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

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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) increase 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 (an)aerobic etiology is required for its correct interpretation; 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 end point 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

Measurement 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) (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 patient 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 I

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

*See also p. 2858.

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Table 1. Eight-question format for performing a systematic health technology assessment

I.	Does lactate measurement perform well in a laboratory setting?
II.	Does lactate monitoring provide important information in a number of clinical situations?
III.	Is there a relationship between lactate levels and metabolic acidosis?
IV.	Does lactate monitoring increase workers' confidence?
V.	Does lactate measurement alter therapeutic decisions?
VI.	Does lactate monitoring result in benefit to the patients?
VII.	Can you expect a similar benefit in your own setting?
VIII.	Are the expected benefits worth the extra costs?

Adapted from Keenan et al (6).

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 ($\dot{D}o_2$) therapy, which we classified in increasing order of importance:

1. Observational cohort studies following implementation of a lactate-guided $\dot{D}o_2$ therapy algorithm;
2. Randomized controlled studies evaluating goal-directed $\dot{D}o_2$ 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 $\dot{D}o_2$ 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 Masurement

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* glycolyis 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 $\dot{D}o_2$ until oxygen demand could no longer be met, and oxygen consumption was limited by $\dot{D}o_2$, this coincided with a sharp increase in lactate levels.

Several other observations also pointed to an anaerobic origin of hyper-

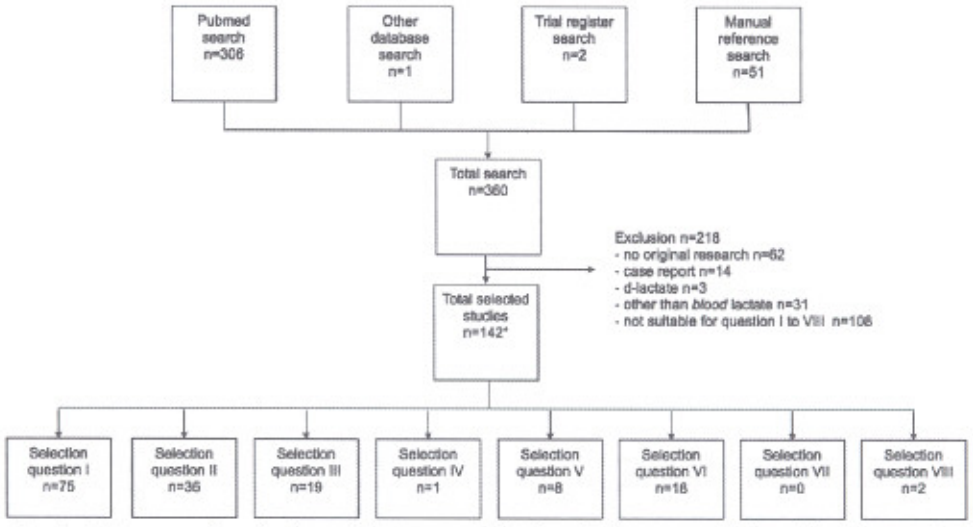

Figure 1. Search and selection process for performing an eight-step systemic health technology assessment. Adapted from Keenan et al (6).

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 acetoacetate 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 ($Scvo_2$) and that increases in $\dot{D}o_2$ were associated with reductions in lactate (40). Similarly, low skin temperature, cardiac output, and mixed venous oxygen saturation ($S\bar{v}o_2$) were associated with higher lactate levels (41).

Regional/Microcirculatory Oxygen Imbalance. No critical level of $\dot{D}o_2$ or $S\bar{v}o_2$ could be associated with hyperlactatemia, which could represent regional differences in $\dot{D}o_2$ 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 $\dot{D}o_2$ 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).
- Alkalosis (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 glycogenolysis, 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-

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

Study	n (Mortality)	Population	Timing	Cutoff Value	Cutoff *a priori*	Sens (95% CI)	Spec (95% CI)	+LR	−LR	PPV (95% CI)	NPV (95% CI)	AUROC (95% CI)
Infection/Sepsis												
Shapiro et al (81)	1278 (8%[a])	Patients with suspected infection	ED admission	2.5	Yes	59% (50–68)	71% (69–74)	2.0	0.5	15% (12–19)	95% (94–96)	0.67
				4.0		36% (27–46)	92% (90–93)	4.5	0.7	28% (21–37)	94% (93–95)	
Howell et al (87)[a,b]	1287 (6%[c])	Patients with suspected infection	ED admission	2.5	Yes	37% (26–49)	73% (71–76)	1.4	0.9	8% (5–11)	95% (94–96)	0.72
				4.0		38% (27–50)	94% (92–95)	6.3	0.7	27% (19–37)	96% (95–97)	
Trzeciak et al (88)	1177 (19%[c])	Patients with infection (60% ED, 22% ICU, 18% non-ICU ward)	In 60% of patients during ED stay (exact timing not available)	2.0	Yes	45% (39–52)	74% (71–77)	1.7	0.7	29% (24–34)	85% (83–88)	—
				4.0		19% (15–23)	93% (91–94)	2.6	0.9	38% (29–48)	83% (81–85)	0.56 (0.53–0.59)
Nguyen et al (123)	111 (42%[c])	Patients with severe sepsis or septic shock	First 6 hrs of ED stay	10% decrease in 6 hrs	Yes	45% (30–60)	84% (73–92)	2.8	0.7	68% (49–83)	68% (56–78)	—
Trauma												
Pal et al (86)	5995 (3%[c])	Trauma patients	Trauma service admission	2.0	Yes	85% (79–90)	38% (37–39)	1.4	0.4	4% (3–5)	99% (98–99)	0.72
Dunne et al (124)	15179 (5%[c])	Trauma patients	Trauma center admission	6.0	Not clear	—	—	—	—	23%	98%	—
Kaplan et al (82)	282 (23%[d])	Major vascular injury patients	ED admission	5.0	Not clear	98% (92–100)	—	—	—	—	—	0.98 (0.96–0.99)
Cardiac Arrest												
Kliegel et al (125)	394 (51%[e])	Post cardiac arrest patients (surviving >48 hrs)	ED admission	2.0	Yes	—	—	—		—	—	—
			24 hrs later			40% (33–47)	68% (61–75)	1.3	0.9	56% (47–64)	52% (46–59)	
			48 hrs later			31% (25–38)	86% (80–91)	2.2	0.8	70% (59–79)	55% (49–60)	
Heterogeneous												
Sankoff et al (126)	176 (11%[f])	Heterogeneous patients with SIRS	ED admission	—	—	—	—	—	—	—	—	0.78 (0.66–0.90)

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.

[a]3 mos inclusion overlap with Shapiro et al (81); [b]sens, spec, LR, PPV, NPV calculated from estimates from figure; [c]in-hospital mortality; [d]ICU mortality; [e]28- (or 30-) day mortality; [f]6-mo mortality; [g]24-hr mortality; [h]unspecified mortality.

