Respiratory Therapy™

The Journal of Pulmonary Technique

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Bilirubin (cobas b 221 system with COOX module)*

Comparison instrument	Slope and intercept	Bias	Corr. coeff. [r]	No. of samples
Hitachi TBil	Y = -0.127+ 0.968*X	+3.7 % abs.	0.986	85

Lactate*

Comparison instrument	Slope and intercept	Bias	Corr. coeff. [r]	No. of samples
Hitachi (Plasma)	Y = -0.286+ 1.149*X	+0.7 %	0.993	60

cobas b 221 blood gas system Instruction for Use version 11.0.*

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Life needs answers

Diagnostic Measurement of Pleural Fluid pH and Glucose

The American Thoracic Society published a paper, Clinically Important Factors Influencing the Diagnostic Measurement of Pleural Fluid pH and Glucose.*

The rationale for the authors' study is that accurate pleural fluid pH and glucose measurement is a key component in diagnosis and management of patients with pleural effusion, but that standardized methods of pleural fluid collection have not been defined. The objectives of the study are to assess the effect of clinical factors that can distort the measurement accuracy of pleural fluid pH and glucose. The researchers collected 92 exudative pleural aspirates and analyzed the samples using a blood gas analyzer for the effects of residual air, lidocaine, heparin and for a 24 hour delay in analysis on pH and glucose measurement. The researchers found that pleural fluid pH was significantly increased by residual air and significantly decreased by residual lidocaine and residual heparin. Pleural fluid pH was stable at normal room temperature for an hour and significantly increased at 4 and 24 hours. Pleural fluid glucose concentration wasn't significantly altered by residual air, lidocaine, or a 24 hour delay in analysis. The authors concluded that accuracy of plural pH is dependent on the sample collection method, and that residual air, lodicaine and analysis delay alters pH and likely impacts on clinical management. However, pleural fluid glucose concentration isn't significantly influenced by these factors. The authors further concluded that protocols defining appropriate sampling and analysis methods are needed.

Background

Approximately 300,000 pleural effusions require diagnostic assessment each year in the United States and the United Kingdom. Near-patient testing of pleural fluid pH is thus an important part of this assessment for pleural infection, including

TB, rheumatoid pleural effusion, and esophageal rupture, as well as for the assessment of malignant effusion. The measurement of pleural fluid pH is advocated in the scientific literature and in management guidelines of the American Thoracic Society, British Thoracic Society, and other professional societies. Low pleural fluid pH implies high metabolic activity in the pleural space. Reduced pH is typically a marker for instituting intercostal tube drainage in patients with likely pleural infection and is used as an initial criteria for clinical studies of pleural infection. Low pleural fluid pH correlates with poor prognosis and is a predictor of pleurodesis failure. Accuracy in diagnostic accuracy from patient to patient requires that inaccuracies inherent to larger samples should be canceled out. Previous studies advocated pH measurement using a blood gas analyzer with one to two hours of collection, but there have been no further studies that defined a sampling algorithm that is best at reducing variation during measurement. Further, there's likely to be substantial variation in collection methods. There have been no comparisons of the effects of such sampling strategies on pleural fluid glucose, a reflector of fluid pH, and which is advocated as a suitable substitute for pH measurement. The authors hypothesized that pleural fluid pH and glucose may be altered by typically observable variations in collection practice. The mixing of fluid with air, residual lidocaine or heparin, or a delay in analysis, could produce important changes in measured pH. The authors also hypothesized that omission of heparin could allow for fibrin clot formation, which can cause blood gas analyzer damage or distort the results of the analysis.

Study parameters

Subjects of the study were patients of a referral respiratory center who presented with a pleural effusion which required thoracentesis, chest drain insertion, or thoracoscopy. Patients with parapneumonic pleural effusions were added, since for these patients, pleural fluid pH is particularly important. Fluid was introduced into prepped syringes which held a maximum of 3mL of preloaded heparin sodium. The syringe was cleared before fluid was drawn into the syringe. Air was expelled and a seal placed on the syringe, and this sample, which would be the standard for comparison, was immediately analyzed. To test the effects of air and lidocaine, syringes were cleared of heparin and residual air, and 1.0mL of air of 2% lidocaine was added to the syringe. Pleural fluid was then introduced into the syringe. To test the effects of heparin, syringes were cleared of air, but not the preloaded heparin, and 3mL of pleural fluid was introduced into the syringe. Pleural fluid samples were analyzed within 10 minutes of collected by a blood gas machine. 195 μL of fluid was

withdrawn to measure pleural fluid pH, O_2 and CO_2, and glucose concentration. The standard syringe was analyzed at 1, 4 and 24 hours. The sample was maintained at room temperature, with air excluded from the syringe after each analysis. The syringe was agitated to remove any fibrinous clots that may have formed within the sample. Glucose was assayed by the blood gas analyzer and by standard lab methods. All pleural fluid samples were sent to the lab for LDH and total protein qualification. Cellular material was centrifuged or filtered from the samples. To assess changes in pleural fluid parameters, a p value of <0.05 was considered statistically significant, and a pH difference of ≥ 0.05 and a glucose difference of ≥ 1.0mmol/L (≥ 18mg/dL) were considered as thresholds of clinical significance.

