Fluid Volume, Lactate Values, and Mortality in Sepsis Patients with Intermediate Lactate Values

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Abstract

Rationale: Patients with severe sepsis without shock or tissue hypoperfusion face substantial mortality; however, treatment guidelines are lacking.

Objectives: To evaluate the association between intravenous fluid resuscitation, lactate clearance, and mortality in patients with “intermediate” lactate values of 2 mmol/L or greater and less than 4 mmol/L.

Measurements and Main Results: This was a retrospective study of 9,190 patients with sepsis with intermediate lactate values. Interval changes between index lactate values and those at 4, 8, and 12 hours were calculated with corresponding weight-based fluid volumes. Outcomes included lactate change and mortality. Repeat lactate tests were completed in 94.7% of patients within 12 hours. Hospital and 30-day mortality were 8.2 and 13.3%, respectively, for patients with lactate clearance; they were 18.7 and 24.7%,

respectively, for those without lactate clearance. Each 10% increase in repeat lactate values was associated with a 9.4% (95% confidence interval [CI] = 7.8–11.1%) increase in the odds of hospital death. Within 4 hours, patients received 32 ($\pm$ 18) ml/kg of fluid. Each 7.5 ml/kg increase was associated with a 1.3% (95% CI = 0.6–2.1%) decrease in repeat lactate. Across an unrestricted range, increased fluid was not associated with improved mortality. However, when limited to less than 45 ml/kg, additional fluid was associated with a trend toward improved survival (odds ratio = 0.92; 95% CI = 0.82–1.03) that was statistically significant among patients with highly concordant fluid records.

Conclusions: Early fluid administration, below 45 ml/kg, was associated with modest improvements in lactate clearance and potential improvements in mortality. Further study is needed to define treatment strategies in this prevalent and morbid group of patients with sepsis.

Keywords: sepsis; lactic acid; mortality

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Sepsis is a common cause of hospitalization, and is associated with high cost, morbidity, and mortality (1–7). In the most severe forms of sepsis—often characterized by

a serum lactate level of 4.0 mmol/L or greater, or a refractory systolic blood pressure of less than 90 mm Hg—hospital mortality exceeds 20–30% (1, 2, 8, 9). In

this gravely ill population, treatment guidelines benefit from a robust evidence base summarized by the Surviving Sepsis Campaign (10). These guidelines emphasize

the early use of central venous catheter-based quantitative fluid resuscitation, commonly known as early goal-directed therapy (EGDT) (9–13).

Although these sepsis patients, with shock or tissue hypoperfusion, have the highest mortality, patients with less severe sepsis also face a considerable risk of death (1). Even those with normal blood pressure and “intermediate” lactate levels (≥ 2.0 and < 4.0 mmol/L) have hospital mortality exceeding 10% (14–18), and, although their mortality rate is lower, their contribution to hospital deaths is on par with that of patients with the most severe sepsis, because they represent a larger fraction of all patients with sepsis (1, 19). Despite this, there are limited data and no established guidelines for treating patients with sepsis with intermediate lactate values (10).

In this study, we sought to evaluate whether fluid resuscitation—a core element of the early resuscitation bundle in the Surviving Sepsis guidelines—is associated with improved outcomes in patients with sepsis with intermediate lactate values. We evaluated patients with sepsis at 21 community hospitals within Kaiser Permanente Northern California (KPNC), an integrated healthcare delivery system. We describe the relationship between lactate values and mortality, and specifically assess whether early intravenous fluid administration was associated with improvements in lactate and hospital mortality.

Methods

This study was approved by the KPNC Institutional Review Board, which has jurisdiction over all study hospitals.