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 3. Prognostic value of blood lactate levels in the ICU

Study	N (Mortality)	Population	Timing	Cutoff Value	Cutoff *a priori*	Sens (95% CI)	Spec (95% CI)	+LR	−LR	PPV (95% CI)	NPV (95% CI)	AUROC (95% CI)
Infection/Sepsis												
Friedman et al (127)	35 (46%[d])	ICU patients with severe sepsis	Timing start study not clear	2.0	Yes	81% (54–96)	47% (24–71)	1.5	0.4	57% (34–77)	75% (43–99)	—
			24 hrs after start study			69% (41–89)	84% (60–97)	4.3	0.4	79% (49–95)	76% (53–92)	
Tamion et al (128)	44 (30%[e])	ICU patients with septic shock	ICU admission	4.5	No	62% (32–86)	68% (49–83)	1.9	0.6	44% (22–69)	81% (61–93)	—
Dondorp et al (103)	268 (17%[h])	ICU patients with severe malaria	ICU admission	—	—	—	—	—	—	—	—	0.66 (0.56–0.76)
Trauma/Surgery												
Meregalli et al (84)	44 (16%[c])	Hemodynamically stable surgical ICU patients	ICU admission (T0) and 24 and 48 hrs later	—	—	—	—	—				T0: 0.58
Singhai et al (129)	30 (50%[e])	Patients with ruptured abdominal aortic aneurysm	Postoperative ICU admission	4.0	No	87% (60–98)	80% (52–96)	4.3	0.2	81% (54–96)	86% (57–98)	—
Mailliet et al (130)	325 (5%[d])	Postcardiac surgery patients	ICU admission	3.0	Yes	69% (38–88)	81% (77–86)	3.6	0.4	15% (7–28)	98% (96–100)	0.84 (0.73–0.95)
			During ICU stay			62%	75%	2.5	0.5	—	—	0.72 (0.57–0.88)
Abramson et al (131)	76 (33%[h])	Multiple trauma patients	24 hrs after ICU admission	2.0	Yes	100% (86–100)	53% (38–67)	2.1	0.0	51% (36–66)	100% (87–100)	—
			48 hrs after ICU admission			76% (55–91)	94% (84–99)	12.7	0.3	86% (65–97)	89% (77–96)	
Martin et al (92)	1298 (18%[c])	Trauma and emergency surgery patients	ICU admission	2.2	Yes	84% (78–88)	34% (32–37)	1.3	0.5	22% (19–25)	91% (87–93)	0.70 (0.67–0.74)
Blow et al (111)	79 (10%[h])	Major trauma patients, hemodynamically stable	ICU admission	2.5	Yes	100% (63–100)	30% (19–42)	1.4	0.0	14% (6–25)	100% (84–100)	—
			24 hrs later			100% (63–100)	92% (83–97)	12.5	0.0	57% (29–82)	100% (94–100)	
Claridge et al (113)[g]	364 (3%)	Major trauma patients	ICU admission	2.5	Yes	92% (64–100)	33% (28–39)	1.4	0.2	5% (3–8)	99% (95–100)	—
			24 hrs later			54% (25–81)	86% (82–89)	3.9	0.5	12% (5–24)	98% (96–99)	
Wahl et al (132)	169 (11%[h])	Postoperative ICU patients	ICU admission	—	—	—	—	—	—	—	—	0.79
Murillo-Cabezas et al (133)	210 (14%[d])	Hemodynamically stable patients with moderate or severe head injury	During first 48 hrs ICU stay	2.2	Yes	53% (34–72)	56% (49–63)	1.2	0.8	17% (10–26)	88% (80–93)	—
Liver disease												
Bernal et al (134)	93 (39%[h]), 85 at T12,	Paracetamol induced acute liver failure (initial sample)	±ICU admission	3.5	No	86% (71–95)	91% (81–97)	9.8	0.2	86% (71–95)	91% (81–97)	—
			±12 hrs later	3.0		82% (65–93)	96% (87–100)	20.5	0.2	93% (77–99)	89% (78–96)	—
	99 (21%[h]), 85 at T12	Paracetamol induced acute liver failure (validation sample)	±ICU admission	3.5	Yes	67% (43–85)	95% (87–99)	13.4	0.3	78% (52–94)	91% (83–96)	—
			±12 hrs later	3.0		76% (53–92)	97% (89–100)	25.3	0.2	89% (65–99)	93% (83–98)	—
Watanabe et al (85)	151 (7%[c])	Post liver resection patients	ICU admission	—	—	—	—	—	—	—	—	0.86
Funk et al (135)	181 (50%[d])	ICU patients with liver cirrhosis	ICU admission	8.9	No	36% (26–46)	99% (94–100)	36.0	0.6	97% (84–100)	61% (53–69)	0.81 (0.75–0.87)
Kruse et al (136)	38 (68%[c])	ICU patients with liver disease	Maximum value during ICU stay	2.2	No	80% (59–93)	62% (32–86)	2.1	0.3	80% (59–93)	62% (32–86)	—
				7.0		52% (31–72)	100% (75–100)	∞	0.5	100% (75–100)	52% (31–72)	
Heterogeneous												
Smith et al (137)	T0: 148 (35%[e]) T24: 131 (31%[e])	Heterogeneous ICU patients	ICU admission (T0) and 24 hrs later	T0: 1.5 T24: 1.0	No	69% (54–81) 68% (52–82)	77% (68–85) 83% (74–90)	3.0 4.0	0.4 0.4	61% (48–74) 65% (49–79)	82% (73–90) 85% (76–92)	0.78 —
Suistomaa et al (138)	98 (13%[c])	Heterogeneous emergency ICU patients	ICU admission during first 24 hrs (12 measurements)	2.0	Yes	69% (39–91) 77% (46–95)	73% (63–83) 55% (44–66)	2.7 1.7	0.4 0.4	29% (14–48) 21% (10–35)	94% (85–98) 94% (83–99)	—
Freire et al (139)	319 (25%[c])	Medical ICU patients	During first 24 hrs of ICU stay	2.0	Yes	77% (66–86)	53% (46–59)	1.6	0.4	35% (28–52)	88% (81–92)	—
				8.0		39% (21–42)	97% (94–99)	10.0	0.7	77% (59–90)	81% (76–85)	
Cusack et al (140)	100 (31%[e])	Heterogeneous ICU patients	ICU admission	—	—	—	—	—		—	—	0.65 (0.52–0.78)
Rocktaeschel et al (95)	300 (28%[c])	Heterogeneous ICU patients	ICU admission	—	—	—	—	—		—	—	0.66 (0.59–0.73)
Marik and Bankov (83)	45 (50%[c])	ICU patients requiring PAC	PAC insertion	—	—	—	—	—		—	—	0.53
Maynard et al (141)	60 (33%[d])	Heterogeneous ICU patients	Any of 3 time points (ICU admission, 12 or 24 hrs later)	2.0	Yes	75% (51–91)	55% (38–71)	1.7	0.5	45% (28–64)	81% (62–94)	—
Dubin et al (142)	935 (11%[e])	Heterogeneous ICU patients	ICU admission	2.4	Yes	—	—	—	—	—	—	0.67 (0.61–0.73)