Study results

Ninety-two pleural fluid samples from 81 patients were obtained, and all samples were used to assess pleural fluid pH and glucose stability. The effects of exposure to air, residual lidocaine or heparin were assessed in 52 samples. The presence of air increased pleural fluid pH by 0.08 ± 0.07, 95% CI 0.06 to 0.09, p<0.001. In 71% of samples, presence of air in the collection syringe resulted in a clinically significant change in pleural fluid pH greater than 0.05. Change in CO_2 and change in pH was correlated in each air exposed sample.

The pH of lidocaine used was 5.40 ± 0.05. A significant reduction in pleural fluid pH was observed in the presence of even minimal volumes of residual lidocaine. A dose dependent reduction of pH with lidocaine was observed with 0.4mL lidocaine and with 1.0mL lidocaine. Presence of residual lidocaine induced a clinical significant reduction in pH in nearly all samples.

Retaining pre-loaded heparin within the blood gas syringe resulted in a small but statistically significant decrease in pH. The pH of the heparin in the blood gas syringes was 6.49 ± 0.16.

Pleural fluid pH measurements changed significantly from baseline over time, and the increase or decrease was variable among samples, although an overall rise in pH over time was observed. No significant mean difference was observed in pleural fluid pH measured at baseline and at 1 hour, but the changes in pH became significant at 4 and 24 hours. At 1 hour, 13% of samples were altered beyond the clinically significant limit (>0.05), compared to 26% at 4 hours and 68% at 24 hours. Change in pH was plotted against baseline pH, and no significant correlation was demonstrated. The pO_2 level in samples showed a consistent increase in samples over time.

To investigate pH change over time, the correlation between change in pH and change in pCO_2 within the same sample was assessed, and there was a significant negative correlation between change in pH and change in pCO_2 at each time point, with a greater correlation seen with increased time.

To assess the contribution of cellular content to changes in pleural fluid pH, pleural fluid samples were centrifuged or filtered to remove cells, and were compared to a paired untreated sample at 0 and 24 hours. Results showed a significant change in pleural fluid pH compared to untreated samples and precluded further analysis.

There was little difference between lab measured and blood gas analyzed glucose concentration.

Glucose concentration was increased slightly but not significantly by the presence of air.

The addition of small volumes of lidocaine caused a clinically insignificant decrease in the pleural fluid glucose concentration. More pronounced reductions in glucose concentration were seen with larger volumes of lidocaine, and were likely due to dilution effect.

Addition of heparin caused clinically insignificant decrease in pleural fluid glucose concentration. Comparable reduction in glucose concentrations with similar volumes of heparin and lidocaine were observed, suggesting that the observed reduction in glucose concentration was the result of dilution.

The stability of glucose concentrations over time was assessed. Syringe-stored pleural fluid glucose levels did not significantly change over 1 and 4 hours. At 24 hrs there was a clinically insignificant decrease in glucose concentration.

Summary

The researchers demonstrated that the accuracy of measured pleural pH is critically dependent on method of sample collection. They noted that there is currently no standardized protocol for pleural fluid collection for pH/glucose measurement and it is therefore likely that the factors they studied were common influences on measurement in typical clinical practice. The authors' clinical data demonstrated that the presence of air or residual lidocaine in the collection syringe result in clinically significant changes in pH. While heparin produces a statistically detectable pH change, this was judged to be of little clinical importance. However, pleural fluid glucose measurements, analyzed by either blood gas machine or conventional laboratory assays, are less susceptible to variations in collection practice or delay in analysis.

This study demonstrated that even small amounts of air in the pleural fluid collection syringe result in a significant increase in pleural fluid pH. The authors' finding applied to all samples, regardless of the baseline pH, and showed that this is capable of artificially elevating the pH sufficiently to change clinical management by, for instance, deferring the drainage of an acidic parapneumonic effusion. The authors hypothesized that the gradient between the partial pressures of CO_2 in pleural fluid and atmospheric air results in rapid CO_2 diffusion through the fluid-air interface, raising the pH. Lidocaine, administered as local anesthetic, appeared clinically important in its potential effect on pH measurement. Even minute amounts of residual lidocaine, compatible with the dead space of fine bore needles, caused a clinically significant drop in pH in 94% of samples, and this effect became more marked as dosage was increased.

Heparin in the sample produced a clinically insignificant change in pH. A small volume of anticoagulant (heparin) added to thoracentesis specimens has been suggested to avoid the development of fibrinous clots in pleural fluid clotting before laboratory analysis.

