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Point-of-care lactate testing for sepsis at presentation to health care:

a systematic review of patient outcomes

Abstract

Background
Lactate is measured in hospital settings to identify patients with sepsis and severe infections, and to guide initiation of early treatment. Point-of-care technology could facilitate measurement of lactate by clinicians in the community. However, there has been little research into its utility in these environments.

Aim
To investigate the effect of using point-of-care lactate at presentation to health care on mortality and other clinical outcomes, in patients presenting with acute infections.

Design and setting
Studies comparing the use of point-of-care lactate to usual care in initial patient assessment at presentation to health care were identified using a maximally sensitive search strategy of six electronic databases.

Method
Two independent authors screened 3063 records for eligibility, and extracted data from eligible studies. Quality assessment for observational studies was performed using the ROBINS-I tool.

Results
Eight studies were eligible for inclusion (3063 patients). Seven studies were recruited from emergency departments, and one from a pre-hospital aeromedical setting. Five studies demonstrated a trend towards reduced mortality with point-of-care lactate; three studies achieved statistical significance. One study demonstrated a significant reduction in length of hospital stay, although another did not find any significant difference. Two studies demonstrated a significant reduction in time to treatment for antibiotics and intravenous fluids.

Conclusion
This review identifies an evidence gap — there is no high-quality evidence to support the use of point-of-care lactate in community settings. There are no randomised controlled trials (RCTs) and no studies in primary care. RCT evidence from community settings is needed to evaluate this potentially beneficial diagnostic technology.

Keywords
general practice; lactate; point-of-care testing; pre-hospital care; primary health care; sepsis.

INTRODUCTION

Sepsis is defined as the life-threatening organ dysfunction caused by a dysregulated host response to infection.[1,2] Severe sepsis is thought to account for around 37 000 deaths annually in the UK[3] — more than breast, bowel, and prostate cancer combined.[4]

Early recognition and treatment are key in preventing deaths from sepsis.[2] Until recently, the focus has been on timely management in secondary care, with the introduction of sepsis care bundles and early warning scores.[4,5] However, the latest National Institute for Health and Care Excellence (NICE) guidance recognises that systems need to extend to primary care, to facilitate timely recognition and prompt treatment.[2] In addition, improving outcomes from sepsis has been highlighted as a clinical priority by the Royal College of General Practitioners[6] and NHS England.[7]

Lactate measurement is frequently used in hospital settings to identify critical medical illness including sepsis and severe infections, and to guide treatment. With the recent increase in availability of point-of-care (POC) testing technology, possibilities for earlier biochemical testing in community settings have arisen.[8]

Community clinicians, the first point of assessment for many patients with sepsis, are in need of guidance regarding the added value of POC lactate in these settings. There are potential disadvantages of using such a test earlier in the pathway, such as increasing the time taken for assessment, false reassurance in emerging septic shock, or a much higher false positive rate in a setting of much lower prevalence, leading to inappropriate care escalation.

Accordingly, a systematic review was undertaken to evaluate whether the use of point-of-care lactate testing at first presentation to any healthcare setting in a population of adults and children with symptoms suggestive of serious bacterial infection reduces mortality or improves other clinical outcomes or markers of quality of care. These include time to antibiotics and length of any subsequent hospital stay, when compared with usual care.

METHOD

Search strategy

The authors searched MEDLINE (1946 to present), Embase (1974 to 3 June 2016), Web of Science (1945 to present), CENTRAL (issue 5 of 12, May 2016), Database of Abstracts of Reviews of Effects (issue 2 of 4, April 2015), and the Cochrane Database of Systematic Reviews (issue 6 of 12, June 2016) for relevant articles, using a maximally sensitive strategy (Appendix 1).

