search. Our grey literature search included scrutinizing reference lists of potential articles and searches of abstracts of major emergency medicine conferences (Society of Academic Emergency Medicine, American College of Emergency Physicians, Canadian Association of Emergency Physicians). We contacted abstract authors for further information.

Study Selection

We included prospective cohort and case-control studies evaluating the diagnostic accuracy of POCUS in the diagnosis of abscess in ED patients. Only studies involving patients with SSTI and clinical uncertainty regarding abscess or cellulitis were included. The index test was the use of POCUS for the detection of abscess in ED patients with SSTI. We used a combined reference standard of: (1) purulent discharge from and incision and drainage, (2) abscess or cellulitis on computed tomography according to radiologist opinion, or (3) final diagnosis from clinical

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follow-up. No restriction was made on the protocol of ultrasonography used to diagnose abscess, and no restriction on the type of emergency physician was made. No restriction on the type of machine or transducer used was applied. We excluded case reports, retrospective studies, and other types of case-control studies. In addition, we excluded studies that did not report sensitivity or specificity, or if data could not be extracted to construct a 2x2 table. Finally, we excluded studies including patients in the primary care or inpatient setting.

Data Collection and Processing

Two review authors independently identified potential articles for inclusion by scanning the titles and abstracts of articles [DC, TJ]. Any disagreement was resolved by consensus. When this did not result in agreement, a third reviewer [JC] was involved to reach agreement. Two review authors [DB, FXS] independently extracted data from the selected articles using prepared data extraction sheets. Disagreement was resolved by consensus or by involvement of a third reviewer [JC]. No attempt was made to mask the author's name or the journal's name. A data extraction form was developed and pilot-tested for validity and accuracy. (Data Supplement S3) We extracted information on: author, title, journal name, year of publication, study design (prospective cohort, case-control), setting in which the study was conducted, protocol of ultrasonography used, reference standard chosen, QUADAS-2 items, (15) and data on sensitivity and specificity or data for 2x2 table if possible.

Outcome Measures

The primary outcome for this study was the sensitivity and specificity of POCUS for the diagnosis of abscess in the ED. Our secondary outcome was the sensitivity and specificity of

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POCUS in the paediatric population subgroup. A post-hoc secondary outcome was the reported change in management due to POCUS reported in the different studies. This was felt to be a clinically important outcome to include in the final review, which we had not initially included in our systematic review protocol.

Validity Assessments

Two review authors [DB, FXS] independently assessed the methodological quality of each selected article using the QUADAS-list. (15) Disagreement was resolved by consensus or involvement of a third reviewer [JC]. The QUADAS-2 assesses 4 potential areas for bias and applicability to the research question: (1) Patient selection- The risk of bias was high if the study was a case-control design, enrolment was nonconsecutive, or the study had inappropriate exclusions; (2) Index test-: If the results from incision and draining were incorporated into the US results, the risk of bias was high; (3) References standard- Risk of bias was high if the reference standard could misclassify the target condition, or the reference standard interpreted with knowledge of POCUS results; and (4) Flow and timing- The risk of bias was high if not all patients received the same POCUS protocol, (index test) not all patients received the same reference standard, or not all patients were included in the analysis.

Primary Data Analysis

We presented individual study results graphically by plotting sensitivity and specificity estimates on a forest plot to visually assess for heterogeneity, and on the hierarchical summary receiver-operating characteristic (HSROC) space to visually assess for the presence of a

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threshold effect. The HSROC may control for the lack of an ideal reference standard, and is recommended in the DTA guidelines. (12)

We explored possible sources of heterogeneity related to spectrum, design characteristics and method of ultrasound used. We combined data for meta-analysis using the HSROC model to obtain summary estimates of the pairs of sensitivity and specificity and a summary line. All data analyses were conducted using Stata (version 11.2, Stata Corp, College Station, TX) and results were managed in REVMAN (version 5.2, the Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Characteristics of Retrieved Studies

Our search strategy returned a total of 3110 citations, which resulted in 3028 citations once duplicates were removed. After reviewing the abstracts of 70 articles and the full text of 25, we selected eight studies for inclusion in the final systematic review and meta-analysis. (Please see Figure 1 for the PRISMA diagram.)