Subjects

We conducted a retrospective study of patients with sepsis aged 18 years or greater admitted to KPNC hospitals through the emergency department (ED) between July 2010 and June 2012. Our cohort included patients with: (1) a diagnosis of sepsis that was “present on admission” (see Table E1 in the online supplement); (2) a first lactate value of 2.0 or greater and less than 4.0 mmol/L (“intermediate”); (3) antibiotics administered within 6 hours of ED arrival; and (4) no “comfort care” order on admission. We excluded patients who were under consideration for, or treated with,

a standardized EGDT protocol based on a lactate value of 4.0 mmol/L or greater (tissue hypoperfusion) or a systolic blood pressure of less than 90 mm Hg (shock); they were manually identified by trained hospital staff in a parallel study of EGDT.

Patient Characteristics

We linked patients with sepsis with corresponding KPNC databases based on methods detailed in prior studies (20–22). We quantified comorbid illness burden with Charlson comorbidity scores and Comorbidity Point Scores, based on an externally validated system incorporating data from the year before hospitalization to estimate disease burden (21–24). We quantified physiologic derangement with Laboratory Acute Physiology Scores (LAPS), which incorporates 15 laboratory and 6 vital sign values preceding inpatient admission into a score that independently predicts mortality (21, 22, 24). Finally, we generated a summary predicted risk of hospital mortality from a validated electronic risk adjustment model developed using over 390,000 KPNC hospitalizations (22). To corroborate the sepsis discharge diagnosis, we identified physician admitting diagnoses assigned at hospital entry.

Lactate Values

We denoted the first ED lactate test as the “index” test, and categorized values into the following groups: 2.00–2.49 mmol/L; 2.50–2.99 mmol/L; 3.00–3.49 mmol/L; and 3.50–4.00 mmol/L. We assigned subsequent lactate tests into 4-, 8-, and 12-hour groups based on their elapsed intervals from index testing using lactate collection times. Within each interval, we used the last value to calculate the percent change compared with the index value. Thus, a repeat test drawn 9 hours after the index test with a value of 2.7 mmol/L, compared with 3.0 mmol/L, represented a -10% change (or 10% lactate improvement) at the 12-hour window if no subsequent tests were performed. We also grouped repeat values based on increased, decreased, or no percent change ($\geq 60\%$, ≥ 30 – 60% , > 0 – 30 , and 0%).

Fluid Administration

We retrieved intravenous fluid records from two sources: the Medication Administration Record (MAR) and the intake/output “flowsheet” record. The MAR captures all physician orders for fluid administration,

including type, rate of infusion, and whether the fluid was “given.” “Given” timestamps are automatically recorded when fluid barcodes are scanned before administration. However, the MAR does not detail how much fluid each patient actually received. The flowsheet record details the amount of fluid given by nursing staff, but it can be incompletely documented, especially within busy clinical environments like the ED. Because KPNC has used electronic medical records for all documentation and order entry since 2009, no other source provides an independent gold standard for fluid administration totals.

To minimize potential discrepancies between MAR- and flowsheet-based records, we chose a strategy that assigned fluid volumes into half-hour intervals starting from ED entry. For MAR records, we totaled volumes within the half-hour interval in which they were documented as given if they were ordered as a “bolus” or at a rate of 500 ml/h or greater. Where the orders prescribed a lower rate, for example 250 ml/h, we would assign 125 ml to each half-hour starting from the given time through the second hour or through completion (e.g., two half-hours for a 250-ml bag). In a similar way, we assigned flowsheet-based volumes into half-hour intervals based on nursing documentation.

For both records, we totaled the fluid administered between the index and repeat lactate tests and divided it by the patient’s most recent prehospital weight to generate a weight-based summary volume (in ml/kg). Total volumes were grouped by 7.5 ml/kg increments to approximate intervals of 500 ml in an average-weight male (70 kg). We compared the consistency of MAR- and flowsheet-based volumes (Figures 1 and 2 and Table E2). In our primary analyses, we included only patients whose discrepancy between fluid records was 30% or less of the higher value, and used the flowsheet-based total. In sensitivity analysis, we used only records with a discrepancy of 10% or less.

Hospital Data

We captured parenteral and intravenous antibiotics and calculated the elapsed time from ED entry to administration. We evaluated patients’ “present on admission” International Classification of Disease version 9 diagnosis codes to quantify associated organ dysfunction based on criteria detailed in prior studies (4, 25).

