Blood lactate monitoring in critically ill patients: A systematic health technology assessment*

Tim C. Jansen, MD; Jasper van Bommel, MD, PhD; Jan Bakker, MD, PhD

Objective: To decide whether the use of blood lactate monitoring in critical care practice is appropriate. We performed a systematic health technology assessment as blood lactate monitoring has been implemented widely but its clinical value in critically ill patients has never been evaluated properly.

Data Source: PubMed, other databases, and citation review.

Study Selection: We searched for lactate combined with critically ill patients as the target patient population. Two reviewers independently selected studies based on relevance for the following questions: Does lactate measurement: 1) perform well in a laboratory setting? 2) provide information in a number of clinical situations? 3) relate to metabolic acidosis? 4) improve workers’ confidence? 5) alter therapeutic decisions? 6) result in benefit to patients? 7) result in similar benefits in your own setting? 8) result in benefits which are worth the extra costs?

Data Extraction and Synthesis: We concluded that blood lactate measurement in critically ill patients: 1) is accurate in terms of measurement technique but adequate understanding of the relationship between lactate and clinical outcomes is required; 2) provides not only diagnostic but also important prognostic information; 3) should be measured directly instead of estimated from other acid-base variables; 4) has an unknown effect on healthcare workers’ confidence; 5) can alter therapeutic decisions; 6) could potentially improve patient outcome when combined with a treatment algorithm to optimize oxygen delivery, but this has only been shown indirectly; 7) is likely to have similar benefits in critical care settings worldwide; and 8) has an unknown cost-effectiveness.

Conclusions: The use of blood lactate monitoring has a place in risk-stratification in critically ill patients, but it is unknown whether the routine use of lactate as a resuscitation endpoint improves outcome. This warrants randomized controlled studies on the efficacy of lactate-directed therapy. (Crit Care Med 2009; 37:2827–2839)

Key Words: health technology assessment; lactate; hyperlactatemia; ICU; cost-effectiveness; efficacy; systematic review

Measurements of lactate in human blood was first described by Scherer in 1843 when he described a lethal case of fulminant septic shock due to puerperal fever in a young woman (1). Blood lactate monitoring is performed frequently in critically ill patients, usually aiming to detect tissue hypoxia (2). However, other processes not related to tissue hypoxia and subsequent anaerobic metabolism can also result in increased blood lactate levels (3), complicating clinical interpretation and therapy in cases of raised lactate levels. The use of blood lactate monitoring remains controversial, which is reflected by its variable clinical use in different hospitals worldwide: Some hospitals routinely measure it whereas others hardly do so. Because the clinical benefit of blood lactate monitoring in critically ill patients has never been subjected to rigorous clinical evaluation, the question remains: Should we routinely monitor lactate in the critically ill and if so, when should we measure it? What would be the therapeutic consequences? And would this improve patient outcome? To address these controversies, we performed a systematic health technology assessment (HTA) investigation (4–6), which includes eight key questions (6) (Table 1).

Methods

Data Sources

PubMed and other databases of English and non-English language literature (up to April 2008) were used: the Cochrane CENTRAL Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the HTA Database, and NHS Economic Evaluation Database. Information on ongoing clinical trials was derived from the U.S. National Institutes of Health Web site (http://www.clinicaltrials.gov).

Study Selection

We performed a systematic search for lactate (Medical Subject Heading [MeSH] terms “lactic acid” or “lactic acidosis”), in combination with critically ill patients as the target population (MeSH terms “intensive care units,” “critical care,” “critical illness,” “hospital emergency service,” “emergency medicine,” or “postoperative care”). References of retrieved literature were reviewed manually for additional relevant material.

Out of the retrieved information, two reviewers (T.C.J. and J.vB.) independently selected studies to be included in this HTA on the basis of relevance for answering the eight key questions. Disagreements were resolved by consensus. General exclusion criteria were: no original research, case reports, and articles describing D-lactate or lactate concentration in other fluids than whole blood or plasma.

For each key question (Table 1), separate inclusion criteria were defined.

Question 1

To evaluate how accurate lactate measurement is in ideal controlled conditions, we first included studies that evaluated the accuracy of the measurement itself by comparison with a gold standard (arterial blood as reference site.
and central hospital laboratory as reference technique) and that used the Bland-Altman method for assessing agreement (7).

To evaluate the diagnostic performance of lactate measurement, we subsequently included studies that investigated the anaerobic and/or aerobic etiology of hyperlactatemia. Because the etiology is complex and we could not find consensus definitions of gold standards for comparison, we did not define specific methodologic or statistical requirements.

**Question II**

In this step, we focused on the use of lactate as a prognostic tool. Because mortality is the most important and least subjective end point, we restricted inclusion to studies that used mortality as the primary end point and that provided sufficient information to construct 2 × 2 contingency tables or area under the receiver operating characteristic curve.

**Question III**

We included studies on the association between blood lactate levels and other acid-base variables. Due to space limitations, we did not include studies on the prognostic value of these acid-base variables.

**Question IV**

We included studies evaluating the effect of blood lactate monitoring on healthcare workers’ confidence.

**Question V**

We included studies that evaluated alterations in treatment following implementation of blood lactate monitoring protocols. We also included professional guidelines providing recommendations on blood lactate monitoring in critically ill patients.

**Question VI**

We included studies that combined the measurement of lactate levels with a treatment algorithm to provide benefit to the patient. Most studies focused on oxygen delivery (D\textsubscript{O}2) therapy, which we classified in increasing order of importance:

1. Observational cohort studies following implementation of a lactate-guided D\textsubscript{O}2 therapy algorithm;
2. Randomized controlled studies evaluating goal-directed D\textsubscript{O}2 therapy that were not specifically lactate-guided but that used lactate levels as a primary or secondary end point;
3. Randomized controlled studies evaluating goal-directed D\textsubscript{O}2 therapy that included a lactate-guided group and a nonlactate-guided group.

For question VI, studies evaluating pre- and intraoperative interventions were excluded to increase homogeneity.

**Question VII**

To estimate whether you could experience the same benefits in your own emergency department (ED) or intensive care unit (ICU), you need to know whether the demographics of your patient population are comparable, whether you have an equally educated and organized team, and whether you have similar access to facilities and equipment. For this question, we were not able to define specific criteria. Instead, we assessed subjectively external validity of the studies selected in steps I to VI.

**Question VIII**

We included studies evaluating costs or cost-effectiveness of blood lactate monitoring.

### RESULTS

The results of the search and selection process are described in Figure 1.