The 8 studies included in the final systematic review and meta-analysis contained 747 eligible patients. (16-22) This included 3 studies from the adult ED setting (16-18) and 5 studies from the paediatric ED setting. (19-22) All studies except one (18) were conducted in the United States. More detailed characteristics of the included studies are available in Table 1. Analysis of the data extraction process by two independent reviewers [DB, FXS] revealed a Kappa value of 0.80 (SE 0.25).

Quality of Included Studies

Assessment of the methodologic quality of the 8 included studies using the QUADAS tool (15) revealed most of the studies to be of moderate to high quality [Figure 2 and 3].

Main Results

The sensitivity of POCUS in the 8 included studies ranged from 65.0% to 100%, and the specificity from 30.0% to 100% (Figure 4). Meta-analysis of the 8 studies included in our final review demonstrated a point estimate of 96.2% (95% CI 91.1-98.4) for the sensitivity of POCUS. The point estimate for specificity is 82.9% (95% CI 60.4-93.9). (Figure 5) The positive likelihood ratio (LR) was 5.6 (95% CI 2.2-14.6) and the negative LR was 0.05 (95% CI .02-.11). The pre-planned, sub-group analysis of paediatric patients demonstrated similar point estimates for sensitivity 93.9% (95% CI 84.8-97.7), and specificity 82.9% (95% CI 34.2-97.9). The positive LR for paediatric patients was 5.5 (95% CI 0.9-33.9) and the negative LR was 0.07 (95% CI .03-.15) [Figure 6].

Analysis of the Cooks' distance for potential influence on the final HSROC point estimates was conducted. Two studies, Marin et al (17) and Tayal et al (20), demonstrated CooksD values greater than 1. (23)

Data supporting changed management (to perform or not perform a drainage) after POCUS was provided in five of seven studies. (15,16,19,21,22) In studies of paediatric patients, the rate of management change ranged from 14-27%. (19,21,22) The proportion of patients who were initially determined to need drainage based on clinical exam and who subsequently ended up not receiving a drainage based on POCUS findings ranged from 12-20%. (19,21) The proportion Page 11 of 38

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of patients who ended up receiving a drainage based on POCUS findings after initially being determined not to require drainage ranged from 13-18%. (19,21) Sivitz and colleagues found that management changes occurred most often in the guintiles representing equivocal pre-test probabilities (i.e. 2-3 out of 5) in 36% of cases.(19) Similarly, Adams et al. demonstrated that POCUS changed management most often in the context of an equivocal physical exam for the presence of abscess or when the pre-test probability of abscess was not high (<90%). (22) Studies in adults demonstrated a slightly higher rate of change in management ranging from 17-56%. (15,16) The proportion of patients who received unplanned drainage after POCUS ranged from 23-40%. (15,16) The proportion of patients who did not receive drainage despite being determined to require it after clinical exam ranged from 12-36%. Separating the pre-test probabilities of the presence of abscess into deciles, it was found that POCUS had an effect on management at every decile from 10 to 90%. (15) Since the study by Marin and colleagues blinded treating physicians to POCUS results, changes in management were unable to be determined. (20)

Discussion

The primary objective was to assess the test accuracy of POCUS to diagnose abscess in ED patients with SSTI. Although the 8 studies differed in terms of sensitivity and specificity, the pooled estimates of 96.2% (95% CI 91.1-98.4) sensitivity and 82.9% (95% CI 60.4-93.9) specificity are favorable. This assists clinicians by demonstrating that POCUS, a rapid, noninvasive, painless, easily repeatable test, can distinguish between abscess and cellulitis in

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the vast majority of cases. This could provide a greater degree of diagnostic certainty in SSTI patients presenting with equivocal signs and symptoms, thus leading to appropriate therapy more rapidly.