Figure 1. Mean hospital mortality (solid line) and 95% confidence interval (dotted lines) based on the magnitude of lactate change within 12 hours compared with index values. Patients with decreased lactate (across percentage strata) are represented toward the right of the figure, whereas those with increased lactate are toward the left. The vertical line demarcates increased and decreased repeat lactate values.

We determined whether patients were admitted to an intensive care unit (ICU) based on bed history records. A total of 10 study hospitals had intermediate care or stepdown wards. In the hospitals without intermediate care units, some at-risk patients could be admitted to the ICU

without meeting traditional entry criteria for critical care based on clinician triage or nursing needs. We ascertained hospital mortality from inpatient records and 30-day mortality from records, KPNC membership tables, and state and national death record files.

Figure 2. Frequency of changes in lactate levels within 4 hours stratified by total fluid volume and magnitude of change. Changes are represented by shading of bars based on whether lactate levels increased (white), decreased (gray), or were unchanged (black).

Statistical Analysis

Continuous data are presented as mean ($\pm$ SD) or mean (95% confidence interval [CI]); categorical data are presented as number (%). We compared characteristics between groups with ANOVA or Chi-square testing and trends across groups using univariable linear regression. We used multivariable linear regression to estimate the effect of fluid on percent change in lactate values and multivariable logistic regression to determine the association between fluid administration and mortality. We grouped model covariates as demographics/severity of illness (age, sex, predicted hospital mortality, LAPS, Comorbidity Point Scores, number of organ dysfunctions; Model A) or as lactate/treatment characteristics (index value, fluid volume received before index test, number of repeat lactate tests, and elapsed time to first lactate collection, to first antibiotic, and between index and repeat testing; Model B). In *post hoc* analysis, we added percent change in lactate as a covariate to assess whether the association between fluid and mortality was mediated by lactate value changes. We conducted analyses using STATA/SE version 11.2 (StataCorp, College Station, TX) and considered a *P* value of less than 0.05 to be significant.

Results

We identified a total of 9,190 patients with sepsis; Table 1 describes baseline characteristics. Mean age was 70.9 ($\pm$ 16.4) years and mean weight was 80.0 ($\pm$ 26.6) kg. Patients with higher index lactate values had more severe illness ($P < 0.001$ for LAPS and predicted mortality), but similar Charlson comorbidity scores ($P = 0.99$). On average, they also had an increased number of organ dysfunctions; however, the absolute difference was minimal (range, 0.4–0.6). From ED entry, the time to index lactate collection was 1.2 ($\pm$ 1.1) hours, to first intravenous fluid given was 1.6 ($\pm$ 1.8) hours, and to first antibiotic given was 2.3 ($\pm$ 1.2) hours. Most patients (78.4%) were admitted to medical-surgical wards from the ED. Predicted hospital mortality was 10.3 ($\pm$ 12.5)%; observed mortality was 10.3%. At 30 days, mortality was 15.6%.

Lactate Testing

Overall, 70.4% of patients had an index lactate value of less than 3.0 mmol/L

Table 1. Baseline patient, treatment, outcome, and lactate test characteristics stratified by baseline lactate level