**I. Does It Perform Well in the Laboratory?**

**Accuracy of Lactate Measurement**

**Device.** Using the hospital’s standard laboratory as the reference method, the selected studies generally reported small biases with clinically acceptable limits of agreement for point-of-care blood gas analyzers including the following: Nova Stat Profile 7,10, ultra, Nova Biomedical, Waltham, MA (8–10); Chiron Diagnostics, 865 series, Fernwald, Germany/Medfield, MA (11–14); and Radiometer ABL 725, Radiometer Medical A/S, Bronshoj, Denmark (15); and the following handheld devices: Accusport/trend, Roche Diagnostics, Mannheim, Germany (9–11, 16); i-STAT CG4+, East Windsor, NJ (15); and Lactate Pro, ARKRAY, Kyoto, Japan (17). Lactate plus (Nova Biomedical, Waltham, MA) produced higher lactate values than the reference method (15, 17).

**Compartment.** Although some described slightly higher peripheral venous (18) or capillary levels (11), most investigators found satisfactory agreement comparing capillary (16, 19, 20), venous (21), or central/mixed venous (22–24) levels with arterial levels as reference. Sample handling: Ongoing in vitro glycolysis was reported to occur after blood sampling, resulting in erroneous elevation of lactate levels (25), particularly in case of leukocytosis or high hematocrit (26). Analysis within 15 mins or storage <4°C was suggested for avoiding this.

**Exogenous Factors.** Infusion of Ringer’s lactate did not hamper accuracy (27), provided that a blood sample was drawn from a catheter that was adequately cleared from Ringer’s lactate (28). Another study showed that the most commonly used critical care drugs neither affected the accuracy (29). Finally, renal replacement therapy eliminated only negligible amounts of lactate and consequently did not interfere with lactate monitoring (30). However, lactate-containing buffer solutions were able to induce transient hyperlactatemia (31–33).

**Etiology of Hyperlactatemia**

### Anaerobic Hyperlactatemia

**Systemic Oxygen Imbalance.** Traditionally, hyperlactatemia is associated with tissue hypoxia. The causal relationship has been confirmed by experimental (34–36) and clinical (2) studies: When reducing the components of systemic D\textsubscript{O}2 until oxygen demand could no longer be met, and oxygen consumption was limited by D\textsubscript{O}2, this coincided with a sharp increase in lactate levels.

Several other observations also pointed to an anaerobic origin of hyper-
lactatemia in critically ill patients. Hemodynamically unstable patients with septic or cardiogenic shock had increased lactate/pyruvate ratios (37) and decreased arterial ketone body ratios (i.e., ratio between acetooacetate to β-hydroxybutyrate: proposed to reflect mitochondrial redox state), suggesting anaerobic production (37, 38). In the early phase of septic shock, hyperlactatemia was accompanied by oxygen supply dependency (39). Rivers and colleagues demonstrated that hyperlactatemia in severe sepsis or septic shock before resuscitation coincided with a low central venous oxygen saturation (ScvO2) and that increases in D˙O2 were associated with reductions in lactate (40). Similarly, low skin temperature, cardiac output, and mixed venous oxygen saturation (SvO2) were associated with higher lactate levels (41).

**Regional/Microcirculatory Oxygen Imbalance.** No critical level of D˙O2 or SvO2 could be associated with hyperlactatemia, which could represent regional differences in D˙O2 and demand (42). Furthermore, improving capillary perfusion was correlated with a reduction in lactate levels in patients with septic shock, independent of changes in systemic hemodynamic variables (43). The latter observation illustrates the hypothesis that, in the absence of low systemic D˙O2 relative to systemic metabolic demand, microcirculatory processes hampering oxygen utilization at the tissue level may raise lactate levels.

**Aerobic Hyperlactatemia**

Selected studies demonstrated that other mechanisms than tissue hypoxia can also account for hyperlactatemia. We found the following aerobic mechanisms:

- Increased aerobic glycolysis, resulting in amounts of pyruvate that exceed the pyruvate dehydrogenase capacity. Such enhanced glycolysis can be triggered by cytokine-mediated uptake of glucose (44, 45) or catecholamine-stimulated increased Na-K-pump activity (46–51), which was supported by a study of Levy et al in septic shock patients, where antagonizing the Na-K-pump completely stopped muscle lactate overproduction (3).

- Mitochondrial dysfunction (52–54).

- Impaired activity of pyruvate dehydrogenase, essential for the conversion of pyruvate into acetyl coenzyme A. This enzyme is inhibited in septic conditions (55, 56) and increasing its activity with dichloroacetate reduces significantly blood lactate levels (57). Thiamin deficiency (beriberi disease) inhibits pyruvate dehydrogenase activity and can cause hyperlactatemia (58).

- Liver dysfunction (59–62) and liver surgery (63). Reduced lactate clearance was also reported post cardiac surgery (64) and in sepsis (65, 66), where it was shown to predict poor outcome (67).

- Not the splanchnic area (68), but the lung can be an important source of lactate, both in pulmonary (61, 69) and extrapulmonary (70) disease, probably reflecting metabolic adaptations in response to inflammatory mediators rather than tissue hypoxia (71).

- Alkalois (72), because an H⁺-linked carrier mechanism is involved in the transport of lactate across the cell membrane that increases cellular lactate efflux during alkalosis.

- Several drugs and intoxications: Nucleosidic reverse transcriptase inhibitors used for the treatment of human immunodeficiency virus (by inducing mitochondrial cytopathy) (73–75), epinephrine (by increased glycolysis, glycolysis, and stimulation of the Na-K-pump) (76, 77), metformin (particularly in the presence of renal insufficiency), although a Cochrane review found no evidence that metformin is associated with increased lactate levels if prescribed under study conditions (78). Intoxications with methanol, cyanide (by inhibition of oxidative phosphorylation) (79), or ethylene-glycol (by artifactual reaction of lactate electrodes) (80) also significantly elevated lactate levels.

**II. Does It Provide Important Information in a Number of Clinical Situations?**

We selected studies on the prognostic value of hyperlactatemia in many different critical care conditions, the ED (Table 2) and the ICU (Table 3). In the ED setting, area under the receiver operating characteristic curve for mortality varied from 0.67 (81) to 0.98 (82), which indicates moder-
ate-to-excellent prognostic accuracy. In the ICU setting, area under the receiver operating characteristic curve varied from 0.53 (83) and 0.58 (84) to 0.86 (85), which indicates poor-to-good prognostic performance.

To answer the question whether a hyperlactatemic patient will die, which is what clinicians want to know when individually assessing patients, the positive predictive value or posttest probability is important. In some of our selected studies, positive predictive values for death in case of abnormal lactate levels (>2.0–2.5 mmol/l) were very low (4%–15% (81, 86, 87). However, comparison of the pretest probability (which is the study population mortality rate) with the posttest probability determines the value that lactate can add in risk-stratification: from our selected studies, it becomes clear that lactate generally increased the ability to predict nonsurvival, both in the ED and in the ICU setting.