Commercially available blood gas syringes, which are commonly used for pleural fluid analysis, are often pre-heparinized. The study's results confirmed that heparin is acidic and that the preloaded heparin in commercially prepared blood gas syringes produces a statistically significant reduction in pH, though this

Roche Diagnostics

Please describe your current blood gas products.
As a world leader in diagnostic testing, the Roche **cobas b 221** blood gas system was uniquely designed to help provide virtually uninterrupted performance. One way of doing this is by resolving blockages often caused by blood clots. Blood clots are commonplace for most blood gas analyzers and it can be time consuming to return the analyzer to reliable performance. If a clot enters the cobas b 221 blood gas system, a powerful fluidic system that includes both peristaltic pump and vacuum pump mechanics can remove the source of trouble and help minimize downtime. The cobas b 221 configurable menu has options for blood gas (pO_2, pCO_2, and pH), electrolytes (Na^+, K^+, Cl^-, Ca^+, Hematocrit), metabolites (glucose, lactate, BUN), and Co-oximetry (O_2Hb, HHb, COHb, MetHb, tHb, Bilirubin). The cobas b 221 blood gas system was the first FDA 510(k) cleared for testing pleural fluid pH. With the ability to trend patient data and automated acid-base mapping trending, the cobas b 221 system provides actionable information and simplifies regulatory compliance. The cobas b 221 blood gas system coupled with cobas bge link Instrument Manager software enables monitoring and control of decentralized system from one location. Cobas bge link enhances operational efficiency of all connected systems through screen sharing to provide immediate real-time performance status, maintenance updates, and remote access for administrative management.

How has your company pursued R&D efforts to improve blood gas technology?
Roche Diagnostics is committed to continuous research and development in blood gas systems. Roche has a new point of care blood gas system in development. This product is currently in development/research stage only and is not available for sale in the US.

How has point of care testing improved clinical decision making?
The cobas b 221 blood gas system can help improve point of care clinical decision making by delivering results in 60 seconds for fast turnaround time and enhanced workflow efficiency. The speed to results combined with the low blood sample volume (88 µl), required by the cobas b 221, helps healthcare professionals get blood gas test results faster and reduces the time for physicians to make critical medical decisions that impact patient outcomes. In addition, the cobas b 221 offers direct interfacing options to the hospital HIS/LIS which allows the respiratory therapist to run the sample and enable the physician to interpret the results in another part of the hospital or remotely. The automated acid-base mapping on the cobas b 221 system can help clinicians rapidly identify metabolic and respiratory acid-base disturbances without the need for a calculator and help differentiate between acute and chronic patient conditions in complex environments such as the ED or ICU.

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How does your product provide for accuracy in measurement?
The cobas b 221 system maintains accuracy through calibration with NIST calibration solutions and an AutoQC module. The cobas b 221 can be programmed to run a 1-point calibration every 30 minutes or 1 hour, 2-point calibration every 4, 8, or 12 hours, and a 2-point system calibration every 8, 12, or 24 hours. The AutoQC module utilizes a 120 ampoule based system that can be programmed to perform individual QC sampling at the times and frequency programmed by the user. A sample can only be run after a valid calibration has been completed. If a calibration error is detected, the cobas b 221 system automatically reruns the calibration. The AutoQC system can also be set to rerun and lock out future samples should they fail in order to assist with regulatory compliance. In the critical care setting, spectrophotometer analysis of hemoglobin and its derivatives (co-oximetry), in combination with blood gas analysis, provides immediate actionable information about oxygen transport in human blood. The accuracy of the hemoglobin and bilirubin results depends on the performance of the co-oximetry technology. The co-oximetry module of the cobas b 221 blood gas system measures both hemoglobin derivatives and bilirubin spectrophotometrically in the visible spectrum (460nm to 660nm). Absorbance of the sample is measured at a total of 512 discrete wavelengths. The concentration of hemoglobin, hemoglobin derivatives and bilirubin are determined by applying an accepted mathematical algorithm. This enables the cobas b 221 systems' co-oximetry technology to detect the presence of light-absorbing substances necessary to prevent the reporting of incorrect values due to interfering substances. This advanced co-oximetry design helps improve the accuracy of patient test results, while demonstrating a high correlation with results from accepted clinical chemistry methods.

What type of training and customer assistance/support programs do you have in place?
Roche Diagnostics provides a variety of educational materials to help healthcare professionals operate the cobas b 221 system properly and help maintain operator certification. These educational materials include: • Onboard video tutorials and a customer-based training CD-ROM along with instruction manuals that provide detailed descriptions to help operators avoid errors using the equipment. • Roche offers a two-day training program at its Indianapolis headquarters for two operators as well as on-site training at the customer facility. • Roche offers extensive on-line support through MyLabOnline, which gives users web-based access to all current documentation such as MSDS sheets, package inserts, customer bulletins and manuals. • Online CEU courses are available for staff members to help maintain their lab and/or Respiratory Therapy accreditation. • Roche's Indianapolis-based Tech Support team provides telephone support for immediate, real-time troubleshooting which may help reduce downtime and the need for a service visit.

Early Lactate Clearance is Associated with Biomarkers of Inflammation, Coagulation, Apoptosis, Organ Dysfunction and Mortality in Severe Sepsis and Septic Shock

H. Bryant Nguyen Manisha Loomba, James J. Yang, Gordon Jacobsen, Kant Shah, Ronny M. Otero, Arturo Suarez, Hemal Parekh, Anja Jaehne, Emanuel P. Rivers

Abstract

Background: Lactate clearance, a surrogate for the magnitude and duration of global tissue hypoxia, is used diagnostically, therapeutically and prognostically. This study examined the association of early lactate clearance with selected inflammatory, coagulation, apoptosis response biomarkers and organ dysfunction scores in severe sepsis and septic shock.