Our findings are particularly important in children, who may not tolerate physical examination, blood testing, and needle aspiration as readily as adults. In our planned subgroup analysis, paediatric patients demonstrated similar point estimates for sensitivity 94.9% (95% CI 88.0-97.8), and specificity 83.1% (95% CI 46.6-96.5). This may provide paediatricians and emergency physicians caring for children with an additional valuable to tool to discern between cellulitis and abscess in children with equivocal signs and symptoms.

A recent review by Alsaawi *et al.* examined this same topic, however we feel that our study is stronger for several important reasons. (10) In our study, two independent reviewers screened all titles for inclusion, potentially minimizing selection bias. In our study, we included the same five studies as Alsaawi *et al.*, and two additional studies, (18,22) one of which was unpublished at the time of the Alsaawi study. In addition, in our study we were able to conduct a quantitative synthesis (meta-analysis) of the available data to provide accurate point estimates of the sensitivity and specificity of POCUS in patients with SSTI in the ED.

Point-of-care ultrasound resulted in management changes—to perform or not perform a drainage—in 14-56% of cases in the reviewed studies. (15,16,19,21,22) The Infectious Disease Society of America defines abscesses as "painful, tender, and fluctuant red nodules, often surmounted by a pustule and surrounded by a rim of erythematous swelling." (24) This definition is challenged by the high rates of management change born out of these studies. This implies that the clinical exam is neither sensitive nor specific for detecting abscesses. In the

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Tayal *et al.* study physicians had an error rate of 30-50% regardless of pre-test probability of abscess based on clinical assessment. (16) For instance, fluctuance is an imprecise indicator of abscess as only six out of 17 patients who underwent drainage of neck abscesses had fluctuance on exam. (18) We demonstrate that POCUS can accurately diagnose abscess in paediatric and adult populations and is likely superior to clinical examination.

Adams et al. suggested that change in management occurred in one in four ultrasound studies performed. (22) The issue of whether or not patient outcomes are impacted by identifying the presence or absence of an abscess has received little study. Three studies stated that small abscesses (e.g. <0.3 mL volume) were deemed too small to drain and only received medical therapy. (19-22) Only Sivitz et al. investigated longer-term outcomes and found that there were no return visits to the emergency department in these patients. (19) It is unknown whether there is a size at which abscesses become clinically significant. Decisions to not drain small abscesses are based on clinical context and expert opinion. Cellulitis and abscess exist on a spectrum of disease in skin and soft tissue infections and can evolve over time. Seven patients with an initial diagnosis of cellulitis without abscess remained febrile despite antibiotic treatment 72 hours after initial treatment. Six of seven patients ended up receiving an incision and drainage after a repeat ultrasound demonstrated an abscess. (18) What remains unknown is what, if any, the clinical significance of these management changes are—it is possible that unrecognized abscesses treated medically with antibiotics will resolve with no sequelae. The utility of POCUS in preventing invasive procedures is more compelling, especially in paediatric populations where principles of reducing painful procedures and avoiding sedation and its associated risks are relevant. (25) A study of adults demonstrated that invasive drainage was

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prevented most often in those with high pre-test probabilities of abscess. (16) Thus, a clinical approach of performing POCUS on patients before proceeding with a drainage attempt is justifiable. Further study on the impact of more accurate abscess diagnosis because of POCUS on patient-oriented outcomes is needed.

Strengths of our study include the comprehensive search strategy, reproducible protocols, and adherence to systematic review methodology. The use of standardized and validated data collection and extraction tools limited bias and increased inter-rater reliability. In summary, the evidence suggests that POCUS can accurately distinguish between cellulitis and abscess in the ED. The accuracy was similar between the adult and paediatric patient population. Further studies are needed to determine the impact of adding POCUS to the clinical assessment of patients presenting with SSTI.