The authors excluded animal studies, case reports, comments, letters, and

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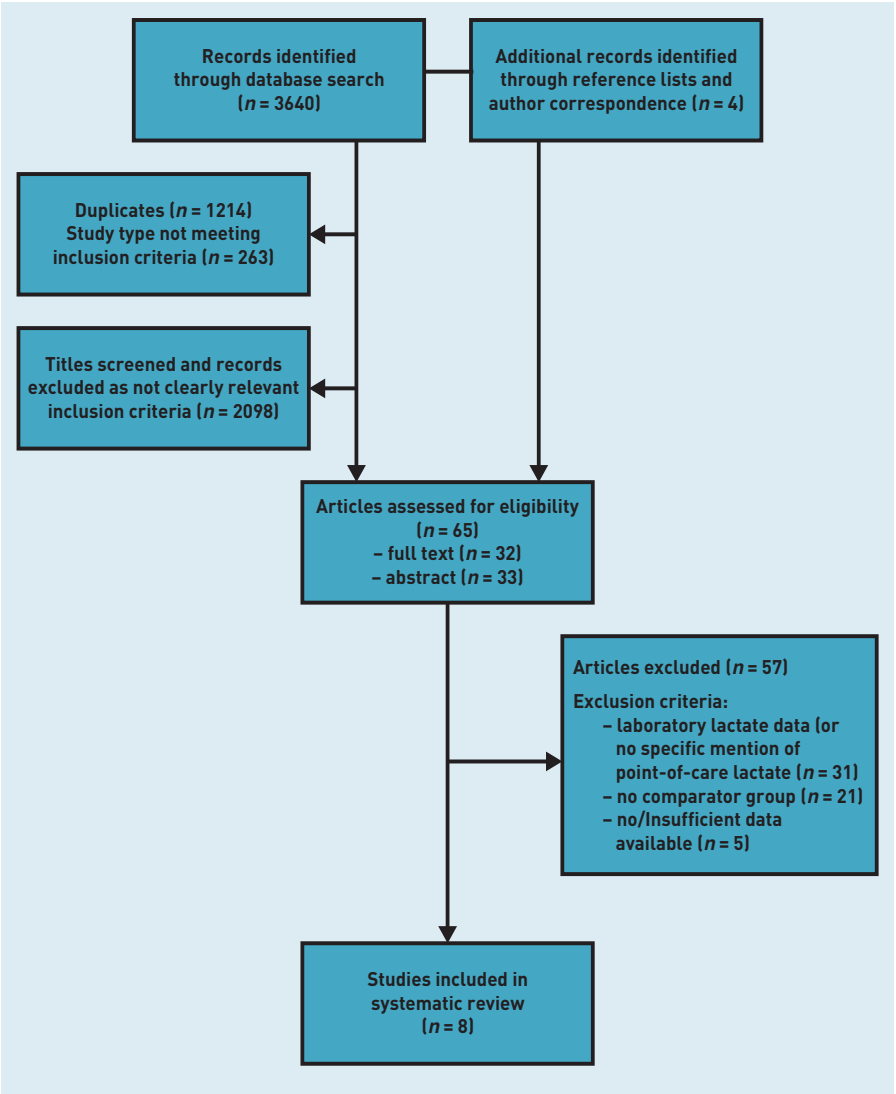
How this fits in

Sepsis accounts for around 37 000 deaths annually in the UK. Lactate is often measured in the hospital setting. The availability of point-of-care lactate allows measurement in community and pre- hospital environments such as primary care. Point-of-care lactate at presentation to healthcare setting may reduce mortality. The quality of evidence is low and no studies have previously been conducted in an out-of-hours or general practice setting.

editorials. All other study types were included in the search strategy. The authors searched for studies in both children and adults. There were no limits on language or date of publication. The authors performed citation searches of all full-text papers retrieved, to identify other relevant studies.

Figure 1. Flowchart of included studies.



Data extraction

Following exclusion of duplicate studies, all titles and abstracts were screened independently by two authors, using the following inclusion criteria:

- population — patients presenting to first-assessment settings, including community-based health care and emergency departments (EDs), with symptoms suggestive of serious bacterial infection;
- intervention — point-of-care lactate testing;
- comparator — usual care; and
- outcomes — at least one patient outcome (for example, mortality, time to treatment, length of stay).

Purely diagnostic accuracy studies were excluded, given this review's focus on clinical outcomes (and the potential circularity of lactate measurement being required for diagnosis of sepsis according to some existing definitions of sepsis). The full texts of remaining articles were independently screened by pairings of two authors, and reviewed for inclusion according to the specified criteria. Disagreements were resolved by discussion with a third reviewer.

Two authors independently extracted data using a proforma. The full papers were used where possible (four studies), with abstracts used if no full paper was available (four studies). The primary outcome was mortality. Secondary outcomes included time to lactate result, time to antibiotic and intravenous (IV) fluid treatment, and length of stay.

Authors were contacted for further clarification or missing data where necessary.

Quality assessment

Quality assessment was undertaken independently by two authors using the ROBINS-I tool for non-randomised studies of interventions.[9] Quality was determined on a scale from low risk of bias (comparable with a well-performed randomised controlled trial [RCT]), to critical risk of bias (too problematic to provide any useful evidence on the effects of the intervention).

Data synthesis

There were insufficient data with acceptable risk of bias to perform meta-analysis.