Table 3.—*Continued*

Study	N (Mortality)	Population	Timing	Cutoff Value	Cutoff *a priori*	Sens (95% CI)	Spec (95% CI)	+LR	−LR	PPV (95% CI)	NPV (95% CI)	AUROC (95% CI)
Aduen et al (8)	46 (41%[b])	Hypotensive ICU/ED patients (76% ICU)	During ICU/ED stay	4.0	No	62% (39–84)	88% (71–98)	5.2	0.4	80% (52–96)	77% (59–90)	—
	353 (16%[b])	Nonhypotensive ICU/ED patients (51% ICU)				29% (17–42)	96% (93–98)	7.3	0.7	57% (37–76)	88% (84–91)	
Levy et al (143)	95 (44%[c])	Heterogeneous ICU patients	ICU admission	—	—	—	—	—	—	—	—	—
			24 hrs later	2.5	No	72% (55–84)	73% (60–85)	2.7	0.4	68% (52–81)	77% (63–87)	0.74
Others												
Sasaki et al (144)	41 (44%[c])	ICU patients with RRT	At onset RRT	3.5	No	83% (59–96)	91% (72–99)	9.2	0.2	88% (64–99)	88% (68–97)	—
Children												
Hatherill et al (145)	705 (10%[b])	PICU children	PICU admission	2.0	Yes	46% (34–58)	97% (96–98)	15.3	0.6	64% (49–77)	94% (92–96)	—
	50 (64%[d]), from cohort of 705	Hyperlactatemic (>2.0) PICU children	PICU admission			—	—	—	—	—	—	0.59 (0.43–0.76)
			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)
Hatherill et al (146)	99 (9%[d])	Post-cardiac surgery children	PICU admission	6.0	No	78% (40–97)	83% (74–90)	4.6	0.3	32% (14–55)	97% (91–100)	—
Hatherill et al (147)	46 (35%[b])	PICU patients with hypotension or ↑ CRT	PICU admission	5.0	No	75% (49–93)	63% (44–80)	2.0	0.4	52% (31–73)	83% (61–95)	0.83 (0.71–0.95)
	38 (21%[b])		24 hrs later			25% (3–65)	83% (65–94)	1.5	0.9	29% (4–71)	81% (63–93)	—
Garcia Sanz et al (148)	500 (7[d])	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)
				3.7	No	56% (38–72)	91% (88–94)	6.2	0.5	33% (21–46)	96% (94–98)	
				5.0	Not clear	47% (30–65)	94% (92–96)	7.8	0.6	41% (24–55)	96% (94–97)	
				7.0	Not clear	32% (19–51)	98% (96–99)	16	0.7	52% (31–73)	95% (93–97)	
Balasubramanyan et al (91)	66 (29%[b])	Heterogeneous PICU patients	Not clear	5.0	Not clear	37% (16–62)	87% (74–95)	2.8	0.7	54% (25–81)	77% (64–88)	0.63
Shime et al (157)	141 (8%[d])	Post cardiac surgery children	PICU admission	3.0	Not clear	64% (31–89)	87% (80–92)	4.9	0.4	29% (13–51)	97% (91–99)	—
				4.0		36% (11–69)	93% (87–96)	5.1	0.7	31% (9–61)	94% (89–98)	
Koliski et al (149)	75 (24[b])	Heterogeneous PICU patients	PICU admission	2.0	Yes	83% (59–96)	39% (26–52)	1.4	0.4	30% (18–44)	88% (69–98)	—
				2.8	No	71% (47–90)	63% (49–76)	1.9	0.5	38% (22–56)	88% (74–96)	0.68
			12 hrs later	1.3	No	64%	61%	1.6	0.6			0.62
			24 hrs later	3.0	No	56%	97%	18.7	0.5			0.81
Gotay-Cruz et al (150)	10 (20%[b])	Heterogeneous PICU patients	Peak during PICU stay	2.5	Yes	100% (16–100)	63% (24–92)	2.7	0.0	40% (5–85)	100% (48–100)	—
Cheung et al (151)	85 (16%[c])	Infants post congenital heart surgery	PICU admission	7.0	No	92% (66–100)	69% (57–79)	3.0	0.1	33% (21–55)	98% (89–100)	—
Cheung et al (152)	74 (20%[b])	Neonates treated with ECMO	NICU admission	25	Yes	40% (16–68)	97% (88–100)	13.3	0.6	75% (35–97)	86% (76–94)	—
			12 hrs later	15		53% (27–79)	100% (94–100)	∞	0.5	100% (63–100)	89% (79–96)	
Durward et al (101)	85 (6%[d])	Post cardiac surgery children	PICU admission	2.0	Yes	60% (15–95)	83% (72–90)	3.5	0.5	18% (4–43)	97% (90–100)	0.71 (0.44–0.98)
				3.0	No	60%	94%	9.6		60%	94%	
			24 hrs later	2.0	Yes	60% (15–95)	83% (72–90)	3.5	0.5	18% (4–43)	97% (90–100)	0.80 (0.56–1.00)

—, not available; sens, sensitivity; spec, specificity; ICU, intensive care unit; CI, confidence interval; +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; RRT, renal replacement therapy; PAC, pulmonary artery catheter; ED, emergency department; ∞, infinite; PICU, pediatric intensive care unit; ECMO, extracorporeal membrane oxygenation; NICU, neonatal intensive care unit.

[a]6-mo inclusion overlap with Blow et al (111); [b]sens, spec, LR, PPV, NPV calculated from estimates from figure; [c]in-hospital mortality; [d]ICU mortality; [e]28-(or 30-) day mortality; [f]6-mo mortality; [g]24-hr mortality; [h]unspecified mortality.

Table 4. Observational cohort studies following implementation of a lactate-guided $\dot{D}o_2$ therapy algorithm

Study	n	Patients	Timing	Goals of Therapy	Provided Therapy	Primary End Point	Lactate on Entry	Lactate After Therapy	Outcome
Rady et al (110)	36	Heterogeneous critically ill ED patients	During ED stay (6 ± 3 hrs)	Lactate <2.0 and Scv_{O_2} ≥65%	22% MV and paralysis, 6% RBCs, 97% fluids, 75% vasoactive agents	Lactate and Scv_2	4.6 ± 3.8	2.6 ± 2.5, ($p < .05$ vs. entry)	↓ Lactate and ↑ Scv_{O_2} (52 ± 18% to 65 ± 13%, $p < .05$) after Do_2 therapy
Blow et al (111)	79	Hemodynamically stable major trauma patients	First 24 hrs of ICU stay	Lactate <2.5	Fluids, RBCs, dopa, dobu (amounts not recorded)	In-hospital mortality	58/79 (73%) Lactate >2.4	14/79 (18%) lactate >2.4 after 24 hrs ($p < 0.05$ vs. entry)	↓ mortality in normo- vs. hyperlactatemia after 24 hrs: 0/65 (0%) vs. 6/14 (43%), $p < .05$
Claridge et al (113)	364	Major trauma patients	First 24 hrs of ICU stay	Lactate <2.5	Fluids, RBCs, dopa, dobu (amounts not recorded)	Infectious complications	246/364 (68%) Lactate >2.4	57/364 (16%) Lactate >2.4 after 24 hrs ($p < .05$ vs. entry)	↑ infection rate late (>12 hrs) vs. early (<12 hrs) normalization lactate: OR = 5.3 (95% CI = 3.1–9.3)
Rossi et al (112)	710 (+1656 historical controls)	Children after congenital heart surgery	Early hrs of ICU stay	Lactate <2.2 or decrease >0.5/hr vs. no lactate in control group	Any method to ↑ $\dot{D}o_2$ or ↓ $\dot{V}o_2$ (type/amount not recorded)	In-hospital mortality	Not available	Not available	↓ mortality on comparison with historical control group: 13/710 (2%) vs. 61/1656 (4)%, $p = .02$)

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/m^2); $\dot{D}o_2$I, oxygen delivery index(mL/min/m^2); $\dot{V}o_2$I, oxygen consumption index (mL/min/m^2).

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; P_{CO_2}; 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 P_{CO_2} 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 $\dot{D}o_2$ 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 $\dot{D}o_2$ therapy algorithm (Table 4). Lactate levels decreased significantly during lactate-guided therapy (110, 111, 113), which coincided with an increase in $Scvo_2$ 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 $\dot{D}o_2$ therapy algorithm (112).