Limitations

A number of issues warrant notice. Owing to the small number of included studies, assessment of publication bias is difficult. It is important to note that different protocols and different reference standards introduce heterogeneity.

A single study included in our meta-analysis, by Quraishi et al 1997, appears to be an outlier for sensitivity.(18) Differences in patient populations, POCUS training or equipment may explain this variation from the other included studies. Multiple attempts to contact the authors for further information were unsuccessful.

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A key element is timing: a patient presenting with an SSTI may initially have cellulitis but develop an abscess; this is especially important if there was a time lag between the index test and the reference standard. SSTI in different anatomic locations may predispose to abscess or cellulitis, as could pre-existing trauma or surgery, and there is no way to ascertain potential direction of bias.

Contributorship Statement

DB and DC conceived the study. DB, DC, JC and TJ developed the protocol, and DB built the search strategy with a health sciences librarian. DC and TJ screened citation titles; JC and FXS screened abstracts and full texts. DB and DC conducted the analysis, and all authors made significant contributions to the draft and final versions of the manuscript.

Competing Interests

The authors have no competing interests to declare.

Funding

The authors received no funding to conduct this study.

Data Sharing Statement

No additional data available

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Table 1 –	Characteristics	of studies	included in	final meta-ana	lvsis
	Character istics	or studies	menuacu m	mai meta ana	1,9313

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Journal	Clinical Otolaryng ology	Acade mic Emerg ency Medicin e	Acade mic Emerg ency Medicin e	Journal of Emerg ency Medicin e	Americ an Journal of Emerg ency Medicin e	Americ an Journal of Emerg ency Medicin e	Acade mic Emerg ency Medicin e	Journal of Pediatrics
Country of study	Ireland	USA	USA	USA	USA	USA	USA	USA
Patient populati on	Pediatric ED	ED	ED	Pediatri c ED	ED	Pediatri c ED	Pediatri c ED	Pediatric ED
Number of patients (lesions)	23 (23)	107 (107)	126 (126)	50 (50)	40 (40)	65 (65)	755 (873)	148 (151)
Number and type of operator s	Unknown	Unkno wn number of emerge ncy physici ans and residen ts	5 emerge ncy physici ans	1 pediatri c emerge ncy physici an and 1 fellow	Unkno wn number of Emerg ency physici ans and residen ts	Unkno wn number of pediatri c emerge ncy physici ans and fellows	8 pediatri c emerge ncy physici ans or fellows	8 pediatric emergency physicians, 2 pediatric emergency medicine fellows
Soft tissue ultrasou nd training or qualifica tions	Unknown	30 minute s of didactic and hands- on training	At least five supervi sed soft tissue scans	30 minute didactic , at least 5 soft tissue scans	15 minute didactic session	2 60- minute didactic and hands- on training session s repeate d quarterl y	6-hour training includin g lecture and hands- on practic e	1-2 day course, plus at least 25 abscess scans reviewed by ultrasound director
Quality assuran ce of	Unknown	Unkno wn	Unkno wn	Images recorde d and	None	Ínterrat er reliabilit	75% of scans reviewe	10% of scans repeated by

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scans				inter- rater agreem ent measur ed		y checke d through out study	d by blinded sonolo gist	second operator
Blinding	No	Unclear	Treatin g clinicia ns blinded , data collecti on unblind ed	Intermit tent	Yes	Intermit tent	Yes	Treating clinicians unblinded; ultrasonogr aphers blinded
US machine and probe	Unclear	BK Hawk 2102 8MHz linear; Sonosit e Titan 10Mhz linear	Shimad zu model 400 & 450 7.5Mhz linear	Sonosit e Microm axx 8- 13Mhz linear	Sonosit e Turbo or Microm axx 10Mhz linear	Siemen Sonolin e G605 linear	Sonosit e Microm axx 6- 13Mhz or 5-10 10Mhz linear, or 2- 5Mhz curved array	Sonosite Edge 6- 13Mhz linear
US protocol	unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Referen ce standar d	Positive I&D	Positiv e I&D and follow- up	Unclear	Positiv e I&D	Positiv e I&D	Positiv e I&D	Positiv e I&D and follow- up	I&D or follow-up
Industry sponsor ed	Unclear	No	No	No	No	No	Unclear	Unclear
Time to complet e US study	Unclear	Not recorde d	Not recorde d	Not recorde d	Not recorde d	Not recorde d	Unclear	Not recorded
Prospec tive or retrospe ctive	prospecti ve	Prospe ctive	Prospe ctive	Prospe ctive	Prospe ctive	Prospe ctive	Prospe ctive	Prospective