RESULTS

Study characteristics

In all, 3644 titles and abstracts were screened, with 65 articles subsequently assessed for eligibility, of which 32 were full texts, and 33 records where abstracts only

Table 1. Characteristics of included studies

Study	Study design	Setting	Intervention, *n*	Control, *n*	Lactate measurement sample/device	Outcome measures
Singer, 2015[10]	Before and after	Emergency department	80	80	Venous sample; portable i-STAT system (Abbott POC)	POCL measurement; resource utilisation; total hospital costs
Singer, 2014[11]	Before and after	Emergency department	80	80	Venous sample; portable i-STAT system (Abbott POC)	POCL measurement; time to lactate result; mortality; resource utilisation; IV fluids; antibiotics
Larsen, 2011[12]	Before, during, and after	Paediatric emergency department	192	55	Venous blood gas sample	POCL measurement; mortality; resource utilisation; sepsis bundle compliance; total hospital costs
Mullen, 2014[13]	Prospective observational cohort	Pre-hospital aeromedical	20	39	Fingerstick; lactate plus POC device (Nova Biomedical)	POCL measurement; mortality; IV fluids; transfusion; intubation; CVC line
Maung, 2014[14]	Observational cohort	Emergency department	363	502	Not specified	POCL measurement; mortality; IV fluids; antibiotics
Choong, 2014[15]	Observational cohort	Emergency department	609	821	Not specified	POCL measurement; mortality
Smith, 2010[16]	Observational cohort	Emergency department	29	181	Not specified	POCL measurement; time to lactate result; IV fluids; antibiotics; CVC line; sepsis bundle compliance
Varpula, 2007[17]	Sub-analysis; prospective observational cohort	Emergency department, intensive care unit	53	39	Arterial blood gas sample	POCL measurement; mortality; sepsis bundle compliance

CVC = central venous catheter. IV = intravenous. POC = point of care. POCL = point-of-care lactate.

were available (Figure 1). Of these, 57 studies were excluded — 31 did not specify point-of-care lactate testing, 21 lacked a comparator group, and five provided insufficient data for inclusion. Eight studies (3063 patients) were included in the analysis (Table 1).

Three before-and-after[10–12] and five observational cohort studies[13–17] were included. In the cohort studies, there was limited description of the nature of allocation to point-of-care testing versus control. Seven studies recruited from emergency departments.[10–12,14–17] Of these, four[14–17] examined only a sub-population admitted from the ED to the intensive care unit (ICU) and, of these, two[14–15] included only patients who were subsequently mechanically ventilated. One study had a pre-hospital setting,[13] describing patients being transported by an aeromedical service. The studies — conducted in the US (five), Singapore (two), and Finland (one) — examined a total of 1346

Table 2. Participant characteristics

Study	Country	*n*	Age, years	Sex, % male	Sepsis, % of cohort	Medical inclusion criteria
Singer, 2015[10]	US	160	71[a]	58	100	Included in sepsis registry, lactate ≥2, suspected infection, at least two SIRS criteria
Singer, 2014[11]	US	160	71[a]	58	100	Included in sepsis registry, lactate ≥2, suspected infection, at least two SIRS criteria
Larsen, 2011[12]	US	247	6[a]	49	100	Septic shock, sepsis (ICD9 code at discharge)
Mullen, 2014[13]	US	59	61[b]	56	91	Critically ill medical patient
Maung, 2014[14]	Singapore	865	62.5[b]	59	58	Mechanically ventilated, in shock, presented via ED
Choong, 2014[15]	Singapore	1430	61.2[b]	60	43	Mechanically ventilated, admitted to ICU, via ED
Smith, 2010[16]	US	210	–	59	100	Suspected infection, critically ill, septic shock, admitted to ICU
Varpula, 2007[17]	Finland	92	57[a]	72	100	Septic shock, admitted to ICU, community-acquired sepsis

[a]Median. [b]Mean. ED = emergency department. ICD = International Classification of Diseases. ICU = intensive care unit. SIRS = systemic inflammatory response syndrome.

Table 3. Quality assessment and risk of bias[a]

Eligible Studies	Risk of bias domains — ROBINS-I							
	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in the selection of the reported result	Overall risk of bias
Singer, 2015[10]	Moderate	Moderate	Low	Low	NI	Low	Low	Moderate
Singer, 2014[11]	Moderate	Moderate	Low	Low	NI	Low	Low	Moderate
Larsen, 2011[12]	Moderate	Moderate	Low	Serious	NI	Moderate	Moderate	Moderate
Mullen, 2014[13]	Serious	Serious	Moderate	Low	NI	Moderate	Moderate	Serious
Maung, 2014[14]	Serious	Serious	Moderate	Low	NI	Moderate	Moderate	Serious
Choong, 2014[15]	Serious	Serious	Moderate	Low	NI	Moderate	Moderate	Serious
Smith, 2010[16]	Serious	Serious	Moderate	Low	NI	Moderate	Moderate	Serious
Varpula, 2007[17]	Serious	Serious	Moderate	Serious	NI	Moderate	Serious	Serious

[a]Low — comparable with a well-performed RCT. Moderate — sound for a non-randomised study but not comparable with a well-performed RCT. Serious — important problems in this domain. Critical — too problematic to provide any useful evidence on the effects of the intervention. NI = no information. RCT = randomised controlled trial.

point-of-care lactate results. Seven studies recruited from adult populations,[10,11,13–17] and one from a paediatric population.[12]

In two studies, the primary focus was not on point-of-care lactate testing, but evaluation of sepsis treatment targets,[17] and introduction of septic shock protocol.[13] There were no studies undertaken in general practice settings, out-of-hours primary care, or ambulance services (Table 2).

