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Morris, Elizabeth; McCartney, David; Lasserson, Daniel; Van den Bruel, Ann; Fisher, Rebecca; Hayward, Gail

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TITLE PAGE

Point-of-care lactate testing for sepsis at presentation to health care: a systematic review of patient outcomes

Authors: Elizabeth Morris[1], David McCartney[1], Daniel Lasserson[1,2], Ann Van den Bruel[1], Rebecca Fisher[1], Gail Hayward[1]

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford
[2]NIHR Oxford Biomedical Research Centre, Department of Geratology, Oxford University Hospitals NHS Foundation Trust

ABSTRACT

Background:

Lactate is measured in hospital settings to identify patients with sepsis and severe infections, and guide initiation of early treatment. Point-of-care technology could facilitate measurement of lactate by first contact 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 healthcare) on mortality and other clinical outcomes, in patients presenting with acute infections.

Design and Setting:

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

Methods:

Two independent authors screened 3640 records for eligibility, and extracted data from eligible studies. Quality assessment for observational studies was performed using the ROBINS-I tool.

Results:

8 studies were eligible for inclusion (3161 patients). Seven studies 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 testing; 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:

There is no high quality evidence to support the use of point-of-care lactate in community settings. However, the available evidence suggests a trend towards reduction in in-hospital mortality associated with point-of-care lactate testing. RCT evidence from community settings is required to evaluate this potentially beneficial diagnostic technology.

Systematic Review Registration Number: CRD42017046052

Keywords:

General Practice, Primary Health Care, Pre-hospital Care, Point-of-Care Testing, Lactate, Sepsis

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 in at presentation to healthcare may reduce mortality. The quality of evidence is low and no studies have been conducted in an Out-Of-Hours or General Practice setting.

INTRODUCTION

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

Early recognition and treatment are key in preventing deaths from sepsis(4). Until recently, the focus has been on timely management in secondary care, with the introduction of sepsis care bundles and early warning scores(3, 5). However, the latest NICE guidance recognises that systems need to extend to primary care, to facilitate timely recognition and prompt treatment(4). In addition, improving outcomes from sepsis has been highlighted as a clinical priority by the RCGP(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 in a population of adults and children setting with symptoms suggestive of serious bacterial infection, reduces mortality or improves other clinical outcomes or markers of quality of care, such as time to antibiotics and length of any subsequent hospital stay.

METHODS

Search Strategy

We searched MEDLINE (1946 to present), EMBASE (1974 to June 03 2016), Web of Science (1945 to present), CENTRAL (Issue 5 of 12, May 2016), Database of Abstracts of Review 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. (Search strategy available in appendix A).

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

Data extraction

Following exclusion of duplicate studies, all titles and abstracts were screened independently by two authors (GH, DM and RF), using the following inclusion criteria: Population: patients presenting to first assessment settings including community based healthcare and emergency departments (EDs), with symptoms suggestive of serious bacterial infection; Intervention: point-of-care lactate testing, Comparator: usual care; Outcomes: at least one patient outcome (eg 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 (GH, DM and EM) and reviewed for inclusion according to the specified criteria. Disagreements were resolved by discussion with a third reviewer.

Two authors (DM and EM) independently extracted data using a proforma. The full papers were used where possible (4 studies), with abstracts used if no full paper was available (4 studies). The primary outcome was mortality. Secondary outcomes included time to lactate result, time to antibiotic and 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 (DM and EM) using the ROBINS-I tool for non-randomised studies of interventions(9). Quality was determined on a scale from low risk of bias (comparable to a well performed 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

3644 titles and abstracts were screened with 65 articles subsequently assessed for eligibility (Figure 1) (of which 32 were full texts, and 33 records where abstracts only were available); 57 studies were excluded; 31 did not specify point-of-care lactate testing, 21 lacked a comparator group, five provided insufficient data for inclusion. Eight studies (3161 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 ED to 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 USA *(five)*, Singapore *(two)* and Finland *(one)*, examined a total of 1,346 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.