Methods: Measurements of serum arterial lactate, biomarkers (interleukin-1 receptor antagonist, interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor-alpha, intercellular adhesion molecule-1, high mobility group box-1, D-Dimer and caspase-3), and organ dysfunction scores (Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology Score II, Multiple Organ Dysfunction Score, and Sequential Organ Failure Assessment) were obtained in conjunction with a prospective, randomized study examining early goal-directed therapy in severe sepsis and septic shock patients presenting to the emergency department (ED). Lactate clearance was defined as the percent change in lactate levels after six hours from a baseline measurement in the ED.

Results: Two-hundred and twenty patients, age 65.0±17.1 years, were examined, with an overall lactate clearance of 35.5±43.1% and in-hospital mortality rate of 35.0%. Patients were divided into four quartiles of lactate clearance, -24.3±42.3, 30.1±7.5, 53.4±6.6, and 75.1±7.1%, respectively (p<0.01). The mean levels of all biomarkers and organ dysfunction scores over 72 hours were significantly lower with higher lactate clearance quartiles (p<0.01). There was a significant decreased in-hospital, 28-day, and 60-day mortality in the higher lactate clearance quartiles (p<0.01).

Conclusions: Early lactate clearance as a surrogate for the resolution of global tissue hypoxia is significantly associated with decreased levels of biomarkers, improvement in organ dysfunction and outcome in severe sepsis and septic shock.

Introduction

The transition from sepsis to severe sepsis and septic shock is associated with a number of hemodynamic perturbations leading to global tissue hypoxia. Global tissue hypoxia accompanies a myriad of pathogenic mechanisms which contribute to the development of the multi-system organ dysfunction syndrome and increased mortality. Although there is significant interaction between inflammation, coagulation and organ dysfunction; a clear cause and effect between global tissue hypoxia and these molecular processes leading to multi-organ failure in severe sepsis and septic shock remains unclear.

There is an increasing body of literature establishing the clinical utility of biomarkers as diagnostic, therapeutic and prognostic indicators in the management of patients presenting with severe sepsis and septic shock. These studies, largely derived from the intensive care unit (ICU) patient population comprise a mixed picture of pro-inflammatory, anti-inflammatory, coagulation and apoptosis biomarker responses. However, the duration of stay for these patients prior to ICU admission whether on the general hospital ward or emergency department (ED) can be up to 24 hours. Despite the abundance of knowledge in the ICU phase of severe sepsis and septic shock, little is known regarding the natural history of the biomarkers during the most proximal stage of disease presentation.

Studies targeting the early detection and eradication of global tissue hypoxia even after normalization of traditional vital signs (heart rate, blood pressure and urine output) have realized significant mortality benefit in severe sepsis and septic shock, As a measure of tissue hypoxia and risk stratification, lactate measurements have now been incorporated into treatment protocols and care bundles. We have previously reported that unresolved global tissue hypoxia reflected by inadequate lactate clearance during

the early phase of resuscitation implicates organ dysfunction and increased mortality in severe sepsis and septic shock. The mechanistic explanation for these observations remains un-elucidated. The purpose of this study is to examine the association of early lactate clearance with the biomarker activity of inflammation, coagulation, and apoptosis and the subsequent relationship to organ failure and outcome in early severe sepsis and septic shock.

Materials and Methods

This study is an analysis of biological samples prospectively collected during and after a randomized, controlled study examining early goal-directed therapy for severe sepsis and septic shock. Patients presenting to the ED of an urban academic tertiary care hospital from March 1997 to March 2001 were consented if they met enrollment criteria. Patients were included if they had 1) a source of infection suspected by the treating physician; 2) at least two of four systemic inflammatory response syndrome (SIRS) criteria; and 3) either systolic blood pressure less than 90 mm Hg after a 20-30 ml/kg crystalloid fluid bolus or lactate greater than or equal to 4 mmol/L. Patients were excluded if they had age less than 18 years, pregnancy, acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, dysrhythmia as a primary diagnosis, contraindication to central venous catheterization, active gastrointestinal hemorrhage, seizure, drug overdose, burn injury, trauma, requirement for immediate surgery, uncured cancer, immunocompromised state, or do-not-resuscitate status. After meeting enrollment criteria, patients were invited to participate in the randomized protocol comparing early goal-directed therapy versus standard care and/or provide blood samples for serial biomarker measurements.

Patient demographics, hemodynamic variables, laboratories, sources of infection, comorbidities, and outcome were collected at baseline. Simultaneous measurements of serum arterial lactate, biomarkers and organ dysfunction scores were obtained at time 0, 6, 12, 24, 36, 48, 60 and 72 hours after enrollment. Therapeutic interventions, such as antibiotics, fluids, packed red cells transfusion, vasoactive agents, and mechanical ventilation, given in the ED and up to 72 hours were recorded. Information required for the Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, Multiple Organ Dysfunction Score (MODS), and Sequential Organ Failure Assessment (SOFA) score calculations were obtained at each time point. Patients were followed until in-hospital death or up to 60 days after enrollment.