Methods of point-of-care lactate testing included arterial,[17] venous,[10–12] and fingerprick samples,[13] and were unclear in three studies.[14–16] Precise timing of point-of-care lactate measurement within the care pathway was also not specified in any study. Average lactate levels ranged from 2.3 to 3.9 mmol/L in the three studies reporting this,[11,16,17] with no significant differences between intervention and control groups. One study used lactate of ≥2 mmol/L as an inclusion criteria.[11] No indicators of illness severity (for example, NEWS, APACHE) were available for between-study comparison.

Lactate result handling was expressly described in two of the papers. In one of these, lactate levels ≥2 were immediately communicated to the attending physician, and patients with a level of ≥4 were escalated to a critical care area; all patients were tested again after 2 hours.[11]

In the pre-hospital aeromedical setting, point-of-care lactate results were reported on hospital arrival to the attending physician.[13]

Table 4. Effect on patient mortality

Outcome	Study	Intervention group, *n* (%)	Usual care, *n* (%)	*P*-value
In-hospital mortality	Singer, 2014[11]	5 (6)	15 (19)	0.02[a]
	Larsen,[b] 2011[12]	9 (5)	6 (11)	0.11
	Mullen, 2014[13]	11 (55)	19 (49)	0.78
	Varpula, 2007[17]	18 (34)	14 (36)	0.66
	Maung, 2014[14]	OR 0.6, 95% CI = 0.46 to 0.8, *P* = 0.001,[a] with POCL testing		
	Choong, 2014[15]	OR 0.71, 95% CI = 0.55 to 0.9, *P* = 0.006,[a] with POCL testing		

[a]Reaches statistical significance. [b]Larsen study figures derived from supplementary data provided by first author correspondence. OR = odds ratio. POCL = point-of-care lactate testing.

Study quality assessment and risk of bias

Study quality assessment and risk of bias is presented in Table 3. All included studies were found to have a moderate or serious risk of bias.

Key limitations identified included: study design (lack of parallel group randomised trials); lack of definition of allocation to point-of-care or usual care lactate testing in prospective cohort studies; use of cohorts enriched for effect due to underlying risk (particularly in cohorts examining ED data only for patients subsequently admitted to the ICU); and potential for confounding of effects due to simultaneous introduction of wider sepsis care bundles.

Due to the study limitations identified, and lack of comparability across study cohorts and sampling methods, no valid meta-analysis of outcome data was possible, and thus outcomes are reported descriptively.

Effects on patient outcomes and healthcare processes

Mortality. Six studies examined the effect on in-hospital mortality (Table 4). Three studies reported a significant reduction in mortality

Table 5. Effect on time to treatment and length of stay

Outcome		Study	Intervention group	Usual care	*P*-value
Length of stay	Length of hospital stay (days)	Singer, 2014[11]	7 (3–13)[a]	8 (4–13)[a]	0.27
		Larsen, 2011[12]	5.8[a]	7.5[a]	<0.05[c]
	Length of ED stay (minutes)	Singer, 2014[11]	352 (246–457)[a]	326 (249–436)[a]	0.5
		Mullen, 2014[13]	396[b]	216[b]	0.02[c]
	Length of ICU stay (days)	Singer, 2014[11]	3 (2–6)[a]	4 (2–6)[a]	0.9
Lactate result	Time to lactate result (minutes)	Singer, 2014[11]	34 (26–55)[a]	122 (82–149)[a]	<0.001[c]
	Lactate result in <1 hour	Smith, 2010[16]	OR 4.6, 95% CI = 1.8 to 11.5, with POCL testing		
IV fluids	Time to IV fluids (minutes)	Singer, 2014[11]	55 (34–83)[a]	71 (42–110)[a]	0.03[c]
	IV fluids in <1 hour (%)	Maung, 2014[14]	48.8	35.5	0.001[c]
	Total volume IV fluids (mL)	Singer, 2014[11]	2000 (2000–3125)[a]	2500 (2000–4000)[a]	0.71
		Mullen, 2014[13]	3300	5000	0.79
	IV fluids (ml/kg)	Smith, 2010[16]	29.3 ± 3.4[b]	17.8 ± 1.4[b]	<0.01[c]
Antibiotics	Time to Abx (minutes)	Singer, 2014[11]	89 (63–182)[a]	97 (55–160)[a]	0.59
	Abx in <1 hour (%)	Maung, 2014[14]	25	15.1	0.007[c]
	Abx in <3 hours	Smith, 2010[16]	OR 4.2, 95% CI = 1.2 to 14.4, with POCL testing		
Transfusion	Received transfusion (%)	Mullen, 2014[13]	50	62	0.41