Characteristics	Overall	Baseline Lactate Level (mmol/L)			
		≥2–2.49	≥2.5–2.99	≥3.0–3.49	≥3.5–3.99
No. Patient	9,190	3,863 (42.0)	2,608 (28.4)	1,619 (17.6)	1,100 (12.0)
Age, yr	70.9 ± 16.4	70.7 ± 16.5	71.3 ± 16.3	70.6 ± 16.2	71.0 ± 16.5
Male	4,699 (51.1)	1,977 (51.2)	1,348 (51.7)	841 (52.0)	533 (48.5)
Weight, kg	80 ± 27	80 ± 26	80 ± 27	80 ± 27	79 ± 26
Severity measure (LAPS)	112 ± 35	108 ± 34	111 ± 36	115 ± 36	120 ± 37
Comorbidity measure (COPS)	52 ± 47	53 ± 47	53 ± 48	52 ± 46	49 ± 45
Charlson comorbidity score	1.9 ± 1.5	1.9 ± 1.5	1.9 ± 1.5	1.9 ± 1.5	1.9 ± 1.5
Predicted mortality	10.3 ± 12.4	9.1 ± 11.2	10.5 ± 12.5	10.9 ± 12.6	12.9 ± 15.0
Mean no. of organ dysfunctions	0.5 ± 0.7	0.4 ± 0.7	0.5 ± 0.7	0.5 ± 0.7	0.6 ± 0.8
ICD9 diagnosis in ED (code)					
Sepsis (038)	8,250 (89.8)	3,449 (89.3)	2,341 (89.8)	1,462 (90.3)	998 (90.7)
'Complications' (996–999)	507 (5.5)	225 (5.8)	142 (5.4)	88 (5.4)	52 (4.7)
All other ICD9 codes	433 (4.7)	189 (4.9)	125 (4.8)	69 (4.3)	50 (4.5)
Treatment					
Hours from ED arrival to					
First lactate sample collected	1.2 ± 1.1	1.2 ± 1.1	1.2 ± 1.1	1.2 ± 1.2	1.1 ± 1.1
First IV fluid given	1.6 ± 1.8	1.8 ± 2.0	1.6 ± 1.6	1.6 ± 1.8	1.4 ± 1.7
First antibiotic given	2.3 ± 1.2	2.3 ± 1.2	2.3 ± 1.2	2.3 ± 1.3	2.1 ± 1.2
Transfer from ED	6.1 ± 3.2	6.2 ± 3.4	6.1 ± 3.2	6.1 ± 3.3	5.9 ± 2.9
Outcomes					
Length of stay, d	6.1 ± 7.8	6.0 ± 7.6	5.9 ± 7.5	6.5 ± 9.6	6.1 ± 5.5
Hospital mortality	947 (10.3)	333 (8.6)	276 (10.6)	194 (12.0)	142 (12.9)
30-d mortality	1,433 (15.6)	515 (13.3)	428 (16.4)	270 (16.7)	219 (19.9)
Lactate					
Mean lactate level	2.7 ± 0.5	2.2 ± 1.4	2.7 ± 1.4	3.2 ± 1.4	3.7 ± 1.4
Repeat lactate checked					
Within 4 h	3,658 (39.8)	1,349 (34.9)	974 (37.4)	776 (47.9)	559 (50.7)
Change, since first, %	−23.9 ± 33.3	−17.3 ± 36.3	−23.3 ± 32.5	−29.0 ± 30.2	−33.5 ± 27.3
Mean time, since first, h	2.7 ± 1.0	2.7 ± 1.1	2.7 ± 1.0	2.7 ± 0.9	2.7 ± 1.0
Within 8 h	8,049 (87.6)	3,290 (85.2)	2,295 (88.0)	1,471 (90.9)	993 (90.3)
Change, since first, %	−24.3 ± 39.3	−18.5 ± 41.6	−24.1 ± 39.6	−30.3 ± 35.0	−35.2 ± 32.5
Mean time, since first, h	5.4 ± 1.7	5.4 ± 1.6	5.4 ± 1.6	5.3 ± 1.7	5.3 ± 1.7
Within 12 hours	8,701 (94.7)	3,632 (94.0)	2,468 (94.6)	1,556 (96.1)	1,045 (95.0)
Change, since first, %	−29.8 ± 38.5	−23.1 ± 40.7	−30.7 ± 38.4	−36.1 ± 34.4	−41.7 ± 31.3
Mean time, since first, h	8.6 ± 2.5	8.5 ± 2.5	8.6 ± 2.5	8.6 ± 2.5	8.6 ± 2.5

Definition of abbreviations: COPS = Comorbidity Point Score; ED = emergency department; ICD9 = International Classification of Diseases, 9th Edition; IV = intravenous; LAPS = Laboratory Acute Physiology Score. Values represent number (%) or mean ± SD.