None of the studies took into account that the real pretest probability not only depends on the mortality rate but also on the clinicians’ ability to estimate risk, using all other available clinical parameters. Some authors therefore called for a future study that captures clinicians’ estimates for probability of death before lactate measurement to evaluate the capacity to influence clinical practice decisions (88).

III. Is There a Relationship Between Lactate Levels and Metabolic Acidosis?

The level of lactate may be estimated from other acid-base variables. However, there was no clinically important relationship between lactate and pH or base excess (89–94), although one study showed that base excess could predict hyperlactatemia (95). Accuracy of the anion gap for screening for hyperlactatemia was generally poor (96–99), but this varied to reasonably accurate (95). Other studies showed that lactate was only responsible for a minor percentage of metabolic acidosis in critically ill patients (93, 100–103). Furthermore, lactate or nonlactate etiologies of metabolic acidosis are associated with different mortality rates (89, 104). Therefore, although hyperlactatemia has often been associated with the presence of a metabolic acidosis (lactic acidosis), this relationship seemed not straightforward at all. Because the conversion of pyruvate to lactate does not directly result in production of H+ ions, it

Table 2. Prognostic value of blood lactate levels in the ED

<table>
<thead>
<tr>
<th>Study</th>
<th>n (Mortality)</th>
<th>Population</th>
<th>Timing</th>
<th>Cutoff Value</th>
<th>Cutoff α priori</th>
<th>Sens (95% CI)</th>
<th>Spec (95% CI)</th>
<th>+LR</th>
<th>−LR</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>AUROC (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Infection/Sepsis</td>
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<tr>
<td>Shapiro et al (81)</td>
<td>1278 (94%)</td>
<td>Patients with suspected infection</td>
<td>ED admission</td>
<td>2.5</td>
<td>Yes</td>
<td>59% (50–68)</td>
<td>71% (69–74)</td>
<td>2.0</td>
<td>0.5</td>
<td>15% (12–19)</td>
<td>95% (94–96)</td>
<td>0.67</td>
</tr>
<tr>
<td>Howard et al (87)a,b</td>
<td>1287 (6%)</td>
<td>Patients with infection</td>
<td>ED admission</td>
<td>2.5</td>
<td>Yes</td>
<td>37% (26–49)</td>
<td>73% (71–76)</td>
<td>1.4</td>
<td>0.9</td>
<td>8% (5–11)</td>
<td>95% (94–96)</td>
<td>0.72</td>
</tr>
<tr>
<td>Treczak et al (88)</td>
<td>1177 (19%)</td>
<td>In 60% of patients during ED</td>
<td></td>
<td>2.0</td>
<td>Yes</td>
<td>45% (39–52)</td>
<td>74% (71–77)</td>
<td>1.7</td>
<td>0.7</td>
<td>29% (24–34)</td>
<td>85% (83–88)</td>
<td>—</td>
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<tr>
<td>Nguyen et al (123)</td>
<td>111 (42%)</td>
<td>First 6 hrs of ED stay</td>
<td></td>
<td>10% decrease</td>
<td>Yes</td>
<td>45% (30–60)</td>
<td>84% (73–92)</td>
<td>2.8</td>
<td>0.7</td>
<td>68% (49–83)</td>
<td>68% (56–78)</td>
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<td>Trauma</td>
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<tr>
<td>Pal et al (86)</td>
<td>5995 (3%)</td>
<td>Trauma patients</td>
<td>Trauma service admission</td>
<td>2.0</td>
<td>Yes</td>
<td>85% (79–90)</td>
<td>38% (37–38)</td>
<td>1.4</td>
<td>0.4</td>
<td>4% (3–5)</td>
<td>99% (98–99)</td>
<td>0.72</td>
</tr>
<tr>
<td>Dunne et al (124)</td>
<td>15179 (5%)</td>
<td>Trauma patients</td>
<td>Trauma center admission</td>
<td>6.0</td>
<td>Not clear</td>
<td>—</td>
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<td>—</td>
<td>23% (98%)</td>
<td>—</td>
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<tr>
<td>Kaplan et al (82)</td>
<td>282 (23%)</td>
<td>Major vascular injury patients</td>
<td>ED admission</td>
<td>5.0</td>
<td>Not clear</td>
<td>98% (82–100)</td>
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<td>—</td>
<td>98% (96–99)</td>
<td>0.98 (0.96–0.99)</td>
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<tr>
<td>Cardiac Arrest</td>
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<tr>
<td>Kliegel et al (125)</td>
<td>394 (51%)</td>
<td>Post cardiac arrest patients</td>
<td>ED admission</td>
<td>2.0</td>
<td>Yes</td>
<td>—</td>
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<td>—</td>
<td>0.78 (0.66–0.90)</td>
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<td>(surviving &gt;48 hrs)</td>
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<td>Heterogeneous</td>
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<tr>
<td>Sankoff et al (126)</td>
<td>176 (11%)</td>
<td>Heterogeneous patients with SIRS</td>
<td>ED admission</td>
<td>—</td>
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</table>

ED, emergency department; CI, confidence interval; —, not available; sens, sensitivity; spec, specificity; +LR, positive likelihood ratio; −LR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; AUROC, area under the receiver operating characteristic curve; CRT, capillary refill time; SIRS, systemic inflammatory response syndrome.

3 mos inclusion overlap with Shapiro et al (81); 4 sens, spec, LR, PPV, NPV calculated from estimates from figure; 5 in-hospital mortality; 6 ICU mortality; 7 28- (or 30-) day mortality; 8 6-mo mortality; 9 24-hr mortality; 10 unspecified mortality.
### Table 3. Prognostic value of blood lactate levels in the ICU