[a]Median (IQR). [b]Mean. [c]Reaches statistical significance. Abx = antibiotics. CI = confidence interval. ED = emergency department. ICU = intensive care unit. IQR = interquartile range. IV = intravenous. OR = odds ratio. POCL = point-of-care lactate.

with point-of-care lactate testing (mortality of 6% versus 19%, *P* = 0.02;[11] odds ratio [OR] 0.6, *P* = 0.001;[14] and OR 0.71, *P* = 0.006).[15] Two studies reported a non-significant trend towards reduction in mortality.[12,17] Only one study, in the aeromedical patient transport setting, did not demonstrate a trend towards reduced mortality with point-of-care lactate testing (55% versus 49%, *P* = 0.78).[13] Two studies additionally reported decreased in-ICU mortality (OR 0.65, *P* = 0.004,[14] and OR 0.64, *P* = 0.005).[15]

Time to treatment. Outcomes for intravenous (IV) fluid administration in five studies included time to IV fluids (minutes), receiving IV fluids in <1 hour, and total volume of IV fluids received (Table 5). Two studies in ED patients demonstrated a significant reduction in time taken for patients to receive IV fluids (median time of 71 versus 55 minutes, *P* = 0.03;[11] 48.8% versus 35.5% receiving IV fluids in less than an hour, *P* = 0.001).[14] No significant difference in the total volume of IV fluids received was found in the two studies examining this (2000 mL versus 2500 mL, *P* = 0.71,[11] and 3300 versus 5000 mL, *P* = 0.79).[13]

Two studies of adult patients in ED demonstrated a statistically significant reduction in time to antibiotic administration with point-of-care lactate testing, with one study demonstrating 25% of patients receiving antibiotics in <1 hour compared with 15.1% (*P* = 0.007),[14] and a second study quoting an odds ratio of 4.2 (95% confidence interval [CI] = 1.2 to 14.4) for receiving antibiotics in <3 hours.[16] However, a third study in a similar setting failed to find any significant difference in time to antibiotic administration (median time of 89 versus 97 minutes, *P* = 0.59).[11]

No significant change in the number of patients receiving blood transfusions, intubation, or central venous catheter (CVC) line insertion (nor time to CVC line insertion), were demonstrated in adult patients,[13] although one study did report an odds ratio of 9.8 (95% CI = 3.5 to 27.4) for measurement of central venous pressure (CVP) in ED with the introduction of point-of-care lactate testing.[16]

In the study of a paediatric population, the proportion of children receiving a fluid bolus within both 1 hour and 15 minutes of ED arrival was significantly increased by implementation of an ED septic shock protocol and care guideline, which included a point-of-care lactate measurement (43% versus 79%, and 10% versus 47% respectively, *P*<0.05).[12] An improvement in the proportion of paediatric patients receiving antibiotics in <3 hours was also evident following implementation of this sepsis protocol. However, insufficient data were available for sub-analysis of any effect due to point-of-care lactate testing alone.[12]

Length of stay. Three studies[11–13] examined length of stay (Table 5). One demonstrated

a significant reduction in median length of paediatric hospital stay, from 7.5 to 5.8 days (P<0.05).[12] Another[11] found no significant difference in duration across total hospital, ED, or ICU length of stay; median hospital stay was 1 day less in patients with point-of-care lactate testing (7 versus 8 days, P = 0.27), although rates of admission to the ICU were significantly lower in patients who had received point-of-care lactate testing (33% versus 51%, P = 0.02).[11]

A third study, in the pre-hospital aeromedical setting, demonstrated a significant increase in ED length of stay in the intervention group with pre-arrival point-of-care testing, from a mean time of 216 to 396 minutes (P = 0.02).[13] However, they do not report subsequent hospital admission or length of stay following this.