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Figure 2 - QUADAS-2 assessment of risk of bias for included studies

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Figure 3 - QUADAS-2 summary graph

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7	Study	TP FP FN TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI) Specificity (95% CI)
8	Quraishi 1997	11 0 6 6	0.65 [0.38, 0.86]	1.00 [0.54, 1.00]	
9	Tayal 2006	58 5 0 63	1.00 [0.94, 1.00]	0.93 [0.84, 0.98]	4 4
10	Sivitz 2010	40 1 4 5	0.91 [0.78, 0.97]	0.83 [0.36, 1.00]	
11	Iverson 2012	61 1 2 2	0.97 [0.85, 1.00]	0.67 [0.22, 0.96]	
12	Marin 2013	149 21 5 9	0.97 [0.93, 0.99]	0.30 [0.15, 0.49]	
13	Adams 2010	130 2 3 14	0.96 [0.92, 0.99]	0.88 [0.62, 0.98]	0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1
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.2 0 .6 .4 Specificity Study estimate Summary point 95% confidence **HSROC** curve region 95% prediction region Figure 5 - HSROC curve of final meta-analysis

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Figure 6 - HSROC curve for paediatric subgroup analysis

41x52mm (300 x 300 DPI)
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PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review. Point-of-care ultrasonography for the diagnosis of abscess in patients presenting with skin and soft tissue infections to the emergency department.

2 Original language title

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

- 3 Anticipated or actual start date Give the date when the systematic review commenced, or is expected to commence. 01/02/2015
- 4 Anticipated completion date Give the date by which the review is expected to be completed. 01/02/2016
- 5 Stage of review at time of this submission

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage Preliminary searches Piloting of the study selection process Formal screening of search results against eligibility criteria	Started Yes Yes Yes	Completed Yes No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact

The named contact acts as the guarantor for the accuracy of the information presented in the register record. David Barbic

- 7 Named contact email Enter the electronic mail address of the named contact. david.barbic@ubc.ca
- Named contact address
 Enter the full postal address for the named contact.
 Emergency Department St Paul's Hospital 1081 Burrard St Vancouver, BC CANADA V6Z 1Y6
- Named contact phone number
 Enter the telephone number for the named contact, including international dialing code.
 604-682-2344
- 10 Organisational affiliation of the review Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

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Review q State the o To investig presenting	uestion(s) question(s) to be add gate the sensitivity a g with skin and soft ti	Iressed / review objecti nd specificity of bedside ssue infections in patie	ves. Please complete a separate box for each question. e ultrasonography for the diagnosis of abscess in patients nts presenting to the emergency department.
Searches Give detai strategy is Investigate proceeding based on t emergence sample re-	s Is of the sources to b not required, but ma ors will search Ovid I gs. An experienced I the research questio y department? The s sult set of twenty-on- ports citing the relev tudies identifies into s [13]. We will condu e past 5 years. We v	be searched, and any re ay be supplied as a link MEDLINE, Ovid Embass nealth sciences librarian n: What is the accuracy search strategy will be i e studies identified by the ant articles identified fre PUBMED and then use ct online bibliographic s vill search manually the d by our primary search	estrictions (e.g. language or publication period). The full sear or attachment. se, and Cochrane Library for journal articles and conference n will develop a preliminary search strategy in Ovid MEDLINE y of bedside of ultrasound for diagnosing abscess in the ndependently reviewed by two librarians and validated agains he primary investigator. We will use Science Citation Index to om our search in MEDLINE and EMBASE and then we will er the Related articles feature as suggested by Sampson and searches of the table of contents for Critical Ultrasound Journ bibliographies of all potential articles (including review article
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Yes