(Table 1). Repeat lactate tests were completed for 39.8, 87.6, and 94.7% of patients within 4, 8, and 12 hours, respectively. By 12 hours, lactate values for most patients (79.5%) had improved; average improvement was greater among those with higher index values (Figure E3). For example, lactate values decreased in 87.9% of patients with index values of 3.5–4.0 mmol/L or greater and repeat testing within 12 hours.

Mortality

Hospital mortality was 8.2% for patients with any lactate improvement at 12 hours; it was 18.7% for those without lactate improvement. Similarly, 30-day mortality was 13.3% for patients with lactate

improvement and 24.7% for those without. Mortality was strongly associated with the magnitude of lactate change (Figure 1). At 12 hours, each 10% increase between repeat and index values was associated with a 9.4% increase in the odds of hospital death (95% CI = 7.8–11.1%). Mortality was substantially decreased (4.7%) for patients with more than 60% lactate improvement at 12 hours (range, 3.7–6.4%). This pattern was consistent across index lactate groups and for 30-day mortality (Figures E4 and E5).

Fluid and Lactate

Overall, 62.7% of patients had 30% or less discrepancy between fluid totals at 4 hours. In this group, patients received 32 (±18)

ml/kg of intravenous fluids by their 4-hour repeat test. As fluid volumes increased, the percentage of patients with lactate improvement increased (Figure 2, $P < 0.001$). However, even among those receiving a modest fluid amount (<7.5 ml/kg), over 80% demonstrated some improvement. After multivariable adjustment, each 7.5 ml/kg increase in fluid was associated with a 1.3% (95% CI = 0.6–2.1%) decrease in repeat lactate values within 4 hours (Table E3).

Fluid and Mortality

The relationship between fluid received and hospital mortality demonstrated variability when stratified by fluid volumes (Figure 3 and Figure E6). At all intervals, volumes of

Figure 3. Mean hospital mortality among patients with decreased lactate within 8 hours of index test, stratified by total fluid received in increments of 7.5 ml/kg based on medication administration record.

45 ml/kg or greater, compared with lesser volumes, were associated with increased mortality ($P < 0.001$). Volumes of less than 7.5 ml/kg were also associated with increased mortality at 8 hours ($P < 0.01$) and, with borderline significance, at 4 and 12 hours ($P \leq 0.08$). Between these inflection points, there was no linear trend in mortality ($P > 0.50$).

Across an unrestricted fluid range, increasing fluid was not associated with improved mortality (Table 2; adjusted odds ratio [AOR] per 7.5 ml/kg of fluid at 8 hours = 1.00; 95% CI = 0.95–1.06). However, when limited to fluid totals between 0 and 45 ml/kg—a range that encompassed over 80% of patients—additional fluid was associated with a trend toward improved mortality (e.g., AOR at 8 hours = 0.94; 95% CI = 0.84–1.06). Among patients with 10% or lower discrepancy in fluid records, the decreased odds of death had borderline statistical significance at 8 hours (e.g., AOR = 0.87; 95% CI = 0.75–0.99). Point estimates were similar for 30-day mortality (AOR = 0.87; 95% CI = 0.77–0.99) and after adjustment for percent lactate change (AOR = 0.87; 95% CI = 0.75–0.99).

Discussion

In this study, we found that patients with sepsis with intermediate lactate values had

substantial hospital and 30-day mortality. Both index lactate values and the magnitude of change between index and repeat values predicted mortality. Early intravenous fluid, administered within 4–8 hours, was associated with modest lactate decreases, although many patients receiving a small fluid volume also demonstrated lactate improvement. After adjusting for patient, treatment, and lactate characteristics, each additional 7.5 ml/kg of fluid—or roughly 500 ml among the majority of patients who received less than 3.2 L total—was associated with a trend toward improved mortality in patients with highly concordant fluid records.

