Early lactate clearance for death prediction in severe sepsis or septic shock patients presenting to the Emergency Department

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Presenter Disclosure

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The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose

Objectives

- Describe multi-hospital system developed sepsis database for evaluation of process and outcome measures.
- Explain results on analysis between early lactate clearance and in-hospital mortality.

Background

- Worldwide burden of sepsis between 15,000,000 and 19,000,000 annually (1).
- Between 2004 and 2009, incidence of severe sepsis increased annually in U.S. by 13.0% (2).
- Severe sepsis mortality rates ranged from 30-50% and accounted for 200,000 U.S. deaths annually (3).
- Public Health concern.

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Background

Sepsis / Severe Sepsis / Septic Shock

Sepsis ICD-9-CM: 995.91	Severe Sepsis ICD-9-CM: 995.92	Septic Shock ICD-9-CM: 995.92 and 785.52
• Suspected infection accompanied by presence of two systemic inflammatory response syndrome (SIRS) conditions	• Vital organ dysfunction accompanies sepsis • The result of an excess of normal antimicrobial host defense mechanisms	• Form of severe sepsis with associated hypotension (low blood pressure) despite adequate fluid resuscitation

Sepsis Initiative

- **CEO of North Shore-LIJ Health System, Michael Dowling,** prioritized sepsis mortality reduction (by 50% in five years) as a performance improvement initiative in 2009.
- **North Shore-LIJ Health System**
  - During study Health System served 7 million people in Long Island, Queens, Manhattan, and Staten Island
    - **11 hospitals: 5 tertiary / 6 community**
    - Over 250,000 inpatient discharges per year
    - Over 500,000 ED visits per year

Sepsis Performance Measures Database

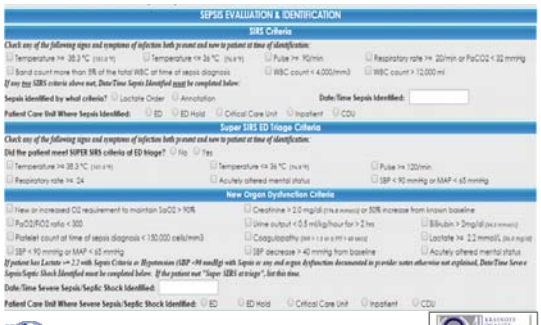
- By end of 2009, clinicians and the quality management team developed uniform sepsis metrics to be captured in central database.
- Data elements related to sepsis diagnosis and treatment were delineated by clinical members of Sepsis Task Force to Krasnoff Quality Management Institute (KQMI).
- Database developed in early 2010.

Sepsis Performance Measures Database

- Expert staff at KQMI developed a user friendly web tool with an Oracle database as a back end to capture demographics, clinical data elements, process and outcome measures.
- Logic was programmed into the web tool to aid in accurate and clean data entry.
- Database provides:
  - Continual monitoring of performance measures
  - In depth retrospective data analysis

Standardized Database

Criteria Elements for Severe Sepsis/Septic Shock


SEPSIS EVALUATION & IDENTIFICATION

SIRS Criteria

Check any of the following signs and symptoms of infection both present and new to patient at time of identification:

Temperature >= 38.3 °C (101.0 °F) | Temperature <= 36 °C (96.8 °F) | Pulse >= 90/min | Respiratory rate >= 20/min or PaCO2 < 32 mmHg

Band count more than 5% of the total WBC at time of sepsis diagnosis | WBC count < 4,000/mm3 | WBC count > 12,000 ml

If any two SIRS criteria above met, Date/Time Sepsis Identified must be completed below:

Sepsis identified by what criteria? Lactate Order | Annotation | Date/Time Sepsis Identified:

Patient Care Unit Where Sepsis Identified: ED | ED Hold | Critical Care Unit | Inpatient | CDU

Super SIRS ED Triage Criteria

Check any of the following signs and symptoms of infection both present and new to patient at time of identification:

Did the patient meet SUPER SIRS criteria at ED triage? No | Yes

Temperature >= 38.3 °C (101.0 °F) | Temperature <= 36 °C (96.8 °F) | Pulse >= 120/min