We selected nine randomized controlled studies that evaluated goal-directed $\dot{D}o_2$ 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 $\dot{D}o_2$ 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 €30,000 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 $\dot{D}o_2$ 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

Table 5. Randomized controlled studies evaluating goal-directed $\dot{D}o_2$ therapy that were not specifically lactate-guided but that used lactate levels as a primary or secondary end point

Study	n (Intervention vs. Control)	Patients	Timing	Goals of Therapy (Differences Intervention vs. Control)	Provided Therapy (Significant Differences Intervention vs. Control)
Tuchschmidt et al (153)	51 (26 vs. 25)	Septic shock patients	72 hrs in the ICU	CI ≥6 vs. CI ≥3	↑ dose dobu (30 ± 1 vs. 12 ± 1 μg/kg/min)
Hayes et al (154)	100 (50 vs. 50)	Heterogeneous ICU patients	During ICI stay	CI ≥4.5, $\dot{D}o_2I$ ≥600 and $\dot{V}o_2I$ ≥170 vs. CI ≥2.8	↑ max dose dobu: (25 vs. 10 μg/kg/min), ↑ max dose nor: (1.2 vs. 0.23 μg/kg/min)
Durham et al (155)	58 (27 vs. 31)	Heterogeneous ICU patients (most trauma)	During indication PAC	$\dot{D}o_2I$ ≥600 or $\dot{V}o_2I$ ≥150 vs. CI >2.5	Not available
Ueno et al (120)	34 (16 vs. 18)	Partial hepatectomy patients	First 24 postoperative hours in ICU	CI ≥4.5, $\dot{D}o_2I$ ≥600 or $\dot{V}o_2I$ ≥170 vs. CI ≥2.8–4.0	↑ dobu (69 vs. 0%), ↑ fluids 12–24 hrs (43 ± 19 vs. 32 ± 6 mL/kg)
Yu et al (119)	105 (64 vs. 41)	Surgical ICU patients (age 50–75 and >75 yrs)	During indication PAC	$\dot{D}o_2I$ ≥600 vs. $\dot{D}o_2I$ ≥450–550	↑ inotropes in 50–75 yrs (91 vs. 52%), ↑ inotropes in >75 yrs (95 vs. 56%)
Alia et al (156)	63 (31 vs. 32)	Severe sepsis/ septic shock	96 hrs in the ICU	$\dot{D}o_2I$ ≥600 vs. $\dot{D}o_2I$ ≥330	↑ dobu (71 vs. 34%)
Rivers et al (40)	263 (130/133)	ED patients with severe sepsis or septic shock	First 6 hrs of ED stay	$ScvO_2$ ≥70% vs. no $ScvO_2$	↑ fluids (5.0 ± 3.0 vs. 3.5 ± 2.4 l) ↑ RBCs (64 vs. 19%), ↑ dobu (14 vs. 1%)
Pearse et al (121)	122 (62 vs. 60)	High-risk general surgery patients	First 8 hrs in the ICU	$\dot{D}o_2I$ ≥600 vs. CVP goals	↑ colloids (1.9 ± 0.9 vs. 1.2 ± 0.9 l), ↑ dopexamine (89% vs. 2%)
Chytra et al (122)	162 (80/82)	Multiple trauma patients (no TBI)	First 12 hrs in the ICU	Esophageal Doppler goals vs. CVP 12–15 mm Hg	↑ colloids (1.7 ± 0.4 vs. 0.7 ± 0.3 l), ↑ nor (23 vs. 40%)

Lactate, mean blood lactate level(mmol/L), CI, cardiac index (L/min/m^2); $\dot{D}o_2I$, oxygen delivery index (ml/min/m^2); $\dot{V}o_2I$, oxygen consumption index (mL/min/m^2); 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 $\dot{D}o_2$ 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.

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Table 5.—*Continued*

Primary End Point	Lactate on Entry (Intervention vs. Control)	Lactate After Therapy (Intervention vs. Control)	Outcome (Intervention vs. Control)
In-hospital mortality	4.7 ± 0.1 vs. 5.1 ± 0.6, $p > .05$	After 72 hrs: 3.8 ± 0.6 vs. 4.5 ± 0.8, $p > .05$	Equal mortality: 13/26 (50%) vs. 18/25 (72%), $p = .14$
In-hospital mortality	2.2 (median, IQR = 1.8–3.5) vs. 2.1 (1.5–3.3), $p = .69$	After 48 hrs: 1.7 (median, IQR = 1.2–2.5) vs. 1.5 (1.1–2.1), $p = .20$	↑ mortality: 27/50 (54%) vs. 17/50 (34%), $p = .04$
Mortality	5.3 ± 2.3 vs. 5.8 ± 2.9, $p = .53$	After 24 hrs: 2.1 ± 1.3 vs. 2.4 ± 2.0, $p = .52$	Equal mortality: 3/27 (11%) vs. 3/31 (10%), $p = .85$
Not clear	3.2 ± 1.0 vs. 3.3 ± 0.8, $p > .05$ (from figure)	• After 12 hrs: 2.0 ± 0.7 vs. 2.9 ± 0.8, $p < .05$ • After 24 hrs: 1.1 ± 0.2 vs. 2.0 ± 0.3, $p < .05$ (from figure)	• ↓ postoperative hyperbilirubinemia: 0/16 (0%) vs. 3/18 (17%), $p < .05$ • Equal mortality: 0/16 (0%) vs. 2/18 (11%), $p > .05$
Mortality	• 50–75 yrs: 2.5 ± 1.7 vs. 2.2 ± 1.4, $p = .44$ • >75 yrs: 3.4 ± 2.3 vs. 3.7 ± 2.8, $p = .76$	After 24 hrs: • 50–75 yrs: 1.8 ± 1.0 vs. 1.5 ± 0.9, $p = .36$ • >75 yrs: 2.1 ± 0.1 vs. 2.3 ± 1.7, $p = .56$	• ↓ mortality (age 50–75 yrs): 9/43 (21%) vs. 12/23 (52%), $p = .01$ • Equal mortality (>75 yrs):12/21 (57%) vs. 11/18 (61%), $p > .99$
ICU mortality	2.6 (median, IQR 1.4–3.9) vs. 1.8 (1.1–3.5), $p = .11$	Average during 96 hrs: 2.0(median,IQR 1.6–3.1) vs. 2.0 (1.3–3.7), $p = .18$	Equal mortality: 23/31 (74%) vs. 21/32 (66%), $p = .46$
In-hospital mortality	7.7 ± 4.7 vs. 6.9 ± 4.5, $p = .17$	4.3 ± 4.2 vs. 4.9 ± 4.7, $p = .01$	↓ in-hospital mortality: 38/130 (47%) vs. 59/133 (31%), $p = .009$
Postoperative complications	Change during 8 hrs: −0.3 ± 0.8 vs. −0.6 ± 1.1, $p = .11$		↓ complications: 27/62 (44%) vs. 41/60 (68%), $p = .003$
Lactate after 12 hrs and 24 hrs	4.2 ± 1.0 vs. 3.9 ± 0.9, $p = .08$	• 2.9 ± 0.5 vs. 3.2 ± 0.5, $p < .001$ (12 hrs) • 2.0 ± 0.4 vs. 2.4 ± 0.6, $p < .001$ (24 hrs)	↓ infectious complications: 15/80 (19%) vs. 28/82 (34%), $p = .032$

Table 6. Randomized controlled studies on goal-directed Do_2 therapy comparing a lactate-guided group and a non lactate-guided group