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 was also not specified in any study. Average lactate levels ranged from 2.3–3.9mmol/L in the three studies(11, 16, 17) reporting this, with no significant differences between intervention and control groups. One study used lactate of ≥2mmol/L as an inclusion criteria(11). No indicators of illness severity (e.g. NEWS, APACHE) were available for between-study comparison.

Lactate result handling was expressly described in two of the papers; in one, 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).

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 4.1). Three studies reported a significant reduction in mortality with point-of-care lactate testing (mortality of 6 vs 19%, p=0.02(11), 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 vs 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 <1hour, and total volume of IV fluids received (Table 4.2). Two studies in ED patients demonstrated a significant reduction in time taken for patients to receive IV fluids; (median time of 72 v 55 minutes (p=0.03)(11); 48.8% v 35.5% receiving IV fluids in less than an hour p=0.001(13)). No significant difference in the total volume of IV fluids received was found in the two studies examining this (2000 vs 2500mls, p=0.71(11), and 3300 vs 5000mls, 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 <1hour compared to 15.1%, (p=0.007)(14), and a second study quoting an odds ratio of 4.2 (95% CI 1.2-14.4) for receiving antibiotics in <3hours(16). However, a third study in a similar setting failed to find any significant difference in time to antibiotic administration (median time of 89 vs 97 minutes, p=0.59)(11).

No significant change in the number of patients receiving blood transfusions, intubation, 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 3.5-27.4) for measurement of 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% vs 79% and 10 vs 47% respectively, p<0.05)(12). An improvement in proportion of paediatric patients receiving antibiotics in <3hours 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 4.2). 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 one day less in patients with point-of-care lactate testing (7 vs 8 days, p=0.27), although rates of admission to the Intensive Care Unit were significantly lower in patients who had received point-of-care lactate testing (33% vs 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 odds ratio of 4.6 (95% CI 1.8-11.5) for acquiring a lactate result in under an hour when using point-of-care testing(16).

<u>DISCUSSION</u>

Main findings

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 significant 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. We 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 to 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). We 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. We undertook a comprehensive literature search which 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 again was managing critically unwell patients. The remaining studies reported findings from

data collected from Emergency Department patients, of which four only 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 randomised controlled trials were identified. The results we present 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 we 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 (4). 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(3, 4, 7, 19), although the utility of scoring systems in primary care to identify sick patients is still debated(4). 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 future 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, OOH primary 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, and the 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 which point to the potential for point-of-care lactate testing to support recognition of sepsis in the community, decreasing mortality, whilst avoiding unnecessary and costly admissions. However, despite the potential challenges of designing such a study to be undertaken in primary care, randomised controlled trial evidence from community settings is now required to evaluate this potentially beneficial diagnostic technology.

NOTES:

