2013/10/09
新光醫院急診科
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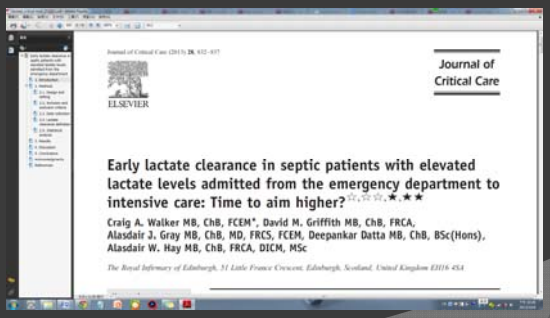
JOURNAL READING



Journal of Critical Care

ELSEVIER

Early lactate clearance in septic patients with elevated lactate levels admitted from the emergency department to intensive care: Time to aim higher?☆,☆☆,★,★★

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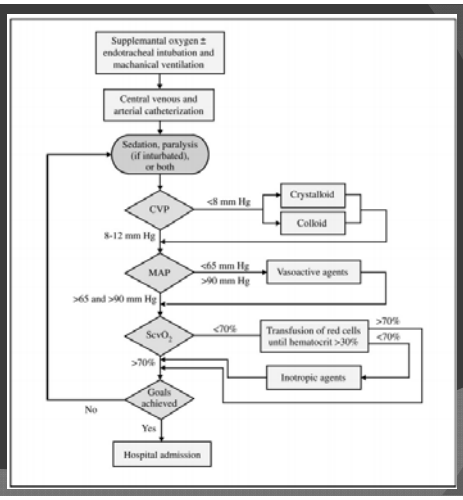
Introduction

- Sepsis is an increasingly common reason for hospital admission
- A prospective observational study of 198 ICUs across 24 European countries:
- 24.7% had a diagnosis,
- mortality rate 27% with sepsis,
- increasing to 54.1% with septic shock.
- Over a 22-year study period, Martin and colleagues:
- sepsis accounted for more than 10 million hospital admissions,
- rising steadily from approximately 164000 in 1979 to 660000 in 2000.

Introduction

- Recent studies: outcome from sepsis may be improved with optimal resuscitation.
- oxygen demand exceeds oxygen delivery: increased lactate production.
- Septic patients with high initial serum lactate have a higher mortality rate,
- independent of other organ failure indicators.
- In 2001, the single-center RCT of Rivers et al: EGDT improved outcome in severe sepsis.
- routine practice
- Surviving Sepsis Guidelines.
- Resuscitation end point: ScvO2 or LC



Introduction

- In 2004, Nguyen et al:
- LC at 6 hours was an independent predictor of survival in severe sepsis and septic shock;
- cut-off value: LC >10% at 6 hours
- => mean LC of 12% in nonsurvivors,
- a large proportion of these nonsurvivors had an LC >10%.
- EMShockNet Investigators:
- target of 10% LC at 6 hours in an EGDT trial comparing LC and ScvO2
- => only 9% (15/166) of septic patients failed to attain 10% LC at 6 hours.
- We believe that this LC target may be too low.

Objectives of study

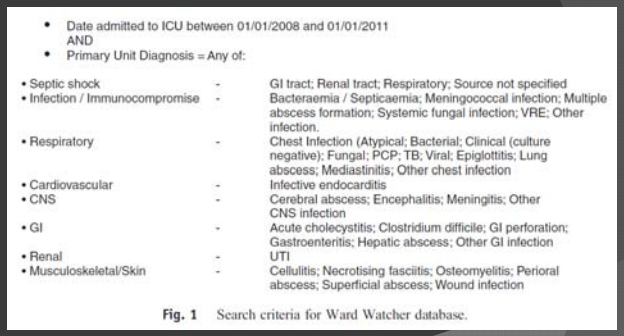
- (1) whether LC predicts mortality of septic patients
- (2) calculate the optimal "cut-off" value for LC

Methods

- 3-year (January 1, 2008, to December 31, 2010)
- single-center retrospective observational study
- consecutive adults (≥16 years)
- sepsis
- admitted directly from the ED to the ICU of a tertiary UK hospital.
- The ICU admits more than 1000 level 3 patients per annum.

Inclusion criteria

- admitted directly from the ED,
- admission ICU diagnosis or primary diagnosis of infection or sepsis (Fig. 1).
- The hospital records were obtained and searched manually to confirm that the presentation diagnosis of sepsis was correct.