Biomarkers were chosen to represent pro-inflammatory, antiinflammatory, coagulation, and apoptosis pathways involved in the pathogenesis of severe sepsis and septic shock. The pro-inflammatory biomarkers included interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1 (ICAM-1), and high mobility group box-1 (HMGB-1). Anti-inflammatory biomarkers included interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10). Coagulation and apoptosis biomarkers included D-Dimer and caspase-8, respectively. Assays were performed using immunometric (sandwich) assays with NeutrAvidin-coated 384-well block microtiter plates and a Genesis RSP 200/8 Workstation. Each sample was tested in duplicate. Before the assays, biotinylated primary antibody was diluted in assay buffer containing 10 mmol/L trishydroxymethylaminomethane HCl (pH 8.0), 150 mmol/L sodium chloride, 1 mmol/L magnesium chloride, 0.1 mmol/L zinc chloride, and 10 mL/L polyvinyl alcohol (9-10 kDa). The concentration of biotinylated antibody was

Table 1 Patient characteristics.

No. Patients	220
Age (years)	65.0 ± 17.1
Male:Female (%)	54.1:45.9
Time from ED arrival to enrollment (hours)	1.6 ± 2.1
Length of hospital stay (days)	13.9 ± 16.6
Vital signs and hemodynamic variables	
Temperature (°C)	36.3 ± 2.8
Heart rate (beats per min)	117.1 ± 30.1
Systolic blood pressure (mm Hg)	107.5 ± 36.2
Mean arterial pressure (mm Hg)	74.8 ± 25.7
Shock index (heart rate/systolic blood pressure)	1.2 ± 0.5
Respiratory rate (breaths per min)	31.5 ± 11.1
CVP (mm Hg)	5.1 ± 8.5
$ScvO_2$ (%)	49.2 ± 12.6
Laboratories	
White blood cells ($\times 10^3$ per mm^3)	14.0 ± 9.0
Hemoglobin (g/dL)	11.4 ± 2.7
Platelets ($\times 10^3$ per μL)	211.5 ± 122.0
Creatinine (mg/dL)	2.9 ± 2.0
Glucose (mg/dL)	259.4 ± 327.8
Anion gap (mEq/L)	21.5 ± 8.0
Total bilirubin (mg/dL)	1.5 ± 2.1
Albumin (g/dL)	2.8 ± 0.7
Lactate (mmol/L)	7.4 ± 4.6
Lactate clearance (%)	35.5 ± 43.1
Septic shock (%)	55.0
Culture positive (%)	65.6
Blood culture positive (%)	37.1
Organ dysfunction scores	
APACHE II	21.5 ± 7.0
SAPS II	49.8 ± 11.0
MODS	7.6 ± 3.1
SOFA	6.5 ± 2.9
Source of infection (%)	
Pneumonia	39.5
Urinary tract infection	13.2
Intra-abdominal	4.1
Other	43.2
Comorbidities (%)	
Chronic obstructive pulmonary disease	16.4
Chronic renal insufficiency	20.9
Congestive heart failure	30.9
Coronary artery disease	22.7
Diabetes mellitus	30.5
Hypertension	67.3
Liver disease	21.4
Outcome (%)	
In-hospital mortality	35.0
28-day mortality	36.4
60-day mortality	42.7

Vital signs, hemodynamic variables, laboratories and organ dysfunction scores represent baseline values at patient enrollment. ED - emergency department; CVP - central venous pressure; $ScvO_2$ - central venous oxygen saturation; Acute Physiology and Chronic Health Evaluation (APACHE) II; Simplified Acute Physiology Score (SAPS) II; Multiple Organ Dysfunction Score (MODS); Sequential Organ Failure Assessment (SOFA).

predetermined by titration. The primary antibody (10 αL per well) was added to the plates and incubated. After washing, 10 g/L bovine serum albumin and 1 g/L sodium azide were added to the plate wells, which were then incubated at room temperature. Next, the plates were washed three times with borate-buffered saline containing 0.02% polyoxyethylene (20) sorbitan monolaurate (BBS-Tween).

Table 2 Patient characteristics, basline vital signs, hemodynamics and laboratories by lactate clearance quartile.