Ethical Approval: No ethical approval was required for this systematic review

Competing interests: None declared

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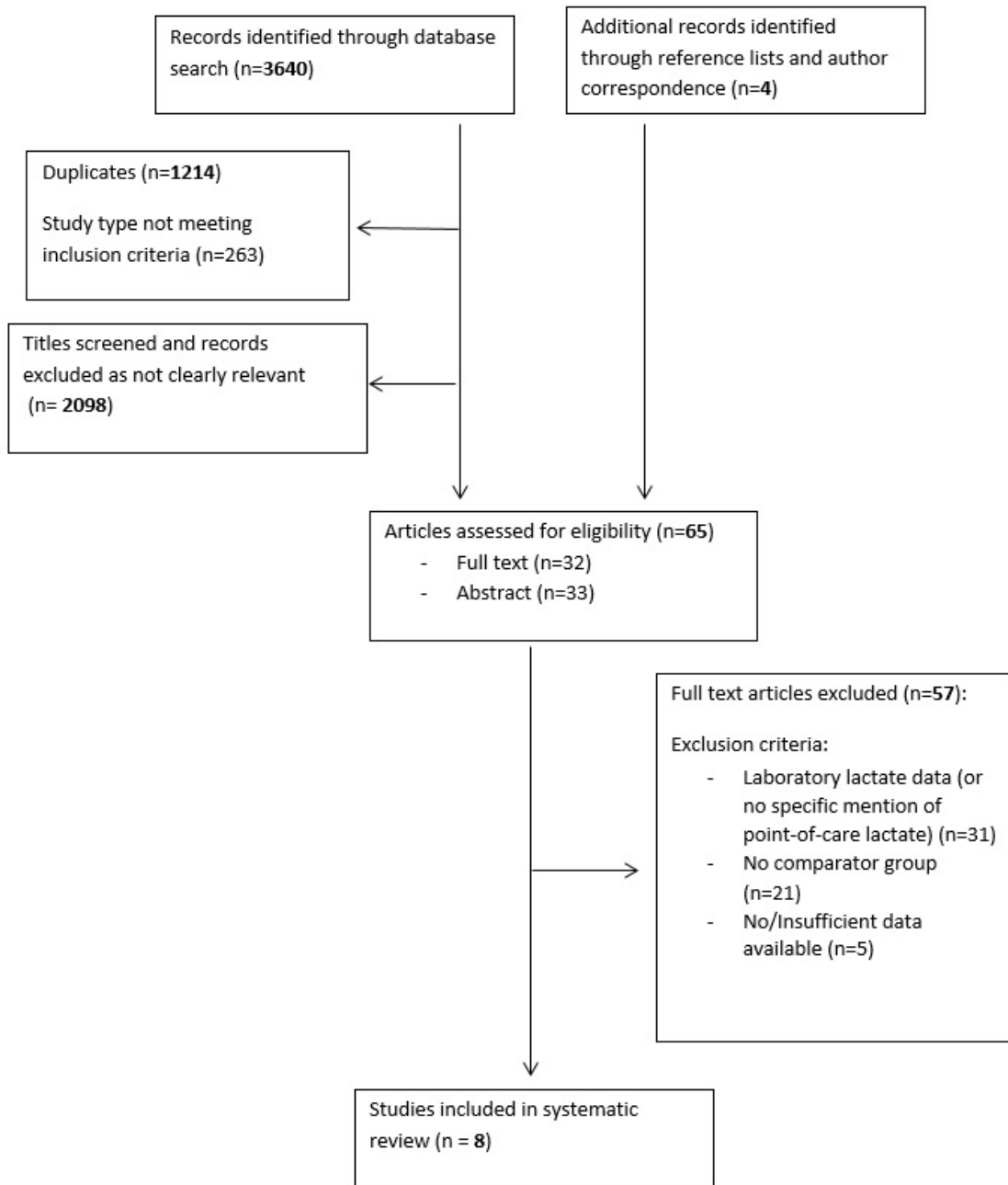
Figure 1: Flowchart of included studies

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Table 1: Characteristics of included studies

Study (Year)	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 (Abbot POC)	POCL measurement Resource utilisation Total Hospital Costs
Singer (2014) (11)	Before and After	Emergency Department	80	80	Venous sample; Portable i-STAT system (Abbot 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)	Subanalysis; Prospective observational cohort	Emergency Department, Intensive Care Unit	53	39	Arterial blood gas sample	POCL measurement Mortality Sepsis bundle compliance

Table 2: Participant Characteristics

Study (Year)	Country	N	Age (years)	Sex (% M)	Sepsis (% of cohort)	Medical inclusion criteria
Singer (2015) (10)	USA	160	71**	58	100	Included in sepsis registry, lactate ≥2, suspected infection, at least 2 SIRS criteria
Singer (2014) (11)	USA	160	71**	58	100	Included in sepsis registry, lactate ≥2, suspected infection, at least 2 SIRS criteria
Larsen (2011) (12)	USA	345	6**	49	100	Septic Shock, Sepsis (ICD9 code at discharge)
Mullen (2014) (13)	USA	59	61*	56	91	"Critically ill", medical patient
Maung (2014) (14)	Singapore	865	62.5*	59	58	Mechanically ventilated, in shock, presented via ED
Choong (2014) (15)	Singapore	1430	61.2*	60	43	Mechanically ventilated, admitted to ICU, via ED

	USA	210	-	59	100	Suspected infection, Critically ill, Septic Shock, Admitted to ICU
Smith (2010) (16)						
Varpula (2007) (17)	Finland	92	57**	72	100	Septic Shock, admitted to ICU, community acquired sepsis