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Cen	tre for Reviews and Dissemination	Health Research
18	Condition or domain being studied Give a short description of the disease, condition or healthcare domain being studied. Thi wellbeing outcomes. Skin and soft tissue infections	is could include health and
19	Participants/population Give summary criteria for the participants or populations being studied by the review. The details of both inclusion and exclusion criteria. Patients presenting to the emergency department	e preferred format includes
20	Intervention(s), exposure(s) Give full and clear descriptions of the nature of the interventions or the exposures to be re Point-of-care ultrasonography for the differentiation of cellulitis and abscess	eviewed
21	Comparator(s)/control Where relevant, give details of the alternatives against which the main subject/topic of the (e.g. another intervention or a non-exposed control group). Computed tomography, results from incision and drainage, or final diagnosis from clinical as reference standards.	e review will be compared follow-up will be accepted
22	Types of study to be included initially Give details of the study designs to be included in the review. If there are no restrictions of eligible for inclusion, this should be stated. Prospective cohorts, case controls, and randomized controlled trials	on the types of study design
23	Context Give summary details of the setting and other relevant characteristics which help define the criteria. All patients presenting to the emergency department with suspected skin and soft tissue is	he inclusion or exclusion
24	Primary outcome(s) Give the most important outcomes. Diagnosis of abscess vs cellulitis	
	Give information on timing and effect measures, as appropriate.	
25	Secondary outcomes List any additional outcomes that will be addressed. If there are no secondary outcomes Time to conduct point-of-care ultrasonography	enter None.
	Give information on timing and effect measures, as appropriate.	
26	Data extraction, (selection and coding) Give the procedure for selecting studies for the review and extracting data, including the review and how discrepancies will be resolved. List the data to be extracted. Two review authors will independently identify potential articles for inclusion by scanning articles. Any disagreement will be resolved by consensus or by involvement of a third rev will independently extract data from the selected articles using prepared data extraction s be resolved by consensus or by involvement of a third reviewer. No attempt will be made or the journal's name during data extraction and management. We will extract information name, year of publication, study design (prospective cohort, case-control), setting in which protocol of ultrasonography used, reference standard chosen, QUADAS-2 items{Whiting: sensitivity and specificity or data for 2x2 table if possible. We will also adhere to guideline meta-analyses of DTA set forth previously.	number of researchers the titles and abstracts of iewer. Two review authors heets. Any disagreement will to mask the author's name on: author, title, journal h the study was conducted, 2011hx}, and data on es for systematic reviews and
27	Risk of bias (quality) assessment State whether and how risk of bias will be assessed, how the quality of individual studies whether and how this will influence the planned synthesis. Two review authors will independently assess the methodological quality of each selected	will be assessed, and d article using the QUADAS-

NHS National Institute for Health Research

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list{Whiting:2011hx}. Any disagreement will be resolved by consensus or involvement of a third reviewer.

28 Strategy for data synthesis

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Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

We will present individual study results graphically by plotting sensitivity and specificity estimates on a forest plot, to visually assess for heterogeneity, and on the ROC space to visually assess for the presence of a threshold effect. We will meta-analyze, if appropriate using the HSROC model to obtain summary estimates of the pairs of sensitivity and specificity and a summary line.

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

We will explore possible sources of heterogeneity related to spectrum, design characteristics and method of ultrasound used, specifically: Patient population: We hypothesize that no difference in test accuracy will exist between ultrasound studies performed in adult and child patients. We will formally explore sources of variation in the HSROC model, by adding covariates indicating patient, method of ultrasound used or design features. This will enable us to explore whether, on average, studies that differ with respect to these features result in different estimates of diagnostic accuracy.