Prior studies have established lactate values as a prognostic marker for sepsis mortality, but have focused primarily on patients with the most severe sepsis (11, 16, 17, 26, 27). A handful of smaller studies evaluated patients with sepsis with intermediate lactate values and reported similar findings (15, 16, 18, 28–30). In our large, modern cohort, we confirm that rising index lactate values were associated with increased mortality. Compared with prior studies, our patients represented a substantially older population, the median age of which was 74 years, versus 56–60 years (16, 18). Nonetheless, our mortality rates—10.3% in the hospital and 15.6% at 30 days—closely matched prior reports (9–10% for hospital mortality, and 16% for 28-d mortality).

Prior studies in septic shock and tissue hypoperfusion have also established dynamic lactate indices as strongly predictive of mortality—a finding that we now confirm in the intermediate sepsis population (9, 31–36). Nguyen and colleagues (32) reported an 11% decrease in the odds of hospital death with each 10% increase in lactate improvement in septic shock and hypoperfusion. We identified a nearly identical relationship in a less severe sepsis population. In a cohort of 5,041 critically ill patients, Nichol and colleagues (35) found that the addition of dynamic lactate indices to existing severity measures dramatically improved outcomes prediction. In this context, the current study confirms a consistent relationship between lactate indices and mortality across a broad population of patients with sepsis that is stratified by, but independent of, shock or the need for critical care (16, 28, 30, 35, 37).

Although the prognostic relationship between lactate values and sepsis mortality is remarkably consistent, there are no established treatment guidelines for patients with intermediate lactate values despite their considerable contribution to overall hospital mortality. Through sepsis quality improvement efforts at KPNC, we have found an equivalent number of annual hospital deaths contributed by patients with septic shock and hypoperfusion versus intermediate lactate patients (roughly 500 deaths each) (19). Thus, even while sepsis is now the most expensive cause of U.S. hospitalizations, we lack basic evidence to guide treatment decisions for the majority of patients, especially those outside of the ICU (38).

We aimed to address this gap by evaluating the impact of fluid administration on lactate values and mortality. In patients with more severe sepsis, early fluid resuscitation has been shown to reduce inflammation and improve microvascular perfusion, organ function, and outcomes (39). As a result, fluid administration is a key initial element in the Surviving Sepsis Campaign's early treatment bundle, which recommends administration of 30 ml/kg of crystalloid followed by central venous catheter-based quantitative resuscitation (10, 11). Among patients with less severe sepsis—the majority of whom were treated outside the ICU without central venous catheters—there are few well established treatment options. Although infection

Table 2. Logistic regression of total fluid administered within 4-, 8-, or 12-hour intervals between lactate results on hospital mortality

	OR for Hospital Death (95% CI) per 7.5 ml/kg increase in fluid		
	At 4 h	At 8 h	At 12 h
Across entire fluid range			
No. of patients	1,358	3,148	3,409
Unadjusted	1.06 (0.98–1.14)	1.07 (1.03–1.12)*	1.06 (1.03–1.10)*
+ Model A	0.95 (0.86–1.05)	0.99 (0.94–1.05)	1.01 (0.97–1.06)
+ Model B	0.94 (0.85–1.04)	1.00 (0.95–1.06)	1.02 (0.97–1.06)
Between 0 and 45 ml/kg			
No. of patients	1,086	2,443	2,528
Unadjusted	1.00 (0.85–1.17)	0.98 (0.88–1.09)	0.98 (0.90–1.09)
+ demographics/illness severity	0.92 (0.77–1.10)	0.93 (0.83–1.04)	0.94 (0.85–1.05)
+ baseline lactate/timing	0.91 (0.76–1.09)	0.94 (0.84–1.06)	0.96 (0.86–1.07)
Between 0 and 45 ml/kg, with <10% discrepancy between records			
No. of patients	782	1,533	1,440
Unadjusted	0.93 (0.78–1.12)	0.91 (0.74–0.99)*	0.89 (0.78–1.02)
+ demographics/illness severity	0.88 (0.71–1.09)	0.85 (0.74–0.99)*	0.82 (0.71–0.95)*
+ baseline lactate/timing	0.85 (0.68–1.05)	0.87 (0.75–0.99)*	0.83 (0.71–0.97)*