Study	n (Intervention vs. Control)	Patients	Timing	Goals of Therapy (Intervention vs. Control)	Provided Therapy (Significant Differences Intervention vs. Control)	Primary End Point	Lactate on Entry: (Intervention vs. Control)	Lactate After Therapy: (Intervention vs. Control)	Outcome: (Intervention vs. Control)
Polonen et al (114)	393 (196 vs. 197)	Postcardiac surgery patients	First 8 hrs of ICU stay	Lactate ≤2.0 and $ScvO_2$ >70% vs. no lactate/ no $ScvO_2$	↑ crystalloids (2.3 ± 1.5 vs. 2.0 ± 1.2 l), ↑ colloids (0.9 ± 0.4 vs. 0.8 ± 0.4), ↑ inotropes after 6 (38 vs. 20%) and 8 (41 vs. 20%) hours, ↓ vasopressors after 0 (8 vs. 15%), 2 (8 vs. 15%), 6 (3 vs. 10%) and 8 (5 vs. 10%) hrs	Hospital length of stay	—	—	↓ hospital stay: 6 (IQR = 5–7) vs. 7 (IQR = 5–8) days
Jansen et al[a] ongoing	Target: n = 350 (2× 175)	Heterogeneous ICU patients with lactate ≥3.0	First 8 hrs of ICU stay	Decrease in lactate ≥20% in two hrs vs. no lactate	—	In-hospital mortality	—	—	—
Shapiro et al[b] ongoing	Target: n = 300	ED patients with severe sepsis or septic shock	First 6 hrs of ED stay	Decrease in lactate >10% in 6 hrs vs. $ScvO_2$ ≥70%	—	In-hospital mortality	—	—	—

IQR, interquartile range; ICU, intensive care unit; ED, emergency department.
[a]Available at: http://clinicaltrials.gov/ct2/show/NCT00270673; [b]available at: http://clinicaltrials.gov/ct2/show/NCT00372502.

REFERENCES

1. Komanje EJ, Jansen TC, van der Hoven B, et al: The first demonstration of lactic acid in human blood in shock by Johann Joseph Scherer (1814–1869) in January 1843. *Intensive Care Med* 2007; 33:1967–1971
2. Ronco JJ, Fenwick JC, Tweeddale MG, et al: Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA* 1993; 270:1724–1730
3. Levy B, Gibot S, Franck P, et al: Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: A prospective study. *Lancet* 2005; 365: 871–875
4. Gattas DJ, Cook DJ: Procalcitonin as a diagnostic test for sepsis: health technology assessment in the ICU. *J Crit Care* 2003; 18: 52–58
5. Jaeschke RZ, Meade MO, Guyatt GH, et al: How to use diagnostic test articles in the intensive care unit: Diagnosing weanability using f/Vt. *Crit Care Med* 1997; 25: 1514–1521
6. Keenan SP, Guyatt GH, Sibbald WJ, et al: How to use articles about diagnostic technology: Gastric tonometry. *Crit Care Med* 1999; 27:1726–1731
7. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1:307–310
8. Aduen J, Bernstein WK, Khastgir T, et al: The use and clinical importance of a substrate-specific electrode for rapid determination of blood lactate concentrations. *JAMA* 1994; 272:1678–1685
9. Slomovitz BM, Lavery RF, Tortella BJ, et al: Validation of a hand-held lactate device in determination of blood lactate in critically injured patients. *Crit Care Med* 1998; 26: 1523–1528
10. Brinkert W, Rommes JH, Bakker J: Lactate measurements in critically ill patients with a hand-held analyser. *Intensive Care Med* 1999; 25:966–969
11. Boldt J, Kumle B, Suttner S, et al: Point-of-care (POC) testing of lactate in the intensive care patient. Accuracy, reliability, and costs of different measurement systems. *Acta Anaesthesiol Scand* 2001; 45: 194–199
12. Noordally O, Vincent JL: Evaluation of a new, rapid lactate analyzer in critical care. *Intensive Care Med* 1999; 25:508–513
13. Divatia JV, Jacques T, Day P, et al: Evaluation of a lactate sensor for rapid repeated measurements of blood lactate concentration. *Anaesth Intensive Care* 1998; 26:184–188
14. Godje O, Fuchs A, Dewald O, et al: [On-site laboratory monitoring on the intensive care unit. Blood gas, electrolyte, glucose, hemoglobin and lactate determination with the CIBA Corning 865 Analysis System]. *Anasthesiol Intensivmed Notfallmed Schmerzther* 1997; 32:549–556
15. Karon BS, Scott R, Burritt MF, et al: Comparison of lactate values between point-of-care and central laboratory analyzers. *Am J Clin Pathol* 2007; 128:168–171
16. Permpikul C, Ratanarat R, Neungton N: Blood lactate determined by a portable device in critically ill patients. *J Med Assoc Thai* 2000; 83:1348–1353
17. Ridenour RV, Gada RP, Brost BC, et al: Comparison and validation of point of care lactate meters as a replacement for fetal pH measurement. *Clin Biochem* 2008; 41: 1461–1465
18. Gallagher EJ, Rodriguez K, Touger M: Agreement between peripheral venous and arterial lactate levels. *Ann Emerg Med* 1997; 29:479–483
19. Fauchere JC, Bauschatz AS, Arlettaz R, et al: Agreement between capillary and arterial lactate in the newborn. *Acta Paediatr* 2002; 91:78–81
20. Frey B, Losa M: The value of capillary whole blood lactate for blood transfusion requirements in anaemia of prematurity. *Intensive Care Med* 2001; 27:222–227
21. Younger JG, Falk JL, Rothrock SG: Relationship between arterial and peripheral venous lactate levels. *Acad Emerg Med* 1996; 3:730–734
22. Weil MH, Michaels S, Rackow EC: Comparison of blood lactate concentrations in central venous, pulmonary artery, and arterial blood. *Crit Care Med* 1987; 15:489–490
23. Middleton P, Kelly AM, Brown J, et al: Agreement between arterial and central venous val-