Review general information

30 Type of review

Select the type of review from the drop down list. Diagnostic

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language. English

Will a summary/abstract be made available in English? Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country. Canada

33 Other registration details

List places where the systematic review title or protocol is registered (such as with he Campbell Collaboration, or The Joanna Briggs Institute). The name of the organisation and any unique identification number assigned to the review by that organization should be included.

34 Reference and/or URL for published protocol

Give the citation for the published protocol, if there is one. Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences. Presentation at scientific meetings for emergency medicine and publication in emergency medicine journal(s)

Do you intend to publish the review on completion? Yes

Page
$1\ 2\ 3\ 4\ 5\ 6\ 7\ 8\ 9\ 11\ 12\ 3\ 4\ 5\ 6\ 7\ 8\ 9\ 11\ 12\ 3\ 4\ 5\ 6\ 7\ 8\ 9\ 11\ 12\ 12\ 12\ 12\ 12\ 12\ 12\ 12\ 12$

36	Keywords Give words or phrases that best describe the review. (One word per box, create a new box for each term) ultrasound
	skin and soft tissue infection
	cellulitis
	abscess
	emergency medicine
37	Details of any existing review of the same topic by the same authors Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.
38	Current review status Review status should be updated when the review is completed and when it is published. Ongoing
39	Any additional information Provide any further information the review team consider relevant to the registration of the review.
40	Details of final report/publication(s) This field should be left empty until details of the completed review are available. Give the full citation for the final report or publication of the systematic review. Give the URL where available.

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Data Supplement S2

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- 2. exp cellulitis/ or exp skin diseases/
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 4. (skin adj4 infection*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 5. exp Suppuration/
- 6. abscess*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 7. suppurat*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 8. cutaneous.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]9. or/1-8
- 10. exp Ultrasonography/
- 11. ultrasound.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 12. us.fs.
- 13. 10 or 11 or 12
- 14. 9 and 13
- 15. exp Emergency Medicine/
- 16. exp Emergency Service, Hospital/
- 17. emergenc*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 18. 15 or 16 or 17
- 19. 14 and 18
- 20. 5 or 6 or 7
- 21. 1 or 2 or 3 or 4 or 8
- 22. 13 and 20 and 21
- 23. 22 not19.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 24. 22 not 19
- 25. 9 and 13
- 26. 25 and 20
- 27. 19 or 24

EMBASE

- 1. exp Soft Tissue Infections/
- 2. exp cellulitis/ or exp skin diseases/

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# 6 16,652 TI=ultrasonography Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years Edit Select to combine sets. Select to delete this set.	
# 5 85,481 TI=ultrasound Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years Edit Select to combine sets. Select to delete this set.	
# 4 3,930 TI=suppurat* Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years Edit Select to combine sets. Select to delete this set.	
# 3 21,490 TI=abscess Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years	

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10	I I=cellulitis
11	Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
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18	1,529
10	TI=soft tissue infection
19	Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE	·		
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
2 Structured summary 3 4	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS	·		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
3 Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
3 Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14 - ເຣລເຄີດ	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ² for each meta-analysis, ງວນງວາງ ເຊິ່ງໃນເຮັດນີ້ ເຮັດການເລັ້ມ ເປັນເປັນເປັນເຫຼັງ ເວັ້ມ ເອກີດ ເຮັດ ເປັນ ເຮັດ ເປັນ ເຮັດ ເປັນ ເຮັດ ເປັນ ເຮັດ ເ	9



PRISMA 2009 Checklist

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5 6 7	Section/topic	#	Checklist item	Reported on page #
8 9	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
10 11 12	Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
13	RESULTS			
12 15 16	Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9,10
17	Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9,10
20	Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
22	Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10
24	Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10
25	Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
27	Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
28	DISCUSSION	1		
30	Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
33 34	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
35 36	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
37	FUNDING	<u> </u>		
39 39 40	Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15
4				

42 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. 43 doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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