	Quartile 1 N = 55	Quartile 2 N = 55	Quartile 3 N = 55	Quartile 4 N = 55	P-value
Lactate clearance (%)	- 24.3 ± 42.3	30.1 ± 7.5	53.4 ± 6.6	75.1 ± 7.1	<0.01
Age (years)	63.2 ± 16.5	68.2 ± 17.5	65.7 ± 15.7	66.7 ± 18.4	0.29
Septic shock (%)	70.9	58.2	54.6	36.4	<0.01
Culture positive (%)	45.5	33.3	42.6	32.7	0.41
Blood culture positive (%)	43.4	34.0	42.3	28.9	0.36
Vital signs and hemodynamics					
Temperature (°C)	36.3 ± 3.0	36.5 ± 3.2	36.1 ± 2.7	36.4 ± 2.5	0.67
Heart rate (beats per min)	113.8 ± 25.4	117.0 ± 27.6	120.0 ± 30.9	117.8 ± 36.0	0.70
Systolic blood pressure (mm Hg)	108.0 ± 39.7	103.3 ± 30.2	108.1 ± 35.0	110.4 ± 40.0	0.88
Mean arterial pressure (mm Hg)	76.1 ± 26.6	71.2 ± 21.8	75.8 ± 26.9	76.1 ± 27.4	0.81
Shock index (HR/SBP)	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.5	1.2 ± 0.6	0.76
Respiratory rate (breaths per min)	29.5 ± 10.3	30.4 ± 10.9	34.2 ± 11.8	32.2 ± 10.9	0.16
CVP (mm Hg)	6.0 ± 8.7	4.5 ± 8.7	3.9 ± 8.9	5.7 ± 8.2	0.16
$ScvO_2$ (%)	49.3 ± 12.9	51.4 ± 12.0	44.1 ± 12.6	51.2 ± 12.3	0.28
Laboratories					
White blood cells (×10³ per mm³)	11.8 ± 7.1	13.5 ± 8.9	15.0 ± 10.5	15.6 ± 9.1	0.13
Hemoglobin (g/dL)	11.6 ± 2.6	11.0 ± 2.9	11.5 ± 2.5	11.3 ± 2.7	0.68
Platelets (×10³ per μL)	163.7 ± 82.2	184.0 ± 116.7	254.1 ± 135.6	244.4 ± 124.8	<0.01
Creatinine (mg/dL)	2.5 ± 2.2	2.5 ± 1.7	2.6 ± 1.9	2.7 ± 2.4	0.94
Glucose (mg/dL)	303.5 ± 421.4	172.1 ± 150.6	240.9 ± 275.0	321.1 ± 382.0	0.07
Anion gap (mEq/L)	22.2 ± 9.6	20.0 ± 7.3	21.5 ± 7.9	22.2 ± 6.9	0.52
Total bilirubin (mg/dL)	1.9 ± 2.3	1.9 ± 3.1	1.2 ± 1.4	0.9 ± 0.7	0.03
Albumin (g/dL)	2.7 ± 0.7	2.8 ± 0.7	2.8 ± 0.7	3.1 ± 0.6	<0.01
Lactate (mmol/L)	7.5 ± 5.8	7.3 ± 4.9	7.3 ± 3.8	7.3 ± 3.5	0.47

Lactate clearance - defined as the percent change in lactate level after six hours from baseline measurement = [(Lactate[ED Presentation] - Lactate[Hour 6])/Lactate[ED Presentation]] × 100. A positive value denotes a decrease or clearance of lactate, whereas a negative value denotes an increase in lactate after 6 hours of intervention. Lactate clearance quartile - derived from sorting the study population by increasing lactate clearance and separating into four groups with equivalent number of patients. HR - heart rate; SBP - systolic blood pressure; CVP - central venous pressure; $ScvO_2$ - central venous oxygen saturation.

Table 3 Therapies during the first 6 hours in the ED and from 7 to 72 hours in the ICU by lactate clearance quartile.

	Quartile 1 N = 55	Quartile 2 N = 55	Quartile 3 N = 55	Quartile 4 N = 55	P-value
Therapies in first 6 hours					
Antibiotics (%)	72.2	77.5	72.1	75.0	0.95
Appropriate Antibiotics (%)	86.3	77.5	90.7	88.9	0.59
Fluids (mL)	4531.2 ± 2745.3	4263.5 ± 2872.9	4266.8 ± 3449.5	3741.7 ± 3136.4	0.27
Transfusion (%)	54.6	41.8	26.4	43.6	0.27
Vasopressor (%)	50.9	36.4	27.3	14.6	<0.01
Inotrope/dobutamine (%)	5.5	3.6	9.1	12.7	0.29
Mechanical ventilation (%)	74.6	50.9	58.2	38.2	<0.01
Therapies from 7 to 72 hours					
Antibiotics (%)	95.0	93.9	100	97.0	0.50
Fluids (mL)	8817.2 ± 5818.1	9666.7 ± 6555.2	10329.8 ± 6866.6	7141.9 ± 4097.8	0.06
Transfusion (%)	23.6	20.0	20.0	27.3	0.77
Vasopressor (%)	47.3	47.3	30.9	18.2	<0.01
Inotrope/dobutamine (%)	10.9	14.6	9.1	12.7	0.83
Mechanical ventilation (%)	12.7	14.6	7.3	7.3	0.48

Lactate clearance quartile - derived from sorting the study population by increasing lactate clearance and separating into four groups with equivalent number of patients.