<table>
<thead>
<tr>
<th>Study</th>
<th>N (Mortality)</th>
<th>Population</th>
<th>Timing</th>
<th>Cutoff Value</th>
<th>Cutoff at a priori</th>
<th>Sens (95% CI)</th>
<th>Spec (95% CI)</th>
<th>+LR −LR</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease</td>
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<tr>
<td>Bernal et al (134)</td>
<td>93 (39%)</td>
<td>Paracetamol induced acute liver failure (initial sample)</td>
<td>ICU admission ±12 hrs later</td>
<td>3.5</td>
<td>No</td>
<td>86% (71–95)</td>
<td>91% (81–97)</td>
<td>0.8</td>
<td>0.77</td>
<td>86% (81–97)</td>
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<tr>
<td></td>
<td>99 (21%)</td>
<td>Paracetamol induced acute liver failure (validation sample)</td>
<td>ICU admission ±12 hrs later</td>
<td>3.5</td>
<td>No</td>
<td>82% (65–93)</td>
<td>96% (87–100)</td>
<td>0.6</td>
<td>0.69</td>
<td>89% (78–86)</td>
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<tr>
<td>Waterane et al (85)</td>
<td>151 (7%)</td>
<td>Post-liver resection patients</td>
<td>ICU admission —</td>
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<td></td>
<td>0.86</td>
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<tr>
<td>Punk et al (135)</td>
<td>181 (50%)</td>
<td>ICU patients with liver cirrhosis</td>
<td>ICU admission —</td>
<td>8.9</td>
<td>No</td>
<td>36% (28–46)</td>
<td>99% (94–100)</td>
<td>0.6</td>
<td>0.72</td>
<td>61% (53–69)</td>
<td>0.81 (0.75–0.87)</td>
</tr>
<tr>
<td>Kruse et al (136)</td>
<td>38 (68%)</td>
<td>ICU patients with liver disease</td>
<td>Maximum value during ICU stay 7.0</td>
<td>2.2</td>
<td>No</td>
<td>80% (59–93)</td>
<td>62% (32–86)</td>
<td>0.3</td>
<td>0.66</td>
<td>62% (32–86)</td>
<td>0.52 (0.45–0.60)</td>
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<td>Heterogeneous</td>
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<tr>
<td>Smith et al (137)</td>
<td></td>
<td>Heterogeneous ICU patients</td>
<td>ICU admission during first 24 hrs (12 measurements)</td>
<td>2.0</td>
<td>Yes</td>
<td>77% (68–85)</td>
<td>78% (74–86)</td>
<td>0.7</td>
<td>0.68</td>
<td>94% (85–88)</td>
<td>0.78</td>
</tr>
<tr>
<td>Suntomason et al (138)</td>
<td>70: 148 (25%)</td>
<td>T2A: 131 (11%) Heterogeneous emergency ICU patients</td>
<td>ICU admission (T0)</td>
<td>1.5</td>
<td>No</td>
<td>69% (54–81)</td>
<td>72% (68–85)</td>
<td>0.3</td>
<td>0.61</td>
<td>82% (73–89)</td>
<td>0.78</td>
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<tr>
<td></td>
<td>98 (13%)</td>
<td>T2A: 1.0 Heterogeneous emergency ICU patients</td>
<td>ICU admission during first 24 hrs (12 measurements)</td>
<td>2.0</td>
<td>Yes</td>
<td>68% (52–82)</td>
<td>83% (74–86)</td>
<td>0.4</td>
<td>0.65</td>
<td>85% (76–82)</td>
<td></td>
</tr>
<tr>
<td>Freire et al (139)</td>
<td>319 (25%)</td>
<td>Medical ICU patients</td>
<td>During first 24 hrs of ICU stay</td>
<td>2.0</td>
<td>Yes</td>
<td>77% (66–86)</td>
<td>53% (46–59)</td>
<td>0.6</td>
<td>0.68</td>
<td>88% (81–92)</td>
<td></td>
</tr>
<tr>
<td>Cusack et al (140)</td>
<td>100 (31%)</td>
<td>Heterogeneous ICU patients</td>
<td>ICU admission —</td>
<td></td>
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<td></td>
<td>0.65 (0.52–0.78)</td>
</tr>
<tr>
<td>Rochtaeschel et al (95)</td>
<td>300 (28%)</td>
<td>Heterogeneous ICU patients</td>
<td>ICU admission —</td>
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<td></td>
<td></td>
<td>0.66 (0.59–0.73)</td>
</tr>
<tr>
<td>Mark and Bankov (83)</td>
<td>45 (50%)</td>
<td>ICU patients requiring PAC insertion</td>
<td>ICU admission —</td>
<td></td>
<td></td>
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<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Maynard et al (141)</td>
<td>60 (33%)</td>
<td>Heterogeneous ICU patients</td>
<td>Any of 3 time points (ICU admission, 12 or 24 hrs later)</td>
<td>2.0</td>
<td>Yes</td>
<td>75% (51–91)</td>
<td>55% (38–71)</td>
<td>1.7</td>
<td>0.5</td>
<td>81% (62–94)</td>
<td></td>
</tr>
<tr>
<td>Dubin et al (142)</td>
<td>935 (11%)</td>
<td>Heterogeneous ICU patients</td>
<td>ICU admission —</td>
<td>2.4</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td>0.67 (0.61–0.73)</td>
</tr>
</tbody>
</table>
### Table 3.—Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>N (Mortality)</th>
<th>Population</th>
<th>Timing</th>
<th>Cutoff Value</th>
<th>Cutoff a priori</th>
<th>Sens (95% CI)</th>
<th>Spec (95% CI)</th>
<th>+LR</th>
<th>-LR</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>AUCROC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adan et al (8)</td>
<td>46 (41%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hypotensive ICU/ED patients (76% ICU)</td>
<td>During ICU/ED stay</td>
<td>4.0</td>
<td>No</td>
<td>62% (39–84)</td>
<td>88% (71–98)</td>
<td>5.2</td>
<td>0.4</td>
<td>80% (52–96)</td>
<td>77% (59–90)</td>
<td>—</td>
</tr>
<tr>
<td>Levy et al (143)</td>
<td>353 (16%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Nonhypotensive ICU/ED patients (51% ICU)</td>
<td>ICU admission</td>
<td>24 hrs later</td>
<td>2.9</td>
<td>No</td>
<td>72% (55–84)</td>
<td>63% (60–85)</td>
<td>0.7</td>
<td>0.4</td>
<td>68% (52–83)</td>
<td>77% (63–87)</td>
</tr>
<tr>
<td>Others Sasaki et al (144)</td>
<td>41 (44%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ICU patients with RRT</td>
<td>At onset RRT</td>
<td>3.5</td>
<td>No</td>
<td>83% (59–96)</td>
<td>61% (72–99)</td>
<td>9.2</td>
<td>0.2</td>
<td>88% (64–99)</td>
<td>88% (68–97)</td>
<td>—</td>
</tr>
</tbody>
</table>