ues for pH, bicarbonate, base excess, and lactate. *Emerg Med J* 2006; 23:622–624
24. Murdoch IA, Turner C, Dalton RN: Arterial or mixed venous lactate measurement in critically ill children. Is there a difference? *Acta Paediatr* 1994; 83:412–413
25. Astles R, Williams CP, Sedor F: Stability of plasma lactate in vitro in the presence of antiglycolytic agents. *Clin Chem* 1994; 40: 1327–1330
26. Andersen O, Haugaard SB, Jorgensen LT, et al: Preanalytical handling of samples for measurement of plasma lactate in HIV patients. *Scand J Clin Lab Invest* 2003; 63: 449–454
27. Didwania A, Miller J, Kassel D, et al: Effect of intravenous lactated Ringer's solution infusion on the circulating lactate concentration: Part 3. Results of a prospective, randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1997; 25:1851–1854
28. Jackson EVJ, Wiese J, Sigal B, et al: Effects of crystalloid solutions on circulating lactate concentrations: Part 1. Implications for the proper handling of blood specimens obtained from critically ill patients. *Crit Care Med* 1997; 25:1840–1846
29. Kost GJ, Nguyen TH, Tang Z: Whole-blood glucose and lactate. Trilayer biosensors, drug interference, metabolism, and practice guidelines. *Arch Pathol Lab Med* 2000; 124: 1128–1134
30. Levraut J, Ciebiera JP, Jambou P, et al: Effect of continuous venovenous hemofiltration with dialysis on lactate clearance in critically ill patients. *Crit Care Med* 1997; 25:58–62
31. Thomas AN, Guy JM, Kishen R, et al: Comparison of lactate and bicarbonate buffered haemofiltration fluids: Use in critically ill patients. *Nephrol Dial Transplant* 1997; 12: 1212–1217
32. Cole L, Bellomo R, Baldwin I, et al: The impact of lactate-buffered high-volume hemofiltration on acid-base balance. *Intensive Care Med* 2003; 29:1113–1120
33. Bollmann MD, Revelly JP, Tappy L, et al: Effect of bicarbonate and lactate buffer on glucose and lactate metabolism during hemodiafiltration in patients with multiple organ failure. *Intensive Care Med* 2004; 30: 1103–1110
34. Cain SM: Appearance of excess lactate in aneshetized dogs during anemic and hypoxic hypoxia. *Am J Physiol* 1965; 209: 604–608
35. Cain SM: Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *J Appl Physiol* 1977; 42:228–234
36. Zhang H, Vincent JL: Oxygen extraction is altered by endotoxin during tamponade-induced stagnant hypoxia in the dog. *Circ Shock* 1993; 40:168–176
37. Levy B, Sadoune LO, Gelot AM, et al: Evolution of lactate/pyruvate and arterial ketone body ratios in the early course of catecholamine-treated septic shock. *Crit Care Med* 2000; 28:114–119
38. Yassen KA, Galley HF, Lee A, et al: Mitochondrial redox state in the critically ill. *Br J Anaesth* 1999; 83:325–327
39. Friedman G, De Backer D, Shahla M, et al: Oxygen supply dependency can characterize septic shock. *Intensive Care Med* 1998; 24: 118–123
40. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
41. Kaplan LJ, McPartland K, Santora TA, et al: Start with a subjective assessment of skin temperature to identify hypoperfusion in intensive care unit patients. *J Trauma* 2001; 50:620–627
42. Astiz ME, Rackow EC, Kaufman B, et al: Relationship of oxygen delivery and mixed venous oxygenation to lactic acidosis in patients with sepsis and acute myocardial infarction. *Crit Care Med* 1988; 16:655–658
43. De Backer D, Creteur J, Dubois MJ, et al: The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. *Crit Care Med* 2006; 34:403–408
44. Haji-Michael PG, Ladriere L, Sener A, et al: Leukocyte glycolysis and lactate output in animal sepsis and ex vivo human blood. *Metabolism* 1999; 48:779–785
45. Meszaros K, Lang CH, Bagby GJ, et al: Contribution of different organs to increased glucose consumption after endotoxin administration. *J Biol Chem* 1987; 262: 10965–10970
46. Luchette FA, Friend LA, Brown CC, et al: Increased skeletal muscle Na+, K+-ATPase activity as a cause of increased lactate production after hemorrhagic shock. *J Trauma* 1998; 44:796–801
47. McCarter FD, James JH, Luchette FA, et al: Adrenergic blockade reduces skeletal muscle glycolysis and Na(+), K(+)-ATPase activity during hemorrhage. *J Surg Res* 2001; 99:235–244
48. Luchette FA, Robinson BR, Friend LA, et al: Adrenergic antagonists reduce lactic acidosis in response to hemorrhagic shock. *J Trauma* 1999; 46:873–880
49. McCarter FD, Nierman SR, James JH, et al: Role of skeletal muscle Na+-K+ ATPase activity in increased lactate production in sub-acute sepsis. *Life Sci* 2002; 70: 1875–1888
50. James JH, Wagner KR, King JK, et al: Stimulation of both aerobic glycolysis and Na(+)-K(+)-ATPase activity in skeletal muscle by epinephrine or amylin. *Am J Physiol* 1999; 277:E176–E186
51. James JH, Fang CH, Schrantz SJ, et al: Linkage of aerobic glycolysis to sodium-potassium transport in rat skeletal muscle. Implications for increased muscle lactate production in sepsis. *J Clin Invest* 1996; 98:2388–2397
52. Brealey D, Brand M, Hargreaves I, et al: Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet* 2002; 360:219–223
53. Crouser ED, Julian MW, Blaho DV, et al: Endotoxin-induced mitochondrial damage correlates with impaired respiratory activity. *Crit Care Med* 2002; 30:276–284
54. Fredriksson K, Hammarqvist F, Strigard K, et al: Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. *Am J Physiol Endocrinol Metab* 2006; 291:E1044–E1050
55. Vary TC, Martin LF: Potentiation of decreased pyruvate dehydrogenase activity by inflammatory stimuli in sepsis. *Circ Shock* 1993; 39:299–305
56. Vary TC: Sepsis-induced alterations in pyruvate dehydrogenase complex activity in rat skeletal muscle: Effects on plasma lactate. *Shock* 1996; 6:89–94
57. Stacpoole PW, Wright EC, Baumgartner TG, et al: A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. *N Engl J Med* 1992; 327:1564–1569
58. Naidoo DP, Gathiram V, Sadhabiriss A, et al: Clinical diagnosis of cardiac beriberi. *S Afr Med J* 1990; 77:125–127
59. Woll PJ, Record CO: Lactate elimination in man: effects of lactate concentration and hepatic dysfunction. *Eur J Clin Invest* 1979; 9:397–404
60. Almenoff PL, Leavy J, Weil MH, et al: Prolongation of the half-life of lactate after maximal exercise in patients with hepatic dysfunction. *Crit Care Med* 1989; 17: 870–873
61. De Backer D, Creteur J, Zhang H, et al: Lactate production by the lungs in acute lung injury. *Am J Respir Crit Care Med* 1997; 156:1099–1104
62. De Jonghe B, Cheval C, Misset B, et al: Relationship between blood lactate and early hepatic dysfunction in acute circulatory failure. *J Crit Care* 1999; 14:7–11
63. Chiolero R, Tappy L, Gillet M, et al: Effect of major hepatectomy on glucose and lactate metabolism. *Ann Surg* 1999; 229:505–513
64. Mustafa I, Roth H, Hanafiah A, et al: Effect of cardiopulmonary bypass on lactate metabolism. *Intensive Care Med* 2003; 29: 1279–1285
65. Levraut J, Ciebiera JP, Chave S, et al: Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. *Am J Respir Crit Care Med* 1998; 157:1021–1026
66. Chrusch C, Bands C, Bose D, et al: Impaired hepatic extraction and increased splanchnic production contribute to lactic acidosis in canine sepsis. *Am J Respir Crit Care Med* 2000; 161:517–526
67. Levraut J, Ichai C, Petit I, et al: Low exogenous lactate clearance as an early predictor of mortality in normolactatemic critically ill septic patients. *Crit Care Med* 2003; 31:705–710
68. De Backer D, Creteur J, Silva E, et al: The