Respiratory rate >= 24 | Acutely altered mental status | SBP < 90 mmHg or MAP < 65 mmHg

New Organ Dysfunction Criteria

New or increased O2 requirement to maintain SaO2 > 90% | Creatinine > 2.0 mg/dl (176.8 mmol/l) or 50% increase from known baseline | Bilirubin > 2mg/dl (34.2 mmol/l)

PaO2/FiO2 ratio < 300 | Urine output < 0.5 ml/kg/hour for > 2 hrs | Lactate >= 2.2 mmol/L (20.0 mg/dl)

Platelet count at time of sepsis diagnosis < 150,000 cells/mm3 | Coagulopathy (INR > 1.5 or a PTT > 60 secs)

SBP < 90 mmHg or MAP < 65 mmHg | SBP decrease > 40 mmHg from baseline | Acutely altered mental status

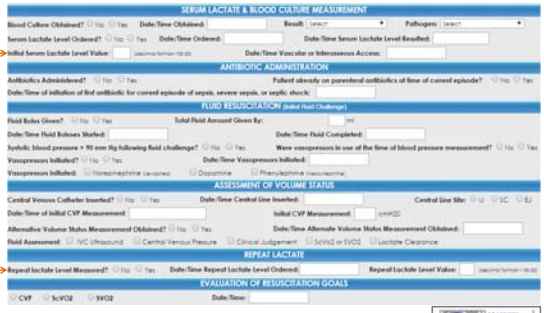
If patient has Lactate >= 2.2 with Sepsis Criteria or Hypotension (SBP <90 mmHg) with Sepsis or any end organ dysfunction documented in provider notes otherwise not explained, Date/Time Severe Sepsis/Septic Shock Identified must be completed below. If the patient met "Super SIRS at triage", list this time.

Date/Time Severe Sepsis/Septic Shock Identified:

Patient Care Unit Where Severe Sepsis/Septic Shock Identified: ED | ED Hold | Critical Care Unit | Inpatient | CDU

Standardized Database

Severe Sepsis Resuscitation Bundle Data Elements



Nguyen et al. 2004

- Groundbreaking research published in Critical Care Medicine: ***Early lactate clearance is associated with improved outcome in severe sepsis and septic shock***
- **Lactate level obtained at hour 0 and hour 6**
- Lactate clearance defined as percent decrease in lactate from ED presentation to hour 6
- "Analysis of lactate clearance cutoffs showed that a **lactate clearance cutoff of 10%** had the maximum sum of sensitivity plus specificity for predicting in-hospital mortality."
- Concluded that "**more trials needed to conclusively establish lactate clearance as resuscitation end point** and outcome measure to be targeted during most proximal phases of severe sepsis and septic shock."

Methods

- **Design**: Retrospective observational study
- **Setting:** North Shore-LIJ Health System emergency departments (5 tertiary and 6 community hospitals)
- **Inclusions:** Patients diagnosed with severe sepsis (ICD-9-CM 995.92) or septic shock (ICD-9-CM 995.92 and 785.52) and discharged between January 1, 2012 and June 30, 2014
- **Exclusions:** Transfer patients, patients under 18 years of age, cases with documented goals of care at the time of sepsis identification that precluded compliance with the treatment bundle
- **Patient Population:** 13,925 patients admitted via the ED
- **Data Entry:** Data abstractors assigned for each site

Statistical Analysis

- T- tests
  - Mean initial lactate for non-survivors vs. survivors
  - Mean lactate clearance for non-survivors vs. survivors
- Logistic Regression
- ROC Curve
- Survival Analysis
- IBM SPSS Statistics for Windows, Version 22.0 | SAS 9.3 for Windows

Results

Mean Initial Lactate Level

Status	Mean Initial Lactate Level	Standard Deviation	N
Survivor	**2.9**	2.1	10,521
Non-Survivor	**4.5**	3.7	2,581

Mean Difference	*P*
-1.6	<0.001

Lactate Clearance

The change in lactate within 6 hours

Lactate clearance=

$(\text{Lactate}_{\text{initial}} - \text{Lactate}_{\text{repeat}}) / \text{Lactate}_{\text{initial}}$

A positive value denotes a decrease in lactate (clearance of lactate) and a negative value denotes an increase in lactate.