| Children | Hatherill et al (145) | 705 (10%)<sup>d</sup> | PICU children | PICU admission | 2.0 | Yes | 46% (34–58) | 97% (96–98) | 15.3 | 0.9 | 64% (49–77) | 94% (92–96) | — |
| | | from cohort of 795 | | | | | | | | | | | — |
| | Blow et al (111) | 79 | Hemodynamically heterogeneous | PICU admission | 24 hrs later | 78% (60–90) | 89% (65–99) | 7.1 | 0.2 | 93% (76–99) | 70% (47–87) | 0.86 (0.73–0.99) |
| | Rady et al (110) | 36 | PICU patients with hypotension or ↑ CRRT | PICU admission | 24 hrs later | 78% (40–97) | 83% (74–90) | 4.6 | 0.3 | 32% (14–54) | 95% (91–100) | — |
| | Garcia Sanz et al (148) | 500 (3%)<sup>e</sup> | Heterogeneous PICU patients | PICU admission | 2.0 | Yes | 65% (46–79) | 71% (66–75) | 2.2 | 0.5 | 16% (9–21) | 97% (94–98) | 0.76 (0.67–0.85) |
| | | | | | | | | | | | | | — |
| | Roller et al (149) | 66 (29%)<sup>f</sup> | Heterogeneous PICU patients | PICU admission | 2.0 | No | 37% (20–55) | 87% (74–95) | 2.8 | 0.7 | 56% (24–58) | 97% (84–90) | 0.63 |
| | Kolski et al (150) | 75 (24%)<sup>g</sup> | Hemodynamically heterogeneous PICU children | PICU admission | 24 hrs later | 56% (37–67) | 63% (49–79) | 1.9 | 0.5 | 32% (16–49) | 88% (74–86) | 0.68 |
| | Golay-Cruz et al (150) | 10 (20%)<sup>h</sup> | Heterogeneous PICU patients | PICU admission | 24 hrs later | 56% (37–67) | 63% (49–79) | 1.9 | 0.5 | 32% (16–49) | 88% (74–86) | 0.68 |
| | Cheung et al (151) | 85 (16%)<sup>i</sup> | PICU patients with congenital heart surgery | PICU admission | 24 hrs later | 70% | No | 66% (56–79) | 84% (71–90) | 3.0 | 0.3 | 35% (23–57) | 91% (80–98) | 0.84 (0.76–0.92) |
| | Cheung et al (152) | 74 (20%)<sup>j</sup> | Neonates treated with ECMO | NICU admission | 15 | No | 53% (27–79) | 61% (54–78) | 1.5 | 0.6 | 25% (14–67) | 98% (88–96) | — |
| | Durward et al (101) | 85 (6%)<sup>k</sup> | Post cardiac surgery children | PICU admission | 24 hrs later | 60% (50–70) | 94% (89–98) | 6.2 | 0.5 | 46% (27–65) | 97% (89–95) | 0.80 (0.73–0.85) |

### Table 4. Observational cohort studies following implementation of a lactate-guided DO2 therapy algorithm

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Patients</th>
<th>Timing</th>
<th>Goals of Therapy</th>
<th>Provided Therapy</th>
<th>Primary End Point</th>
<th>Lactate on Entry</th>
<th>Lactate After Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rady et al (110)</td>
<td>36</td>
<td>Heterogeneous critically ill ED patients</td>
<td>During ED stay (6 ± 3 hrs)</td>
<td>Lactate &lt;2.0 and Svo2 ≥65%</td>
<td>Fluids, RBCs, dopamine, dobutamine (amounts not recorded)</td>
<td>In-hospital mortality</td>
<td>Lactate &lt; 2.0, Lactate and Svo2 &lt; 2.0</td>
<td>4.6 ± 3.8</td>
<td>2.6 ± 2.5, p &lt; .05 vs. entry</td>
</tr>
<tr>
<td>Blow et al (111)</td>
<td>79</td>
<td>Hemodynamically stable major trauma patients</td>
<td>First 24 hrs of ICU stay</td>
<td>Lactate &lt;2.5</td>
<td>Fluids, RBCs, dopamine, dobutamine (amounts not recorded)</td>
<td>In-hospital mortality</td>
<td>Lactate &lt; 2.0</td>
<td>58/79 (73%)</td>
<td>14/79 (18%)</td>
</tr>
<tr>
<td>Claridge et al (113)</td>
<td>364</td>
<td>Major trauma patients</td>
<td>First 24 hrs of ICU stay</td>
<td>Lactate &lt;2.5</td>
<td>Fluids, RBCs, dopamine, dobutamine (amounts not recorded)</td>
<td>In-hospital mortality</td>
<td>Lactate &lt; 2.0</td>
<td>16/364 (4%)</td>
<td>57/364 (16%)</td>
</tr>
<tr>
<td>Rossi et al (112)</td>
<td>710</td>
<td>Children after congenital heart surgery</td>
<td>Early hrs of ICU stay</td>
<td>Lactate &lt;2.2 or decrease &gt;0.5/hr vs. no lactate in control group</td>
<td>Any method to ↑ DO2 or ↓ VO2 (type/amount not recorded)</td>
<td>In-hospital mortality</td>
<td>Not available</td>
<td>Not available</td>
<td>mortality on comparison with historical control group: 13/70 (20%) vs. 61/1656 (4%), p = .02</td>
</tr>
</tbody>
</table>

Lactate, mean blood lactate level (mmol/L); ED, emergency department; MV, mechanical ventilation; RBCs, red blood cells; ICU, intensive care unit; CI, cardiac index (L/min/m²); DO2I, oxygen delivery index (mL/min/m²); VO2I, oxygen consumption index (mL/min/m²).
was hypothesized that only if the H+ ions generated during the hydrolysis of adenosine triphosphate cannot be recycled in the mitochondria, i.e., in anaerobic conditions, acidosis coincides with hyperlactatemia (105). Following this hypothesis, it has been argued that the presence of metabolic acidosis can be used to distinguish aerobic from anaerobic hyperlactatemia (106).

The weak correlation between hyperlactatemia and metabolic acidosis has also been explained from another point of view. In Stewart’s acid-base classification, three independent variables control pH: strong ion difference; PCO2; and the sum of the weak acids and proteins in plasma (107). An increased lactate level reduces strong ion difference, which has an acidifying effect. However, in Stewart’s model, this does not necessarily result in acidosis because other simultaneous alterations in strong ion difference, changes in the amount of weak acids and proteins, or changes in PCO2 can all influence pH (93, 100).

IV. Does It Increase Healthcare Workers’ Confidence?

Information provided by a parameter may lead to increased confidence among healthcare providers. Although questionable if no other clinical end point (mortality, morbidity, costs) is improved, increased confidence might be an important goal when decisions are made in conditions of uncertainty in critical care. For instance, in a trial on perioperative pulse oximetry, the rate of complications was not reduced, but 80% of the anesthesiologists felt more secure when using a pulse oximeter (108). It seems likely that lactate determinations could increase workers’ confidence because rapidly available and definite end points of resuscitation are scarce. An observation that the nursing team expressed a positive attitude toward implementation of a hemodynamic protocol that included frequent lactate measurements indirectly supports this (109). However, we were not able to find a study that specifically evaluated the effect on healthcare workers’ confidence.

V. Are Therapeutic Decisions Altered as a Result of Blood Lactate Levels?

In studies on treatment alterations post implementation of lactate monitoring, hyperlactatemia was interpreted as a result of anaerobic conditions due to systemic oxygen imbalance and this was a trigger to increase DO2 or decrease oxygen demand (110–113). This included administration of fluids, inotropic agents, red blood cell transfusion, mechanical ventilation, paralytic agents, sedatives, and analgesics. In the only randomized controlled study in which measurement of lactate was compared with not measuring lactate, more fluids and inotropes were administered in the lactate group (114).