For each sample, 10 αL aliquots were added to each plate well and the plates were incubated. Following this incubation, the plates were washed three times and alkaline phosphatase-conjugated antibody (10 αL per well) was added to each plate well and further incubated. The concentration of the alkaline phosphatase-conjugated antibody was predetermined to ensure a linear profile in the dynamic range of interest. After additional incubation, the plates were washed nine times with BBS-Tween. AttoPhos substrate, a fluorescence-enhancing substrate previously diluted in AttoPhos buffer (S1021, Promega), was then added to aid in the measurement of the activity of antibody-conjugated alkaline phosphatase bound in each well. The plates were then scanned in a fluorometer using an excitation wavelength of 430 nm and an emission wavelength of 570 nm. Each well was scanned 6 times at 114-sec intervals, and the rate of fluorescence generation was calculated. Calibration curves were derived from eight points tested at multiple locations on the assay plate using a 4-parameter logistic fit, from which sample concentrations were subsequently calculated. Each plate included calibration wells consisting of multiple analyte concentrations and control samples. Calibration curves for each biomarker assay were generated for IL-1ra, IL-6, IL-8, IL-10, TNF-α, ICAM-1, HMGB-1, D-Dimer, and caspase-3.

Lactate clearance was defined as the percent change in lactate

Table 4 Biomarker levels and organ dysfunction scores averaged over 72 hours by lactate clearance quartile.

	Quartile 1 N = 55	Quartile 2 N = 55	Quartile 3 N = 55	Quartile 4 N = 55	P-value
Biomarkers over 72 hours					
IL-1ra (ng/mL)	8455.9 ± 8838.4	7565.4 ± 8289.1	6421.3 ± 7957.5	2792.6 ± 3635.7	<0.01
IL-6 (pg/mL)	2839.5 ± 3487.0	2680.1 ± 3174.0	2426.7 ± 3269.4	663.2 ± 1583.5	<0.01
IL-8 (pg/mL)	480.3 ± 802.4	355.3 ± 559.1	356.3 ± 735.1	76.4 ± 218.0	<0.01
IL-10 (pg/mL)	303.6 ± 298.7	227.4 ± 218.5	180.2 ± 243.4	85.4 ± 121.9	<0.01
TNF-α (pg/mL)	65.2 ± 105.9	50.9 ± 69.2	47.4 ± 72.8	19.6 ± 19.8	<0.01
ICAM-1 (ng/mL)	409.1 ± 208.1	413.3 ± 204.5	379.7 ± 213.8	299.2 ± 156.1	<0.01
HMGB-1 (ng/mL)	4.6 ± 8.3	5.0 ± 10.4	2.5 ± 3.3	1.6 ± 2.4	<0.01
D-Dimer (μ/mL)	20.8 ± 9.5	18.9 ± 9.5	18.1 ± 8.9	15.7 ± 9.7	0.04
Caspase-3 (ng/mL)	3.8 ± 7.5	2.4 ± 3.8	1.9 ± 2.6	1.1 ± 0.8	<0.01
Organ dysfunction over 72 hours					
APACHE II	16.8 ± 6.3	16.6 ± 6.4	14.8 ± 6.9	11.6 ± 6.0	<0.01
SAPS II	43.9 ± 12.4	44.6 ± 43.5	39.5 ± 12.0	34.2 ± 11.9	<0.01
MODS	8.0 ± 3.5	7.0 ± 4.0	5.7 ± 4.2	3.4 ± 2.5	<0.01
SOFA	8.8 ± 3.3	8.0 ± 3.4	6.8 ± 4.3	4.4 ± 2.7	<0.01
Outcome (%)					
In-hospital mortality	52.7	41.8	29.1	16.4	<0.01
28-day mortality	54.9	49.0	33.5	21.6	<0.01
60-day mortality	63.1	52.9	38.0	33.6	0.01

Lactate clearance quartile - derived from sorting the study population by increasing lactate clearance and separating into four groups with equivalent number of patients. IL-1ra - interleukin-1 receptor antagonist; IL-6 - interleukin-6; IL-8 - interleukin-8; IL-10 - interleukin-10; TNF-α - tumor necrosis factor-α; ICAM-1 - intercellular adhesion molecule-1; HMGB-1 - high mobility group box-1; Acute Physiology and Chronic Health Evaluation (APACHE) II; Simplified Acute Physiology Score (SAPS) II; Multiple Organ Dysfunction Score (MODS); Sequential Organ Failure Assessment (SOFA).

level after six hours from a baseline measurement. It is calculated by using the following formula: lactate at ED presentation (hour 0) minus lactate at hour 6, divided by lactate at ED presentation, then multiplied by 100. A positive value denotes a decrease or clearance of lactate, whereas a negative value denotes an increase in lactate after 6 hours of intervention. The study population was sorted by increasing lactate clearance and divided into four groups with equivalent number of patients for comparisons among lactate clearance quartiles.

For the purpose of this study, lactate clearance, biomarkers and organ dysfunction scores were analyzed in all patients enrolled in the study, irrespective of the treatment group assigned to the patients. We a priori accepted that lactate clearance is a reflection of the therapies received by the patients, such as fluids, red cells transfusion, vasopressors, and inotrope; rather than a function of the randomization assignment to early goal-directed therapy or standard care.