Results

Mean Lactate Clearance

Status	Mean Lactate Clearance	Standard Deviation	N
Survivor	**0.24**	0.48	3,010
Non-Survivor	**0.04**	0.83	835

Mean Difference	*P*
0.20	<0.001

Results – Response Variable: Mortality

Model 1 – Lactate clearance as a continuous variable

Covariate		Adjusted Odds Ratio Exp (B)	95% Confidence Interval for Exp (B)	*P*
Age		1.026	1.019, 1.032	<0.001
Weight		0.996	0.992, 1.000	0.067
Admission unit	Inpatient Unit	Referent		<0.001
	Immediate Care Unit	1.135	0.845, 1.525	0.400
	Critical Care Unit	2.052	1.662, 2.533	<0.001
	Other Unit	1.394	0.554, 3.505	0.480
Hospital	Hospital (11)	Referent		<0.001
	Hospital (1)	0.471	0.287, 0.774	0.003
	Hospital (2)	0.464	0.317, 0.679	<0.001
	Hospital (3)	0.513	0.159, 1.659	0.265
	Hospital (4)	0.567	0.372, 0.864	0.008
	Hospital (5)	0.597	0.385, 0.925	0.021
	Hospital (6)	0.659	0.404, 1.075	0.095
	Hospital (7)	0.571	0.409, 0.797	<0.001
	Hospital (8)	0.864	0.623, 1.198	0.407
	Hospital (9)	0.496	0.323, 0.762	<0.001
	Hospital (10)	1.211	0.905, 1.620	0.381
Initial lactate		1.205	1.170, 1.240	<0.001
Lactate clearance		**0.501**	**0.427, 0.587**	**<0.001**

Results

Logistic Regression Model 1 – Interpretation

With lactate clearance as a continuous variable, odds ratio (OR) of 0.501 shows that with a unit increase in lactate clearance, holding all other covariates constant, there is a 50% decrease in odds of in-hospital mortality.

Interpretation of odds ratios for continuous variable not as clear mainly because there is no reference group to compare the odds.

- Adjusted OR 0.501 (0.427-0.587); P<.001 .

Death Prediction – Model 1

- For a 70 year old, weighing 70 kilograms, admitted into critical care unit, at hospital #5, with an initial lactate of 3.5 mmol/L and a lactate clearance of 0.05,

probability of death=19.3%

$$\frac{\text{Exp}(-3.722+0.025(70)-0.004(70)+0.719(1)-0.516(1)+0.186(3.5)-0.691(0.05))}{1+\text{Exp}(-3.722+0.025(70)-0.004(70)+0.719(1)-0.516(1)+0.186(3.5)-0.691(0.05))}$$

- For a 70 year old, weighing 70 kilograms, admitted into critical care unit, at hospital #5, with an initial lactate of 3.5 mmol/L and a lactate clearance of 0.30,

probability of death=16.7%

$$\frac{\text{Exp}(-3.722+0.025(70)-0.004(70)+0.719(1)-0.516(1)+0.186(3.5)-0.691(0.30))}{1+\text{Exp}(-3.722+0.025(70)-0.004(70)+0.719(1)-0.516(1)+0.186(3.5)-0.691(0.30))}$$