Time to available lactate result. Two studies compared point-of-care to laboratory lactate testing. One study demonstrated a significant reduction in time-to-lactate result (from time of arrival) from a median of 122 minutes to 34 minutes in an ED setting (P<0.001).[11] A second study quoted an OR of 4.6 (95% CI = 1.8 to 11.5) for acquiring a lactate result in <1 hour when using point-of-care testing (Table 5).[16]

DISCUSSION

Summary

This review identifies an important gap in the evidence needed to guide community clinicians regarding the clinical benefit of point-of-care lactate testing for suspected sepsis in community settings. There were no randomised controlled trials and no studies in primary care. The observational studies identified suffered from serious limitations, and represented very heterogeneous study populations. The majority of included patients were severely unwell, with confirmed sepsis or septic shock, and a high proportion were admitted to ICU and mechanically ventilated.

However, available evidence suggests that point-of-care lactate testing was associated with a trend towards decreased subsequent in-hospital mortality. The authors found that point-of-care lactate testing at initial assessment was associated with a reduction in the time to IV fluids and, in two studies, time to IV antibiotics, as well as an expected reduction in time to result compared with laboratory lactate. Sepsis is a time-critical condition. For every hour delay in IV antibiotic administration there is an estimated 8% increase in mortality.[18] The authors found variable evidence of benefit on length of stay.

Strengths and limitations

This is the first systematic review to explore the evidence for the impact on mortality of point-of-care lactate testing in suspected sepsis at initial healthcare assessment. The authors undertook a comprehensive literature search that is unlikely to have missed relevant studies.

There are several limitations. There were no studies set in primary care (including out-of-hours general practice) and only one study in a pre-hospital (highly specialised aeromedical) setting,[13] which was managing critically unwell patients. The remaining studies reported findings from data collected from emergency department patients, of which only four included patients subsequently transferred to ICU. There are likely to be substantial differences, most notably in severity of illness, between patients presenting to emergency departments and those presenting to primary care. It is unclear to what extent the results from this study can be extrapolated to these settings.

In addition, no RCTs were identified. The results presented, therefore, only suggest association between the intervention and outcome with no evidence of causality. In two of the studies,[12,17] point-of-care lactate was introduced alongside a number of additional interventions aimed at reducing mortality from sepsis, and it was not possible to determine the contribution of point-of-care lactate alone to improvements observed. A single paper[12] looked at a paediatric population and therefore the authors were unable to assess the influence of age on outcomes.

Comparison with existing literature

The NICE sepsis guidance from 2016 highlights that systems need to extend to primary care to facilitate early recognition and prompt treatment, and transfer of patients to the most appropriate location of care in a timely fashion.[2] However, the identification of sepsis in a general practice setting can be challenging. Use of vital sign recording has been highlighted as a key way to improve sepsis recognition in the community,[2,4,7,19] although the utility of scoring systems in primary care to identify sick patients is still debated.[2] Despite this, there will still be some patients with sepsis with normal observations that are missed. These individuals may however have an elevated lactate (cryptic shock), and evidence suggests their mortality rate is as high as in those with overt septic shock.[19–21] Therefore, the addition of point-of-care lactate may be of value, and handheld

meters have been suggested to be reliable when compared to laboratory-based lactate assays.[22,23]

Furthermore, testing may inform decisions about administration of immediate antimicrobial treatment (for the most unwell), timing and speed of transfer to hospital, or appropriateness of alternatives to hospital admission. A recent systematic review of primary care physicians described a positive approach to the potential utility of point-of-care diagnostics in reducing diagnostic certainty and increasing more effective targeting of treatment. However, it highlighted the need for reassurance about accuracy and utility of testing — and the possibility of misleading results and resultant over-treatment.[24]

Implications for research and practice

At present, there is a complete lack of evidence to support the use of point-of-care lactate testing in primary care, out-of-hours primary care, or ambulance settings to improve patient outcomes. Furthermore, the appropriate threshold and prognostic values for lactate may be different at first assessment in the community, given that established thresholds have been validated in secondary care cohorts with a different spectrum of illness severity, and more established pathophysiological change later in the course of an illness. Additionally, there are potential disadvantages of using such a test earlier in the pathway of care, such as increasing the time taken for assessment, false reassurance in emerging septic shock, or a much higher false positive rate in a setting of much lower prevalence leading to inappropriate care escalation. Consideration must also be given to the potential cost of equipment, reagents, and staff training in the context of a lower potential frequency of testing in primary care.

In the limited evidence base described in this review, there are trends towards reduced mortality and reduced time to treatment that point to the potential for point-of-care lactate testing to support recognition of sepsis in the community, decreasing mortality while avoiding unnecessary and costly admissions. However, despite the potential challenges of designing such a study, randomised controlled trial evidence from community settings is now required. This might include evaluation in ambulatory community or out-of-hours primary care settings, where the prevalence of sepsis is higher, or evaluation of POC lactate as an addition to a diagnostic algorithm appropriate for community settings. Such studies would have the potential to offer the robust evidence needed for this potentially beneficial diagnostic technology.