- Date admitted to ICU between 01/01/2008 and 01/01/2011
  AND
- Primary Unit Diagnosis = Any of:

• Septic shock	-	GI tract; Renal tract; Respiratory; Source not specified
• Infection / Immunocompromise	-	Bacteraemia / Septicaemia; Meningococcal infection; Multiple abscess formation; Systemic fungal infection; VRE; Other infection.
• Respiratory	-	Chest Infection (Atypical; Bacterial; Clinical (culture negative); Fungal; PCP; TB; Viral; Epiglottitis; Lung abscess; Mediastinitis; Other chest infection
• Cardiovascular	-	Infective endocarditis
• CNS	-	Cerebral abscess; Encephalitis; Meningitis; Other CNS infection
• GI	-	Acute cholecystitis; Clostridium difficile; GI perforation; Gastroenteritis; Hepatic abscess; Other GI infection
• Renal	-	UTI
• Musculoskeletal/Skin	-	Cellulitis; Necrotising fasciitis; Osteomyelitis; Perioral abscess; Superficial abscess; Wound infection

Fig. 1 Search criteria for Ward Watcher database.

exclusion criteria

- no record of arterial lactate in the ED
- confirmed diagnosis on review of medical notes was not sepsis or infection
- hospital written records were unobtainable

Data collection

- Ward Watcher database, hospital, and ED records:
- Age
- Sex
- Infection type
- Initial ED lactate
- 6-hour lactate
- Acute Physiology and Chronic Health Evaluation (APACHE) II scores at 24 hours after admission
- 30-day survival.

Definition

- Percentage LC:

$$\text{Lactate clearance} = \frac{\left(\text{Lactate}^{\text{ED presentation}} - \text{Lactate}^{6\text{ hours}}\right)}{\text{Lactate}^{\text{ED Presentation}}} \times 100$$

Statistical analysis

- Logistic regression: relationship between LC and death
- Univariate analysis,
- Potential confounders :
  age, sex, APACHE II score, and initial lactate
- For patients who had an abnormal initial lactate concentration (≥2 mmol/L):
- ROC curves: initial lactate and LC
- to test the ability to predict mortality at 30 days.

Statistical analysis

- LC was converted into lactate "non-clearance" by converting the percentage LC into a proportion and subtracting from 1.
- ROC curves:
  (i) all patients
  (ii) subgroup of patients with abnormal initial lactate concentration (≥2 mmol/L)
- AUC:
  => Optimal cut-off points: maximizing Youden's index.
- Youden index = sensitivity+specificity-1
- maximize (sensitivity+specificity)

Results

- 106 patients were initially identified.
- 78 patients were available (Fig. 2).
- Characteristics of the included patients are summarized in Table 1.

Table 1 Patient characteristics

	Participants
Age, median (IQR)	56 (40-66)
Female, n (%)	34 (43%)
APACHE II, mean (95% CI)	24.6 (22.5-26.7)
Initial lactate, median (IQR)	4.9 (2.1-7.8)
LC, median (IQR)	26.9% (−0.1 to 50.6)
30-d mortality	32.1% (25/78)

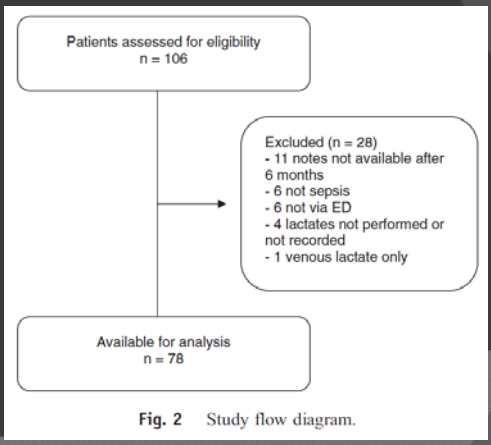


Fig. 2 Study flow diagram.

Results

- **Median initial lactate values** (interquartile range [IQR]):
  survivors: 3.4 mmol/L (1.8-6.4)
  nonsurvivors: 6.0 mmol/ L (4.2-13.3)
- **6-hour LC** (95% confidence interval [CI]):
  survivors: 37.2% (1.4-55.0)
  nonsurvivors: 10.5% (−0.7 to 29.5)
- As percentage LC increased, mortality reduced (odds ratio for each unit change 0.99; 95% CI, 0.98-1.00).

Results

- On univariate testing,
  APACHE II (P < .001),
  initial lactate (P < .001),
  age (P = .01)
  but not sex (P = .13)
  were associated with 30-day mortality
- After adjustment for those confounders
  => LC was independently associated with 30-day mortality (P = .04; Table 2).
- Interaction term for LC and initial lactate did not reach statistical significance (P = .30).

Table 2 Logistic regression model: variables and mortality odds ratios

Variable	Odds ratio (95% CI)	*P*
LC (per % change lactate)	0.99 (0.97-1.00)	.04
Initial lactate (per mmol/L)	1.21 (1.06-1.42)	.01
Age (per year)	1.04 (1.00-1.09)	.05
APACHE II score (per point)	1.06 (1.02-1.19)	.02

Results

- 64 patients had abnormal lactates at presentation, the other 14 patients all survived.
- AUC for initial lactate:
- in all patients: 0.68 (95% CI, 0.57-0.80);
  Optimal initial lactate cut-off: 4.2 mmol/L.
- in patients with an abnormal initial lactate (≥2 mmol/L): 0.57 (95% CI, 0.43-0.71).
- ROC curve for lactate nonclearance (Fig. 3):
- AUC 0.79 (95% CI, 0.68-0.90).
  Optimal cut-off: 0.64, corresponding to an LC of 36%.