Results – Response Variable: Mortality

Model 2 – Lactate clearance as a binary variable

Covariate		Adjusted Odds Ratio Exp (B)	95% Confidence Interval for Exp (B)	*P*
Age		1.025	1.019, 1.032	<0.001
Weight		0.996	0.992, 1.000	0.071
Admission unit	Inpatient Unit	Referent		<0.001
	Immediate Care Unit	1.133	0.844, 1.520	0.407
	Critical Care Unit	2.092	1.696, 2.580	<0.001
	Other Unit	1.333	0.523, 3.402	0.547
Hospital	Hospital (11)	Referent		<0.001
	Hospital (1)	0.447	0.271, 0.736	0.002
	Hospital (2)	0.459	0.315, 0.669	<0.001
	Hospital (3)	0.526	0.163, 1.639	0.282
	Hospital (4)	0.591	0.389, 0.898	0.014
	Hospital (5)	0.578	0.373, 0.898	0.015
	Hospital (6)	0.665	0.408, 1.084	0.101
	Hospital (7)	0.562	0.403, 0.784	0.001
	Hospital (8)	0.871	0.629, 1.207	0.407
	Hospital (9)	0.488	0.318, 0.750	0.001
	Hospital (10)	1.193	0.892, 1.596	0.233
Initial lactate		1.192	1.158, 1.227	<0.001
Lactate clearance	**<10%**	**Referent**		
	≥10%	**0.443**	**0.368, 0.533**	**<0.001**

Results

Logistic Regression Model 2 – Interpretation

Holding all other covariates at a fixed value, the odds of expiring in the hospital for patients with a lactate clearance of 10% or more within 6 hours is 0.557 less than for patients with a lactate clearance less than 10% within 6 hours.

- Lactate clearance adjusted OR 0.443 (95%CI, 368-0.533); P<.001

Death Prediction – Model 2

- For a 70 year old, weighing 70 kilograms, admitted into critical care unit, at hospital #5, with an initial lactate of 3.5 mmol/L and a lactate clearance less than 0.10,

probability of death=28.2%

$$\frac{\text{Exp}(-3.209+0.025(70)-0.004(70)+0.738(1)-0.548(1)+0.176(3.5))}{1+\text{Exp}(-3.209+0.025(70)-0.004(70)+0.738(1)-0.548(1)+0.176(3.5))}$$

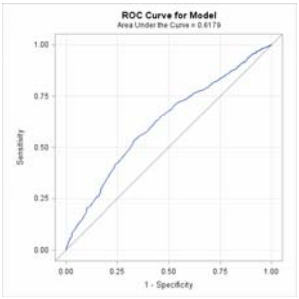
- For a 70 year old, weighing 70 kilograms, admitted into critical care unit, at hospital #5, with an initial lactate of 3.5 mmol/L and a lactate clearance greater than or equal to 0.10,

probability of death=14.8%

$$\frac{\text{Exp}(-3.209+0.025(70)-0.004(70)+0.738(1)-0.548(1)+0.176(3.5)-0.814(1))}{1+\text{Exp}(-3.209+0.025(70)-0.004(70)+0.738(1)-0.548(1)+0.176(3.5)-0.814(1))}$$

Results

ROC Curve predicting In-hospital Mortality



Unadjusted Area Under Curve for **change in lactate within the first 6 hours**

0.62 (95% CI=0.60, 0.64)

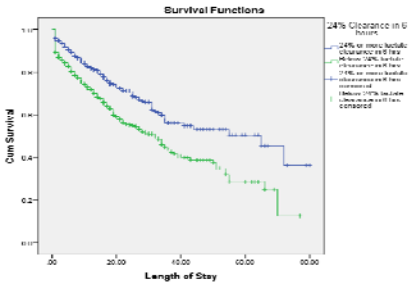
P-value<0.001

Cut off 0.10
Sensitivity 74%, Specificity 42%
Cut off 0.24
Sensitivity 60%, Specificity 59%

Results

Kaplan-Meier Survival Plot

Lactate clearance cut off at 24%



Conclusion

- Lactate clearance is an independent predictor of in-hospital mortality.
- Improvement in 6 hour lactate clearance among patients admitted from the ED with severe sepsis and septic shock is associated with decreased in-hospital mortality.
- This information may be useful in assessing the response to short term emergency treatment of severe sepsis in the acute care setting.

Limitations

- As an observational study only association between lactate clearance and mortality can be assessed. **Causal relationship cannot be inferred.**
- Missing date/time values.
- Retrospective in design therefore potentially subject to systematic error and bias.
- Results cannot be compared to studies with repeat lactate at hour 6 (we studied within 6 hours).

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Questions ?

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