hepatosplanchnic area is not a common source of lactate in patients with severe sepsis. *Crit Care Med* 2001; 29:256–261
69. Kellum JA, Kramer DJ, Mankad S, et al: Release of lactate by the lung in acute lung injury. *Adv Exp Med Biol* 1997; 411: 281–285
70. Walsh TS, McLellan S, Mackenzie SJ, et al: Hyperlactatemia and pulmonary lactate production in patients with fulminant hepatic failure. *Chest* 1999; 116:471–476
71. Routsi C, Bardouniotou H, Deliovria-Ioannidou V, et al: Pulmonary lactate release in patients with acute lung injury is not attributable to lung tissue hypoxia. *Crit Care Med* 1999; 27:2469–2473
72. Druml W, Grimm G, Laggner AN, et al: Lactic acid kinetics in respiratory alkalosis. *Crit Care Med* 1991; 19:1120–1124
73. Lonergan JT, Behling C, Pfander H, et al: Hyperlactatemia and hepatic abnormalities in 10 human immunodeficiency virus-infected patients receiving nucleoside analogue combination regimens. *Clin Infect Dis* 2000; 31:162–166
74. Claessens YE, Cariou A, Monchi M, et al: Detecting life-threatening lactic acidosis related to nucleoside-analog treatment of human immunodeficiency virus-infected patients, and treatment with L-carnitine. *Crit Care Med* 2003; 31:1042–1047
75. Bonnet F, Bonarek M, Abridj A, et al: Severe lactic acidosis in HIV-infected patients treated with nucleosidic reverse transcriptase analogs: A report of 9 cases. *La Revue de medecine interne/fondee* 2003; 24:11–16
76. Day NP, Phu NH, Bethell DP, et al: The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. *Lancet* 1996; 348:219–223
77. Levy B, Mansart A, Bollaert PE, et al: Effects of epinephrine and norepinephrine on hemodynamics, oxidative metabolism, and organ energetics in endotoxemic rats. *Intensive Care Med* 2003; 29:292–300
78. Salpeter S, Greyber E, Pasternak G, et al: Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2006; (1):CD002967
79. Baud FJ, Borron SW, Megarbane B, et al: Value of lactic acidosis in the assessment of the severity of acute cyanide poisoning. *Crit Care Med* 2002; 30:2044–2050
80. Morgan TJ, Clark C, Clague A: Artifactual elevation of measured plasma L-lactate concentration in the presence of glycolate. *Crit Care Med* 1999; 27:2177–2179
81. Shapiro NI, Howell MD, Talmor D, et al: Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 2005; 45:524–528
82. Kaplan LJ, Kellum JA: Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. *Crit Care Med* 2004; 32:1120–1124
83. Marik PE, Bankov A: Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients. *Crit Care Med* 2003; 31:818–822
84. Meregalli A, Oliveira RP, Friedman G: Occult hypoperfusion is associated with increased mortality in hemodynamically stable, high-risk, surgical patients. *Crit Care* 2004; 8:R60–R65
85. Watanabe I, Mayumi T, Arishima T, et al: Hyperlactemia can predict the prognosis of liver resection. *Shock* 2007; 28:35–38
86. Pal JD, Victorino GP, Twomey P, et al: Admission serum lactate levels do not predict mortality in the acutely injured patient. *J Trauma* 2006; 60:583–587; discussion 587–589
87. Howell MD, Donnino M, Clardy P, et al: Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med* 2007; 33:1892–1899. Epub 2007 July 6
88. Trzeciak S, Dellinger RP, Chansky ME, et al: Serum lactate as a predictor of mortality in patients with infection. *Intensive Care Med* 2007; 33:970–977
89. Brill SA, Stewart TR, Brundage SI, et al: Base deficit does not predict mortality when secondary to hyperchloremic acidosis. *Shock* 2002; 17:459–462
90. Aduen J, Bernstein WK, Miller J, et al: Relationship between blood lactate concentrations and ionized calcium, glucose, and acid-base status in critically ill and noncritically ill patients. *Crit Care Med* 1995; 23:246–252
91. Balasubramanyan N, Havens PL, Hoffman GM: Unmeasured anions identified by the Fencl-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. *Crit Care Med* 1999; 27:1577–1581
92. Martin MJ, FitzSullivan E, Salim A, et al: Discordance between lactate and base deficit in the surgical intensive care unit: Which one do you trust?. *Am J Surg* 2006; 191:625–630
93. Maciel AT, Park M: Unmeasured anions account for most of the metabolic acidosis in patients with hyperlactatemia. *Clinics* 2007; 62:55–62
94. Deshpande SA, Platt MP: Association between blood lactate and acid-base status and mortality in ventilated babies. *Arch Dis Child Fetal Neonatal Ed* 1997; 76:F15–F20
95. Rocktaeschel J, Morimatsu H, Uchino S, et al: Unmeasured anions in critically ill patients: Can they predict mortality? *Crit Care Med* 2003; 31:2131–2136
96. Aufricht C, Ties M, Hartl I, et al: The anion gap—Screening for hyperlactatemia in critically ill children? *Klin Padiatr* 1992; 204: 378–381
97. Adams BD, Bonzani TA, Hunter CJ: The anion gap does not accurately screen for lactic acidosis in emergency department patients. *Emerg Med J* 2006; 23:179–182
98. Moviat M, van Haren F, van der Hoeven H: Conventional or physicochemical approach in intensive care unit patients with metabolic acidosis. *Crit Care* 2003; 7:R41–R45
99. Lorenz JM, Kleinman LI, Markarian K, et al: Serum anion gap in the differential diagnosis of metabolic acidosis in critically ill newborns. *J Pediatr* 1999; 135:751–755
100. Murray DM, Olhsson V, Fraser JI: Defining acidosis in postoperative cardiac patients using Stewart's method of strong ion difference. *Pediatr Crit Care Med* 2004; 5:240–245
101. Durward A, Tibby SM, Skellett S, et al: The strong ion gap predicts mortality in children following cardiopulmonary bypass surgery. *Pediatr Crit Care Med* 2005; 6:281–285
102. Durward A, Skellett S, Mayer A, et al: The value of the chloride: sodium ratio in differentiating the aetiology of metabolic acidosis. *Intensive Care Med* 2001; 27:828–835
103. Dondorp AM, Chau TT, Phu NH, et al: Unidentified acids of strong prognostic significance in severe malaria. *Crit Care Med* 2004; 32:1683–1688
104. Gunnerson KJ, Saul M, He S, et al: Lactate versus non-lactate metabolic acidosis: A retrospective outcome evaluation of critically ill patients. *Crit Care* 2006; 10:R22
105. Gutierrez G, Wulf ME: Lactic acidosis in sepsis: a commentary. *Intensive Care Med* 1996; 22:6–16
106. Handy J: The origin and interpretation of hyperlactataemia during low oxygen delivery states. *Crit Care* 2007; 11:104
107. Stewart PA: Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 1983; 61:1444–1461
108. Moller JT, Pedersen T, Rasmussen LS, et al: Randomized evaluation of pulse oximetry in 20,802 patients: I. Design, demography, pulse oximetry failure rate, and overall complication rate. *Anesthesiology* 1993; 78: 436–444
109. Vallee F, Fourcade O, Marty P, et al: The hemodynamic "target": A visual tool of goal-directed therapy for septic patients. *Clinics* 2007; 62:447–454
110. Rady MY, Rivers EP, Nowak RM: Resuscitation of the critically ill in the ED: Responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. *Am J Emerg Med* 1996; 14:218–225
111. Blow O, Magliore L, Claridge JA, et al: The golden hour and the silver day: Detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. *J Trauma* 1999; 47:964–969
112. Rossi AF, Khan DM, Hannan R, et al: Goal-directed medical therapy and point-of-care testing improve outcomes after congenital heart surgery. *Intensive Care Med* 2005; 31:98–104
113. Claridge JA, Crabtree TD, Pelletier SJ, et al: Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. *J Trauma* 2000; 48:8–5
114. Polonen P, Ruokonen E, Hippelainen M, et al: A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac

surgical patients. *Anesth Analg* 2000; 90: 1052–1059
115. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008; 34:17–60. Epub 2007 Dec 4
116. Tisherman SA, Barie P, Bokhari F, et al: Clinical practice guideline: endpoints of resuscitation. *J Trauma* 2004; 57:898–912
117. Antonelli M, Levy M, Andrews PJ, et al: Hemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27–28 April 2006. *Intensive Care Med* 2007; 33:575–590
118. Mathieu D, Neviere R, Billard V, et al: Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: A prospective, controlled clinical study. *Crit Care Med* 1991; 19:1352–1356
119. Yu M, Burchell S, Hasaniya NW, et al: Relationship of mortality to increasing oxygen delivery in patients > or = 50 years of age: A prospective, randomized trial. *Crit Care Med* 1998; 26:1011–1019
120. Ueno S, Tanabe G, Yamada H, et al: Response of patients with cirrhosis who have undergone partial hepatectomy to treatment aimed at achieving supranormal oxygen delivery and consumption. *Surgery* 1998; 123:278–286
121. Pearse R, Dawson D, Fawcett J, et al: Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit Care* 2005; 9:R687–R693
122. Chytra I, Pradl R, Bosman R, et al: Esophageal Doppler-guided fluid management decreases blood lactate levels in multiple-trauma patients: A randomized controlled trial. *Crit Care* 2007; 11:R24
123. Nguyen HB, Rivers EP, Knoblich BP, et al: Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 2004; 32: 1637–1642
124. Dunne JR, Tracy JK, Scalea TM, et al: Lactate and base deficit in trauma: does alcohol or drug use impair their predictive accuracy? *J Trauma* 2005; 58:959–966
125. Kliegel A, Losert H, Sterz F, et al: Serial lactate determinations for prediction of outcome after cardiac arrest. *Medicine* 2004; 83:274–279
126. Sankoff JD, Goyal M, Gaieski DF, et al: Validation of the Mortality in Emergency Department Sepsis (MEDS) score in patients with the systemic inflammatory response syndrome (SIRS). *Crit Care Med* 2008; 36: 421–426
127. Friedman G, Berlot G, Kahn RJ, et al: Combined measurements of blood lactate concentrations and gastric intramucosal pH in patients with severe sepsis. *Crit Care Med* 1995; 23:1184–1193
128. Tamion F, Le Cam-Duchez V, Menard JF, et al: Erythropoietin and renin as biological markers in critically ill patients. *Crit Care* 2004; 8(5):R328–R335
129. Singhal R, Coghill JE, Guy A, et al: Serum lactate and base deficit as predictors of mortality after ruptured abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 2005; 30:263–266
130. Maillet JM, Le Besnerais P, Cantoni M, et al: Frequency, risk factors, and outcome of hyperlactatemia after cardiac surgery. *Chest* 2003; 123:1361–1366
131. Abramson D, Scalea TM, Hitchcock R, et al: Lactate clearance and survival following injury. *J Trauma* 1993; 35:584–588
132. Wahl W, Pelletier K, Schmidtmann S, et al: [Experiences with various scores in evaluating the prognosis of postoperative intensive care patients]. *Chirurg* 1996; 67: 710–717; discussion 718
133. Murillo-Cabezas F, Amaya-Villar R, Rincon-Ferrari MD, et al: Evidence of occult systemic hypoperfussion in head injured patients. Preliminary study. *Neurocirugia (Astur)* 2005; 16:323–332
134. Bernal W, Donaldson N, Wyncoll D, et al: Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: A cohort study. *Lancet* 2002; 359: 558–563
135. Funk GC, Doberer D, Kneidinger N, et al: Acid-base disturbances in critically ill patients with cirrhosis. *Liver Int* 2007; 27: 901–909
136. Kruse JA, Zaidi SA, Carlson RW: Significance of blood lactate levels in critically ill patients with liver disease. *Am J Med* 1987; 83:77–82
137. Smith I, Kumar P, Molloy S, et al: Base excess and lactate as prognostic indicators for patients admitted to intensive care. *Intensive Care Med* 2001; 27:74–83
138. Suistomaa M, Ruokonen E, Kari A, et al: Time-pattern of lactate and lactate to pyruvate ratio in the first 24 hours of intensive care emergency admissions. *Shock* 2000; 14:8–12
139. Freire AX, Bridges L, Umpierrez GE, et al: Admission hyperglycemia and other risk factors as predictors of hospital mortality in a medical ICU population. *Chest* 2005; 128: 3109–3116
140. Cusack RJ, Rhodes A, Lochhead P, et al: The strong ion gap does not have prognostic value in critically ill patients in a mixed medical/surgical adult ICU. *Intensive Care Med* 2002; 28:864–869
141. Maynard N, Bihari D, Beale R, et al: Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *JAMA* 1993; 270: 1203–1210
142. Dubin A, Menises MM, Masevicius FD, et al: Comparison of three different methods of evaluation of metabolic acid-base disorders. *Crit Care Med* 2007; 35:1264–1270
143. Levy B, Gawalkiewicz P, Vallet B, et al: Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. *Crit Care Med* 2003; 31: 474–480
144. Sasaki S, Gando S, Kobayashi S, et al: Predictors of mortality in patients treated with continuous hemodiafiltration for acute renal failure in an intensive care setting. *Asaio J* 2001; 47:86–91
145. Hatherill M, McIntyre AG, Wattie M, et al: Early hyperlactataemia in critically ill children. *Intensive Care Med* 2000; 26:314–318
146. Hatherill M, Sajjanhar T, Tibby SM, et al: Serum lactate as a predictor of mortality after paediatric cardiac surgery. *Arch Dis Child* 1997; 77:235–238
147. Hatherill M, Waggie Z, Purves L, et al: Mortality and the nature of metabolic acidosis in children with shock. *Intensive Care Med* 2003; 29:286–291
148. Garcia Sanz C, Ruperez Lucas M, Lopez-Herce Cid J, et al: Prognostic value of the pediatric index of mortality (PIM) score and lactate values in critically-ill children. *An Esp Pediatr* 2002; 57:394–400
149. Koliski A, Cat I, Giraldi DJ, et al: Blood lactate concentration as prognostic marker in critically ill children. *J Pediatr (Rio J)* 2005; 81:287–292
150. Gotay-Cruz F, Avilés-Rivera DH, Fernández-Sein A: Lactic acid levels as a prognostic measure in acutely ill patients. *P R Health Sci J* 1991; 10:9–13
151. Cheung PY, Chui N, Joffe AR, et al: Postoperative lactate concentrations predict the outcome of infants aged 6 weeks or less after intracardiac surgery: A cohort follow-up to 18 months. *J Thorac Cardiovasc Surg* 2005; 130:837–843
152. Cheung PY, Etches PC, Weardon M, et al: Use of plasma lactate to predict early mortality and adverse outcome after neonatal extracorporeal membrane oxygenation: A prospective cohort in early childhood. *Crit Care Med* 2002; 30:2135–2139
153. Tuchschmidt J, Fried J, Astiz ME, et al: Elevation of cardiac output and oxygen delivery improves outcome in septic shock. *Chest* 1992; 102:216–220
154. Hayes MA, Timmins AC, Yau EH, et al: Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330:1717–1722
155. Durham RM, Neunaber K, Mazuski JE, et al: The use of oxygen consumption and delivery as endpoints for resuscitation in critically ill patients. *J Trauma* 1996; 41:32–39
156. Alia I, Esteban A, Gordo F, et al: A randomized and controlled trial of the effect of treatment aimed at maximizing oxygen delivery in patients with severe sepsis or septic shock. *Chest* 1999; 115:453–461 bf
157. Shime N, Ashida H, Hiramatsu N, et al: Arterial ketone body ratio for the assessment of the severity of illness in pediatric patients following cardiac surgery. *J Crit Care* 2001; 16:102–107