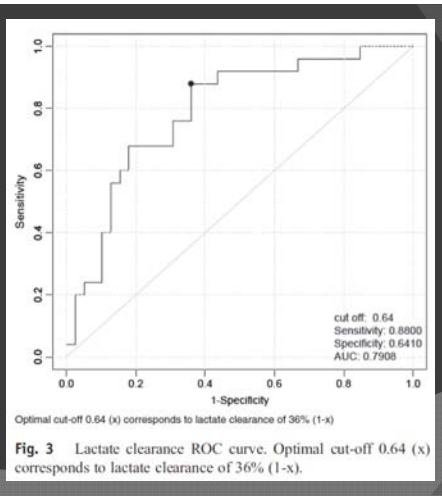


Fig. 3 Lactate clearance ROC curve. Optimal cut-off 0.64 (x) corresponds to lactate clearance of 36% (1-x).

Results

- **Mortality rate**:
- LC =< 36%: 61.1% (22/36)
- LC > 36%: 10.7% (3/28)
- **LC at 6 hours** of =< 36% predicted mortality with:
  sensitivity: 88.0%,
  specificity: 64.1%,
  positive predictive value: 61.1%,
  negative predictive value: 89.3%.
- Patients with an LC of =< 36% were much more likely to die
  (hazard ratio 7.33 [95% CI, 2.17-24.73]; P < .001).

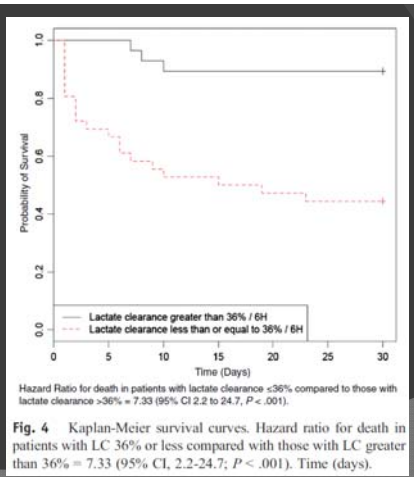


Fig. 4 Kaplan-Meier survival curves. Hazard ratio for death in patients with LC 36% or less compared with those with LC greater than 36% = 7.33 (95% CI, 2.2-24.7; *P* < .001). Time (days).

Discussion

- **Early LC** (AUC, 0.79) > **Initial lact**ate (AUC, 0.57)
- remarkably well as a predictor of 30-day mortality
- more discriminant test

- **Optimal cut-off values**:
  Initial lactate (for all patients): 4.2 mmol/L
  6-hour LC: 36%

- **Mortality** was significantly worse in patients with LC =< 36% compared > 36%
  (61.1% vs 10.7%; P < .001).

Discussion

- In 2011, Nguyen et al: addition of an LC target to a sepsis bundle improved outcome.
- 3 EGDT RCTs, which have investigated resuscitation guided by an LC target.
- EMShockNet Investigators:
- comparing a target LC of >10% at 6 hours with an ScvO2 target of >70% at 6 hours and found comparable mortality rates
  (17% vs 23%).
- => LC can be used as an equivalent or alternative to targeting ScvO2?

Discussion

- Jansen et al: with and without a target LC of 20% every 2 hours in a heterogenous group of ICU patients but demonstrated no significant outcome benefit for the intervention.
- => high LC in both the intervention and control arms suggesting that aggressive resuscitation may provide good LC without the need for an explicit LC target.

- Tian et al randomized septic shock patients to 6 hours of either target LC greater than 30%, target LC greater than 10%, or standard EGDT.
- 62 patients analyzed, 28-day mortality rates were significantly lower in the 30% LC group (28.6%) and the 10% group (36.4%) than the control group (63.2%); P < .05.
- => targeting high LC

Discussion

- The utility of LC to guide the resuscitation of septic patients may depend on the target set.
- Our logistic regression model also demonstrates that there is an incremental improvement in survival with increasing clearance, suggesting that a higher target may be set.
- Indeed, the updated Surviving Sepsis Campaign (2012) guidelines advocate targeting resuscitation to normalize lactate in patients with elevated lactate levels.

Strengths

- Included extremely sensitive search criteria
  => reduced the likelihood of overlooking appropriate patients.
- Ward Watcher database
  => tightly governed and accurate data set with less than 6% of patients incorrectly assigned as having sepsis.
- We subsequently searched ED and hospital notes manually to maximize data completion.

Limitation

- **Relatively low sample size**:
- comparable with previous reported studies
- only included patients admitted directly from the ED to the ICU: to ensure that aggressive resuscitation was provided

- **Retrospective sampling**

- **Derived optimal LC**:
- only to those patients with elevated initial serum lactate levels
- support continuing to resuscitate patients as per current EGDT targets while further research into LC is undertaken.

Conclusions

- In ED patients admitted to intensive care with severe sepsis or septic shock, we found that:
- 6-hour LC was a significantly better predictor of mortality than initial lactate
- independent of other markers of organ dysfunction.
- Lactate clearance provides important additional information over and above other measures.
- Best cut-off value for LC was 36%.
  This is a significantly higher LC than previously reported, and we would support further research targeting a higher LC of 36% as a distinct resuscitation end point in patients with severe sepsis and septic shock.

Thanks for your Attention!