We also selected professional guidelines: the Surviving Sepsis Campaign recommends the use of lactate as a trigger for early goal-directed therapy (>4 mmol/L) (115). The Clinical Practice Guideline concerning trauma resuscitation recommends lactate as a resuscitation end point but acknowledged that evidence of improved survival of such strategy has not been shown (116). Finally, the International Consensus Conference 2006 on hemodynamic monitoring and management of patients in shock also stresses the lack of clinical trials investigating the clinical value of incorporating lactate in a treatment protocol (117).

VI. Does Application of Blood Lactate Monitoring Result in Benefit to Patients?

As monitoring itself will not change outcome, an integrated treatment algorithm has to provide the benefit to patients. This has to be aimed at the conditions leading to hyperlactatemia rather than at reduction of lactate levels alone. For instance, improving pyruvate metabolism by administration of dichloroacetate decreased lactate levels (57) but this was not associated with a clinical benefit. Another study showed that bicarbonate therapy did not improve hemodynamic variables in patients with lactic acidosis (118). These observations indicate that the detrimental outcome associated with hyperlactatemia is more likely to be determined by the underlying cause than by the hyperlactatemia itself.

We selected four observational studies evaluating implementation of a lactate-guided DO2 therapy algorithm (Table 4). Lactate levels decreased significantly during lactate-guided therapy (110, 111, 113), which coincided with an increase in Scvo2 in one study (110). Patients who responded with normalization of lactate had lower mortality than those who remained hyperlactatemic (111, 113). One observational study made a comparison with a historical control group and found lower mortality post implementation of a lactate-guided DO2 therapy algorithm (112).

We selected nine randomized controlled studies that evaluated goal-directed DO2 therapy, which was not specifically lactate-guided, but that used lactate levels as a primary or secondary end point (Table 5). Out of the five studies that showed a positive outcome (40, 119–122), three studies reported a decrease of lactate in the intervention group compared with the control group (40, 120, 122).

However, we found only one completed randomized controlled study evaluating goal-directed DO2 therapy that included a lactate-guided group and a nonlactate-guided group (Table 6). This study in a postcardiac surgery population showed a reduction in length of stay in the lactate-guided group (114). Two studies are currently ongoing.

VII. Can You Expect a Similar Benefit in Your Own Setting?

To answer this question, the external validity of the previously selected studies needs to be determined. Given that lactate measurement is generally considered as easy and accurate, that it is commonly available worldwide, and given that evidence on the prognostic value of hyperlactatemia has been very consistent and applies to many different populations, it is clear that lactate can be used as a prognostic marker in your own setting. However, the value of lactate as a therapeutic tool remains unclear.

VIII. Are the Expected Benefits Worth the Costs?

A handheld lactate device, such as Accutrend (Roche, Basel, Switzerland) costs around €200 and a test strip costs €2. The price of a blood gas analyzer is around €3,000 and total costs per sample are €2 (10). In a German study, total costs were lowest with €1 per measurement, using the handheld device, followed by €2 using the blood gas analyzer (Chiron 865 series, Novartis Vaccines and Diagnostics, Emeryville, CA), and €5 when using the central hospital’s laboratory (11). In the Netherlands, external budget costs per measurement are €12. We did not find a study on the cost-effectiveness of lactate monitoring. Although costs of lactate measurement itself are relatively low,
costs of subsequent therapeutic consequences and use of health care resources are unknown.

**DISCUSSION**

We found that lactate performs well in the laboratory: The measurement itself is accurate and clinicians at the bedside can trust the numerical value of lactate levels they collect. However, sufficient understanding of anaerobic and aerobic mechanisms of production and clearance is essential for the correct interpretation of hyperlactemia. Although the prognostic accuracy of lactate varied considerably, lactate generally increased the ability to predict nonsurvival, both in the ED and ICU. The consistency of this finding means that lactate certainly has a place in the risk-stratification of critically ill patients. Because of the weak correlation between hyperlactatemia and metabolic acidosis, lactate should be directly measured instead of estimated from other acid-base variables. Furthermore, lactic or nonlactic metabolic acidoses are associated with different mortality.

Concerning the clinical impact of lactate monitoring, it seems likely that it can increase healthcare workers' confidence although we were not able to find studies on this topic. Lactate monitoring has the potential to alter therapeutic decisions as hyperlactatemia in critically ill patients is often interpreted as a result of systemic oxygen imbalance, triggering goal-directed $D\dot{O}_2$ therapy. Indirect evidence supports the therapeutic benefit of lactate monitoring. However, there is a lack of clinical trials investigating the clinical value of lactate-directed therapy; the only single-center clinical trial advocating its efficacy was performed in postcardiac surgery patients and this cannot easily be extrapolated to other patients.

**Table 5. Randomized controlled studies evaluating goal-directed $D\dot{O}_2$ therapy that were not specifically lactate-guided but that used lactate levels as a primary or secondary end point**