Key: * Mean, **Median

Table 3: Quality assessment and Risk of Bias

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 et al 2015 (10)	Moderate	Moderate	Low	Low	NI	Low	Low	Moderate
Singer et al 2014 (11)	Moderate	Moderate	Low	Low	NI	Low	Low	Moderate
Larsen et al 2011 (12)	Moderate	Moderate	Low	Serious	NI	Moderate	Moderate	Moderate
Mullen et al 2014 (13)	Serious	Serious	Moderate	Low	NI	Moderate	Moderate	Serious
Maung et al 2014 (14)	Serious	Serious	Moderate	Low	NI	Moderate	Moderate	Serious
Choong et al 2014 (15)	Serious	Serious	Moderate	Low	NI	Moderate	Moderate	Serious
Smith et al 2010 (16)	Serious	Serious	Moderate	Low	NI	Moderate	Moderate	Serious
Varpula et al 2007	Serious	Serious	Moderate	Serious	NI	Moderate	Serious	Serious

(17)								

Table 3: Quality assessment. Risk of bias as assessed using ROBINS-I tool. Key: Low – comparable to a well performed RCT; Moderate - sound for a non-randomised study but not comparable to 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.

Table 4.1: Results (A): Mortality

Outcome	Study	Intervention Group, n/total (%)	Usual Care, n/total (%)	p	
In-hospital Mortality	Singer 2014 (11)	5/80 (6)	15/80 (19)	0.02	†
	Larsen 2011* (12)	9/192 (5)	6/55 (11)	0.11	
	Mullen 2014 (13)	11/20 (55)	19/39 (49)	0.78	
	Varpula 2007 (17)	18/53 (34)	14/39 (36)	0.66	
	Maung 2014 (14)	*OR 0.6 (0.46-0.8 95% CI) p=0.001 with POCL testing*			
	Choong 2014 (15)	*0.71 (0.55-0.9 95% CI) p=0.006 with POCL testing*			

Key: † Reaches statistical significance; *Larsen study figures derived from supplementary data provided by first author correspondence*

Table 4.2: Results (B): Time to treatment and length of stay.

Outcome		Study	Intervention group	Usual Care	p	
Length of stay	Length of hospital stay (days)	Singer 2014 (11)	7 (3-13)**	8 (4-13)**	0.27	
		Larsen 2011 (12)	5.8**	7.5**	<0.05 †	
	Length of ED stay (mins)	Singer 2014 (11)	352 (246-457)**	326 (249-436)**	0.5	
		Mullen 2014 (13)	396*	216*	0.02 †	
	Length of ICU stay (days)	Singer 2014 (11)	3 (2-6)**	4 (2-6)**	0.9	
Lactate result	Time to lactate result (Mins)	Singer 2014 (11)	34 (26-55)**	122 (82-149)**	<0.001 †	
	Lactate result in <1hour	Smith 2010 (16)	*OR 4.6 (1.8-11.5 95% CI) with POCL testing*			
IV Fluids	Time to IV fluids (mins)	Singer 2014 (11)	55 (34-83)**	71 (42-110)**	0.03	†
	IV fluids in <1hour (%)	Maung 2014 (14)	48.8	35.5	0.001 †	

	Total volume IV Fluids (ml)	Singer 2014 (11)	2000 (2000-3125)**	2500 (2000-4000)**	0.71	
		Mullen 2014 (13)	3300	5000	0.79	
	IV fluids (ml/kg)	Smith 2010 (16)	29.3 ± 3.4*	17.8 ± 1.4*	<0.01	†
Antibiotics	Time to Abx (mins)	Singer 2014 (11)	89 (63-182)**	97 (55-160)**	0.59	
	Abx in <1hr (%)	Maung 2014 (14)	25	15.1	0.007	†
	Abx in <3hr	Smith 2010 (16)	*OR 4.2 (1.2-14.4) with POCL testing*			
Transfusion	Received transfusion (%)	Mullen 2014 (13)	50	62	0.41	

Key: † Reaches statistical significance; * Mean, **Median (IQR)