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Competing interests

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Appendix 1. Search strategy

Search strategy: MEDLINE database

# Δ	Searches	Results
1	Ambulatory Care/	38 320
2	exp Ambulatory Care Facilities/	49 281
3	general practice/ or family practice/	68 949
4	general practitioners/ or physicians, family/ or physicians, primary care/	22 034
5	Primary Health Care/	60 672
6	Office Visits/	5998
7	exp Emergency Service, Hospital/	57 499
8	Emergency Medical Services/	35 438
9	(ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.	14 318
10	((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.	101 275
11	(primary care or primary health care or primary healthcare).ti,ab.	100 603
12	(emergency adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.	84 890
13	ed.ti,ab.	43 416
14	(after hour? or afterhour? or "out of hour?" or ooh).ti,ab.	3657
15	(clinic? or visit?).ti,ab.	374 546
16	((health* or medical) adj2 (center? or centre?)).ti,ab.	95 929
17	point-of-care systems/ or point-of-care testing/	9213
18	(("point of care" or poc or rapid or "near patient" or bedside or bed-side or "same time" or "same visit" or portable or handheld or hand-held) adj3 (test* or diagnos* or analys* or analyz* or assay? or monitor* or device?)).ti,ab.	62 397
19	("point of care" or poc or poct).ti.	3958
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	903 740
21	Lactic Acid/an, bl [Analysis, Blood]	8676
22	Lactates/an, bl [Analysis, Blood]	14 443
23	(lactate? or lactic acid).ti,ab.	108 786
24	21 or 22 or 23	116 951
25	exp bacterial infections/ or exp infection/	1 231 179
26	(septic* or sepsis).ti,ab.	120 136
27	(infection? or infectious).ti,ab.	1 214 085
28	bacter?emi*.ti,ab.	26 382
29	pneumonia.ti,ab.	92 403
30	cellulitis.ti,ab.	7101
31	meningitis.ti,ab.	45 135
32	pyelonephritis.ti,ab.	11 629
33	((infective or reactive) adj2 arthritis).ti,ab.	2434
34	Systemic Inflammatory Response Syndrome/	4530
35	Systemic Inflammatory Response Syndrome.ti,ab.	3674
36	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	2 118 860
37	20 and 24 and 36	572
38	(("point of care" or poc or rapid or "near patient" or bedside or bed-side or "same time" or "same visit" or portable or handheld or hand-held) adj3 (lactate? or lactic acid)).ti,ab.	330
39	37 or 38	876
40	exp animals/ not humans.sh.	4 260 612
41	(mouse or mice or murine or rats or rat or rodent? or pig or pigs or piglet? or porcine or cattle or bull or bulls or cow or cows or calf or calves or bovine or sheep or ewe or ewes or ovine or horse? or equine or dog or dogs or canine or cat or cats or feline or rabbit? or ruminant?).ti.	1 964 783
42	40 or 41	4 561 022
43	39 not 42	738

... continued

Appendix 1 continued. Search strategy

Search strategy: Embase database

# Δ	Searches	Results
1	ambulatory care/	32 546
2	general practice/	74 818
3	general practitioner/	73 644
4	Primary Health Care/	52 145
5	Primary Medical Care/	74 311
6	emergency ward/	83 516
7	(ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.	17 971
8	((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.	126 166
9	(primary care or primary health care or primary healthcare).ti,ab.	124 505
10	(emergency adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.	116 714
11	ed.ti,ab.	68 889
12	(after hour? or afterhour? or "out of hour?" or ooh).ti,ab.	4895
13	(clinic? or visit?).ti,ab.	544 944
14	((health* or medical) adj2 (center? or centre?)).ti,ab.	127 269
15	"point of care testing"/	7014
16	(("point of care" or poc or rapid or "near patient" or bedside or bed-side or "same time" or "same visit" or portable or handheld or hand-held) adj3 (test* or diagnos* or analys* or analyz* or assay? or monitor* or device?)).ti,ab.	78 227
17	("point of care" or poc or poct).ti.	5335
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	1 169 598
19	*lactic acid/	17 557
20	(lactate? or lactic acid).ti,ab.	128 852
21	19 or 20	132 107
22	exp *infection/	1 957 032
23	(septic* or sepsis).ti,ab.	162 521
24	(infection? or infectious).ti,ab.	1 491 393
25	bacter?emi*.ti,ab.	32 883
26	pneumonia.ti,ab.	125 628
27	cellulitis.ti,ab.	9542
28	meningitis.ti,ab.	53 217
29	pyelonephritis.ti,ab.	14 281
30	((infective or reactive) adj2 arthritis).ti,ab.	3058
31	systemic inflammatory response syndrome/	8693
32	Systemic Inflammatory Response Syndrome.ti,ab.	5070
33	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	2 839 449
34	18 and 21 and 33	1275
35	(("point of care" or poc or rapid or "near patient" or bedside or bed-side or "same time" or "same visit" or portable or handheld or hand-held) adj3 (lactate? or lactic acid)).ti,ab.	431
36	34 or 35	1651
37	(exp animals/ or nonhuman/) not human/	5 979 837
38	(mouse or mice or murine or rats or rat or rodent? or pig or pigs or piglet? or porcine or cattle or bull or bulls or cow or cows or calf or calves or bovine or sheep or ewe or ewes or ovine or horse? or equine or dog or dogs or canine or cat or cats or feline or rabbit? or ruminant?).ti.	2 200 031
39	37 or 38	6 276 204
40	36 not 39	1472