<table>
<thead>
<tr>
<th>Study</th>
<th>n (Intervention vs. Control)</th>
<th>Patients</th>
<th>Timing</th>
<th>Goals of Therapy (Differences Intervention vs. Control)</th>
<th>Provided Therapy (Significant Differences Intervention vs. Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuchschmidt et al (153)</td>
<td>51 (26 vs. 25)</td>
<td>Septic shock patients</td>
<td>72 hrs in the ICU</td>
<td>$CI \geq 6$ vs. $CI \geq 3$</td>
<td>↑ dose dobu (30 ± 1 vs. 12 ± 1 μg/kg/min)</td>
</tr>
<tr>
<td>Hayes et al (154)</td>
<td>100 (50 vs. 50)</td>
<td>Heterogeneous ICU patients</td>
<td>During ICI stay</td>
<td>$CI \geq 4.5$, $D\dot{O}_2I \geq 600$ and $V\dot{O}_2I \geq 170$ vs. $CI \geq 2.8$</td>
<td>↑ max dose dobu: (25 vs. 10 μg/kg/min), ↑ max dose nor: (1.2 vs. 0.23 μg/kg/min)</td>
</tr>
<tr>
<td>Durham et al (155)</td>
<td>58 (27 vs. 31)</td>
<td>Heterogeneous ICU patients (most trauma)</td>
<td>During indication PAC</td>
<td>$D\dot{O}_2I \geq 600$ or $V\dot{O}_2I \geq 150$ vs. $CI \geq 2.5$</td>
<td>Not available</td>
</tr>
<tr>
<td>Ueno et al (120)</td>
<td>34 (16 vs. 18)</td>
<td>Partial hepatectomy patients</td>
<td>First 24 postoperative hours in ICU</td>
<td>$CI \geq 4.5$, $D\dot{O}_2I \geq 600$ or $V\dot{O}_2I \geq 170$ vs. $CI \geq 2.8–4.0$</td>
<td>↑ dobu (69 vs. 0%), ↑ fluids 12–24 hrs (43 ± 19 vs. 32 ± 6 mL/kg)</td>
</tr>
<tr>
<td>Yu et al (119)</td>
<td>105 (64 vs. 41)</td>
<td>Surgical ICU patients (age 50–75 and &gt;75 yrs)</td>
<td>During indication PAC</td>
<td>$D\dot{O}_2I \geq 600$ or $D\dot{O}_2I \geq 450–550$</td>
<td>↑ inotropes in 50–75 yrs (91 vs. 52%), ↑ inotropes in &gt;75 yrs (95 vs. 56%)</td>
</tr>
<tr>
<td>Alia et al (156)</td>
<td>63 (31 vs. 32)</td>
<td>Severe sepsis/septic shock</td>
<td>96 hrs in the ICU</td>
<td>$D\dot{O}_2I \geq 600$ vs. $D\dot{O}_2I \geq 330$</td>
<td>↑ dobu (71 vs. 34%)</td>
</tr>
<tr>
<td>Rivers et al (40)</td>
<td>263 (130/133)</td>
<td>ED patients with severe sepsis or septic shock</td>
<td>First 6 hrs of ED stay</td>
<td>$ScvO_2 \geq 70%$ vs. no $ScvO_2$</td>
<td>↑ fluids (5.0 ± 3.0 vs. 3.5 ± 2.4 l), ↑ RBCs (64 vs. 19%), ↑ dobu (14 vs. 1%)</td>
</tr>
<tr>
<td>Pearse et al (121)</td>
<td>122 (62 vs. 60)</td>
<td>High-risk general surgery patients</td>
<td>First 8 hrs in the ICU</td>
<td>$D\dot{O}_2I \geq 600$ vs. CVP goals</td>
<td>↑ colloids (1.9 ± 0.9 vs. 1.2 ± 0.9 l), ↑ dopexamine (89% vs. 2%), ↑ nor (19% vs. 7%)</td>
</tr>
<tr>
<td>Chytra et al (122)</td>
<td>162 (80/82)</td>
<td>Multiple trauma patients (no TBI)</td>
<td>First 12 hrs in the ICU</td>
<td>Esophageal Doppler goals vs. CVP 12–15 mm Hg</td>
<td>↑ colloids (1.7 ± 0.4 vs. 0.7 ± 0.3 l), ↑ nor (23 vs. 40%)</td>
</tr>
</tbody>
</table>

Lactate, mean blood lactate level (mmol/L); $CI$, cardiac index (L/min/m²); $D\dot{O}_2I$, oxygen delivery index (ml/min/m²); $V\dot{O}_2I$, oxygen consumption index (ml/L/min/m²); CVP, central venous pressure; RBC, red blood cell transfusion; PAC, pulmonary artery catheter; nor, norepinephrine; dobu, dobutamine; dopa, dopamine; TBI, traumatic brain injury.

Studies evaluating preoperative or perioperative $D\dot{O}_2$ optimization were excluded.
critical care populations. In addition, although costs of lactate measurement itself are relatively low, cost-effectiveness of lactate measurements is unknown.

Strengths of our study include the systematic search and selection strategy and the eight-question format that provides a complete and clinically relevant assessment of the real value of lactate monitoring. Our study also has limitations. We did not perform a methodologic quality assessment of the selected studies. The variety of study designs was too large for a single methodologic quality score. We did not perform a meta-analysis, which would have been valuable when evaluating prognostic accuracy or efficacy of lactate-directed therapy. However, the studies were far too heterogeneous (large variations in patient categories, mortality rates, lactate cutoff values, and timing of measurements or interventions). Finally, the results of this study need to be interpreted in the light of the search and selection criteria, and we might have missed information.

CONCLUSIONS

Based on the results of this systematic HTA, blood lactate monitoring is recommended in critical care settings as the ED and ICU because it clearly has a place in the risk-stratification of critically ill patients. However, it is unknown whether the routine use of lactate as a resuscitation end point improves outcome. This warrants randomized controlled studies on the efficacy of lactate-directed therapy.

ACKNOWLEDGMENT

We thank Dr. W. J. Sibbald, who provided us with the outline of this HTA and who encouraged us to write this manuscript.

Table 5—Continued

<table>
<thead>
<tr>
<th>Primary End Point</th>
<th>Lactate on Entry (Intervention vs. Control)</th>
<th>Lactate After Therapy (Intervention vs. Control)</th>
<th>Outcome (Intervention vs. Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>4.7 ± 0.1 vs. 5.1 ± 0.6, p &gt; .05</td>
<td>After 72 hrs: 3.8 ± 0.6 vs. 4.5 ± 0.8, p &gt; .05</td>
<td>Equal mortality: 13/26 (50%) vs. 18/25 (72%), p = .14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 48 hrs: 1.7 (median, IQR 1.2–2.5) vs. 1.5 (1.1–2.1), p = .20</td>
<td>Equal mortality: 27/50 (54%) vs. 17/50 (34%), p = .04</td>
</tr>
<tr>
<td>Mortality</td>
<td>5.3 ± 2.3 vs. 5.8 ± 2.9, p = .53</td>
<td>After 24 hrs: 2.1 ± 1.3 vs. 2.4 ± 2.0, p = .52</td>
<td>Equal mortality: 3/21 (11%) vs. 3/31 (10%), p = .85</td>
</tr>
<tr>
<td>Not clear</td>
<td>3.2 ± 1.0 vs. 3.3 ± 0.8, p &gt; .05 (from figure)</td>
<td>After 12 hrs: 2.0 ± 0.7 vs. 2.9 ± 0.8, p &lt; .05</td>
<td>↓ postoperative hyperbilirubinemia: 0/16 (0%) vs. 3/18 (17%), p &lt; .05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 24 hrs: 1.1 ± 0.2 vs. 2.0 ± 0.3, p &lt; .05 (from figure)</td>
<td>Equal mortality: 0/16 (0%) vs. 2/18 (11%), p &gt; .05</td>
</tr>
<tr>
<td>Mortality</td>
<td>● 50–75 yrs: 2.5 ± 1.7 vs. 2.2 ± 1.4, p = .44</td>
<td>After 24 hrs: 1.8 ± 1.0 vs. 1.5 ± 0.9, p = .36</td>
<td>↓ mortality (age 50–75 yrs): 9/43 (21%) vs. 12/23 (52%), p = .01</td>
</tr>
<tr>
<td></td>
<td>● &gt;75 yrs: 3.4 ± 2.3 vs. 3.7 ± 2.8, p = .76</td>
<td>● &gt;75 yrs: 2.1 ± 0.1 vs. 2.3 ± 1.7, p = .56</td>
<td>Equal mortality (&gt;75 yrs): 12/21 (57%) vs. 11/18 (61%), p &gt; .99</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>2.6 (median, IQR 1.4–3.9) vs. 1.8 (1.1–3.5), p = .11</td>
<td>Average during 96 hrs: 2.0 (median, IQR 1.6–3.1) vs. 2.0 (1.3–3.7), p = .18</td>
<td>Equal mortality: 23/31 (74%) vs. 21/32 (66%), p = .46</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>7.7 ± 4.7 vs. 6.9 ± 4.5, p = .17</td>
<td>After 48 hrs: 4.3 ± 4.2 vs. 4.9 ± 4.7, p = .01</td>
<td>↓ in-hospital mortality: 38/130 (47%) vs. 59/133 (31%), p = .009</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>Change during 8 hrs: −0.3 ± 0.8 vs. −0.6 ± 1.1, p = .11</td>
<td>Average during 96 hrs: 2.0 (median, IQR 1.6–3.1) vs. 2.0 (1.3–3.7), p = .18</td>
<td>↓ complications: 27/62 (44%) vs. 41/60 (68%), p = .003</td>
</tr>
<tr>
<td>Lactate after 12 hrs and 24 hrs</td>
<td>4.2 ± 1.0 vs. 3.9 ± 0.9, p = .08</td>
<td>● 2.9 ± 0.5 vs. 3.2 ± 0.5, p &lt; .001 (12 hrs)</td>
<td>↓ infectious complications: 15/80 (19%) vs. 26/82 (34%), p = .032</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● 2.0 ± 0.4 vs. 2.4 ± 0.6, p &lt; .001 (24 hrs)</td>
<td></td>
</tr>
</tbody>
</table>
Table 6. Randomized controlled studies on goal-directed $\text{DO}_2$ therapy comparing a lactate-guided group and a non lactate-guided group