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

Adjusted models include demographics/severity of illness (age, sex, predicted mortality, physiology, comorbid illness, number of organ dysfunctions; Model A) and baseline lactate/timing (baseline lactate value, elapsed time to first lactate check, elapsed time to first antibiotic, elapsed time between index and repeat lactate testing, intravenous fluid received before first lactate check, number of lactate values checked; Model B) covariates.

* $P \leq 0.05$.

source control and early appropriate antimicrobials are key elements, fluid administration represents one of the only modifiable and noninvasive therapies currently used by providers.

In the intermediate sepsis population, we found that early intravenous fluid was associated with improvements in serial lactate values; however, their impact was modest. On average, in a 70-kg person, lactate values improved by just 5.2% after 2 L. Thus, even while lactate indices were strongly predictive of outcomes, their relationship with fluid resuscitation was less pronounced. This likely results from the fact that serum lactate values are a surrogate measure for the physiologic balance between lactate production and utilization—a process that can be affected by multiple factors, including the etiology of lactate production, tissue hypoperfusion or impaired oxygenation, hepatic or renal failure, and medications (40). In light of this complexity and the underlying heterogeneity of patients with sepsis, our findings may not be surprising. We did find that the observed trend toward improved

mortality with increased fluid administration was independent of the percent change in repeat lactate values.

Prior studies have suggested that lactate-targeted resuscitation protocols can benefit critically ill patients with sepsis. Jones and colleagues (9) found a noninferior mortality of 17% among patients receiving lactate-guided quantitative resuscitation, versus 23% in patients receiving standard central venous oxygen saturation-based resuscitation. However, only a small fraction of all patients enrolled in the study received resuscitation elements determined by the intervention (dobutamine or red cell transfusions). Jansen and colleagues (34) found a significant improvement in mortality among critically ill patients with sepsis, including those with lactate levels over 3.0 mmol/L, with a lactate-targeted resuscitation protocol compared with standard therapy. Interestingly, although both groups had similar improvements in lactate values, those in the lactate-targeted group received more fluid and vasodilator therapy in the early phase. Although the current study supports serial lactate values to determine patient

prognosis in patients with intermediate sepsis, it is unclear if lactate-targeted protocols in this population would improve outcomes, especially without other quantitative resuscitation targets and interventions.

Our results should be interpreted in light of the study's limitations. First, we conducted a retrospective study, making it prone to potential selection and misclassification bias. However, this study benefitted from a parallel study of EGDT in which patients with more severe sepsis were manually identified by lactate levels and blood pressure, and removed from consideration in the intermediate lactate category. This study also benefitted from a multicenter population of community-based hospitals, albeit ones located within a single healthcare system, which has seen dramatic quality improvements in sepsis care over time (19). Second, we found significant discrepancies in records detailing fluid administration within the retrospective electronic medical record.

Although we executed an extensive manual chart review to uncover other independent sources of fluid administration, we were unable to identify any that provided equivalent, much less improved, reliability or validity. Furthermore, as this was not a protocolized prospective study, our results cannot establish causal relationships between fluid administration and outcomes. We believe that this is an important consideration that should be addressed by future prospective study. Finally, this study did not address clinical changes after index lactate values (e.g., incident hypotension or organ failure) that might have altered lactate values or fluid administration practice independently of our observed variables (14, 18, 29, 41).

In summary, patients with sepsis with intermediate lactate values have a substantial risk of hospital and 30-day mortality that parallels that of patients with severe sepsis and septic shock. Early fluid administration, below 45 ml/kg, modestly improves lactate clearance and potentially reduces mortality. However, further study is needed to define treatment strategies that can improve outcomes for this understudied group of patients with sepsis. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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