... *continued*

Appendix 1 continued. Search strategy

Search strategy: Cochrane database

#1	MeSH descriptor: [Lactates] explode all trees
#2	lactate* or "lactic acid":ti,ab,kw (Word variations have been searched)
#3	#1 or #2
#4	MeSH descriptor: [Ambulatory Care] this term only
#5	MeSH descriptor: [Ambulatory Care Facilities] explode all trees
#6	MeSH descriptor: [General Practice] explode all trees
#7	MeSH descriptor: [General Practitioners] explode all trees
#8	MeSH descriptor: [Physicians, Family] explode all trees
#9	MeSH descriptor: [Physicians, Primary Care] explode all trees
#10	MeSH descriptor: [Primary Health Care] this term only
#11	MeSH descriptor: [Office Visits] this term only
#12	MeSH descriptor: [Emergency Service, Hospital] explode all trees
#13	MeSH descriptor: [Emergency Medical Services] this term only
#14	(ambulatory near/3 (care or setting* or facilit* or ward* or department* or service*)):ti,ab,kw (Word variations have been searched)
#15	((general or family) near/2 (practi* or physician* or doctor*)):ti,ab,kw (Word variations have been searched)
#16	primary care or "primary health care" or "primary healthcare":ti,ab,kw (Word variations have been searched)
#17	(emergency near/3 (care or setting* or facilit* or ward* or department* or service*)):ti,ab,kw (Word variations have been searched)
#18	ed:ti,ab,kw (Word variations have been searched)
#19	after hour* or afterhour* or "out of hour*" or ooh:ti,ab,kw (Word variations have been searched)
#20	clinic or clinics or visit or visits:ti,ab,kw (Word variations have been searched)
#21	((health* or medical) adj2 (center* or centre*)):ti,ab,kw (Word variations have been searched)
#22	MeSH descriptor: [Point-of-Care Systems] explode all trees
#23	(("point of care" or poc or rapid or "near patient" or bedside or bed-side or "same time" or "same visit" or portable or handheld or hand-held) near/3 (test* or diagnos* or analys* or analyz* or assay* or monitor* or device*)):ti,ab,kw (Word variations have been searched)
#24	point of care or poc or poct:ti (Word variations have been searched)
#25	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#3 and #25
#27	(("point of care" or poc or rapid or "near patient" or bedside or bed-side or "same time" or "same visit" or portable or handheld or hand-held) near/3 (lactate* or "lactic acid")):ti,ab,kw (Word variations have been searched)
#28	#26 or #27

... continued

Appendix 1 continued. Search strategy

Search strategy: Web of Science database

Set		
	Results	Save search history and/or create an alertOpen a saved search history
# 8	1134	#7 OR #6
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 7	521	TOPIC: ((("point of care" or poc or rapid or "near patient" or bedside or bed-side or "same time" or "same visit" or portable or handheld or hand-held) NEAR/3 (lactate* or "lactic acid")))
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 6	666	#5 AND #4 AND #3
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 5	1 395 723	TOPIC: (infection* OR infectious) OR TOPIC: (bacteremia OR bacteraemia OR septic OR sepsis) OR TOPIC: (pneumonia OR cellulitis OR meningitis OR pyelonephritis) OR TOPIC: ((infective or reactive) NEAR/2 arthritis) OR TOPIC: ("Systemic Inflammatory Response Syndrome")
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 4	134 718	TOPIC: (lactate* or "lactic acid")
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 3	664 586	#2 OR #1
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
# 2	93 998	TOPIC: ((("point of care" or poc or rapid or "near patient" or bedside or bed-side or "same time" or "same visit" or portable or handheld or hand-held) near/3 (test* or diagnos* or analys* or analyz* or assay* or monitor* or device*)))
# 1	575 763	medical) NEAR/2 (center* or centre*)))
		Indexes=SCI-EXPANDED, CPCI-S Timespan=All years