<table>
<thead>
<tr>
<th>Study</th>
<th>n (Intervention vs. Control)</th>
<th>Patients</th>
<th>Timing</th>
<th>Provided Therapy (Significant Differences)</th>
<th>Lactate on Entry (Intervention vs. Control)</th>
<th>Lactate After Therapy (Intervention vs. Control)</th>
<th>Outcome (Intervention vs. Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polonen et al (114)</td>
<td>393 (196 vs. 197) Postcardiac surgery patients</td>
<td>First 8 hrs of ICU stay</td>
<td>Lactate $\leq$ 2.0 and $\text{ScvO}_2$ $&gt;$ 70% vs. no lactate/ no $\text{ScvO}_2$</td>
<td>Hospital length of stay</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Jansen et al ongoing</td>
<td>Target: n = 350 (2 x 175) Heterogeneous ICU patients with lactate $\geq$ 3.0</td>
<td>First 8 hrs of ICU stay</td>
<td>Decrease in lactate $\geq$ 20% in two hrs vs. no lactate</td>
<td>---</td>
<td>In-hospital mortality</td>
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<td>Shapiro et al ongoing</td>
<td>Target: n = 300 ED patients with severe sepsis or septic shock</td>
<td>First 6 hrs of ED stay</td>
<td>Decrease in lactate $\geq$ 10% in 6 hrs vs. $\text{ScvO}_2$ $\geq$ 70%</td>
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<td>In-hospital mortality</td>
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IQR, interquartile range; ICU, intensive care unit; ED, emergency department.


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Abstract

Early identification of haemodynamic shock is widely acknowledged as a vital step towards improving survival. A report in the previous issue of Critical Care describes the relationship between lactate concentrations in blood samples analysed in the prehospital environment and subsequent hospital mortality. These preliminary data indicate a promising avenue of research into the treatment of haemodynamic shock. Larger observational and interventional trials are needed to confirm the clinical value of serum lactate measurement in the prehospital environment.

In the previous issue of Critical Care an interesting observational study suggests a promising avenue of research that has the potential to improve clinical outcomes [1]. The early identification and rapid treatment of haemodynamic shock is widely acknowledged as a vital step towards improving survival [2]. In prehospital care, this process is particularly challenging. Limitations of time, equipment, available skill set and environment render the objective diagnosis of haemodynamic shock difficult.

The utility of serum lactate as a tool to identify the most seriously ill patients and to monitor their response to treatment has long been recognised [3-5]. This latest investigation describes the prognostic value of peripheral venous or capillary blood lactate concentration, measured in 124 patients before hospital arrival by paramedic ambulance staff using hand-held battery-powered technology [1]. The findings confirm the expected relationship between the prehospital serum lactate concentration and subsequent hospital mortality. Similar findings in a much smaller investigation have been published previously [6]. These data should encourage further research into the prehospital use of serum lactate to facilitate prompt identification and treatment of haemodynamic shock and/or to indicate those patients who might benefit from advanced activation of medical staff in the destination hospital. Some important issues do, however, remain unresolved.

The authors suggest that a single value of serum lactate measured in the prehospital environment predicts hospital mortality in this population. This suggestion may, however, be a subtle overinterpretation of the findings. Whilst lactate levels are clearly much greater in those patients who die, this variable does not appear to have been included in the multivariate analysis. It is the change in serum lactate, between the first measurement in the community and the second on hospital arrival, that is independently associated with death. The importance of this distinction would depend upon how these findings are applied in clinical practice. If lactate measurement is incorporated into routine prehospital care, it would probably be as part of a specific treatment algorithm. Indeed, biomarkers can only be used to improve clinical outcome when used as a trigger for a specific intervention, or less commonly when used as a therapeutic target. Accurate data on threshold values are essential if lactate measurement is to be used in this way. In this study, receiver operator characteristic curve analysis suggests a lactate concentration of 3.5 mmol/l as the optimal cutoff value for mortality prediction. If lactate is not an independent predictor of outcome, however, then the utility of this threshold value may be limited. As the authors themselves suggest, larger trials are required to validate these findings. The sample population is also too small and too heterogeneous to support specific conclusions regarding threshold values for specific subgroups of patients (for example, septic shock patients).

For similar reasons, the accuracy of lactate measurement in peripheral venous or capillary blood samples must be carefully considered. This is a simple and attractive approach that allows the measurement of serum lactate in the great majority of patients attended in the prehospital environment. The relationship between the lactate concentration in such samples and those drawn from an arterial or central venous catheter, however, has not been established. Anecdotal
experience suggests that lactate concentrations are often greater in peripheral blood samples but not by a constant or predictable margin. Any difference is likely to be of greater importance in more severely shocked patients.

The authors are to be congratulated for completing this first phase of a promising line of investigation. Future research should further clarify the clinical significance of lactate concentrations in patients with haemodynamic shock. Intervventional trials may then confirm the efficacy of serum lactate measurements to aid the identification of these patients and to guide their subsequent treatment.

Competing interests
The author declares that they have no competing interests.

References