Results
Two hundred and twenty-two patients, age 65.0±17.1 years, were enrolled within 1.6±2.1 hours of ED presentation. The initial hemodynamic parameters included central venous pressure of 5.1±8.5 mm Hg, mean arterial pressure 74.8±25.7 mm Hg, central venous oxygen saturation 49.2±12.6 percent, and lactate 7.4±4.6 mmol/L. Fifty-five percent of patients had septic shock, 37.1% had blood culture positive, and the most common source of infection was pneumonia. Lactate clearance was 35.5±43.1 percent and in-hospital mortality rate 35.0%. The lactate clearance quartiles were -24.3±42.3, 30.1±7.5, 53.4±6.6, and 75.1±7.1%, respectively. There was no significant difference among the lactate clearance quartiles with respect to age, demographics, co-morbidities, blood culture positive, hemodynamic variables, baseline lactate, and other laboratories (except platelets, total bilirubin and albumin). There was significant difference in the number of septic shock patients among the lactate clearance quartiles, with the highest percent of septic shock patients in the lowest clearance quartile (p<0.01). Quartiles with lower lactate clearance required

significantly more vasopressor and mechanical ventilation during the first 6 hours. After 6 hours, only vasopressor remained significantly higher in lower lactate clearance quartiles. The mean levels of all biomarkers averaged over 72 hours were significantly lower with higher lactate clearance quartiles. Similarly, the mean organ dysfunction scores averaged over 72 hours were significantly lower with higher lactate clearance quartiles. There was significant decreased in-hospital, 28-day and 60-day mortality for higher lactate clearance quartiles. Kaplan-Meier survival analysis showed a survival benefit over 12 months for patients in the higher lactat quartiles.

Discussion
The current pathogenesis of severe sepsis and septic shock is described as a complex interaction of pro- and anti-inflammation, coagulation, and apoptosis triggered by the infecting microorganism. The bacteria outer membrane lipopolysaccharide molecule (LPS, endotoxin) activates a toll-like receptor 4 (TLR-4) signaling pathway that results in translocation of nuclear factor-αB (NF-αB) and production of inflammatory cytokines. The result is a production of pro-inflammatory cytokines that are balanced by an array of anti-inflammatory cytokines. The coagulation pathway is also activated by LPS-mediated signaling and further regulated by the cytokines, inducing the production of tissue factor, prothrombin conversion to thrombin, and fibrin production. Fibrinolysis is impaired due to increased production of plasminogen-activator inhibitor type-1 (PAI-1), decreased generation of plasmin and reduced removal of fibrin. The procoagulant state further down regulates the anticoagulant proteins, antithrombin, protein C, and tissue factor pathway inhibitor. The net result is deposition of fibrin clots throughout the endothelium, resulting in inadequate blood flow, organ hypoperfusion, global tissue hypoxia and cell death.

Clinically, lactate has been studied as a measure of illness severity in circulatory shock for several decades dating back to the 1800s. Although there are various explanations regarding the mechanisms responsible for lactate accumulation in severe

1A. Pro-inflammatory markers
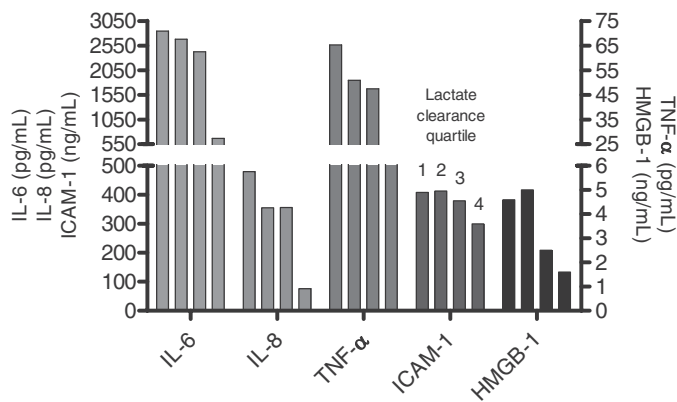
1B. Anti-inflammatory, coagulation, and apoptosis markers
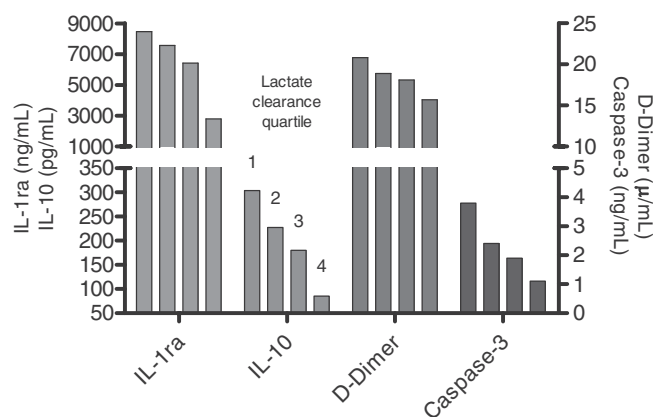
Figure 1. Mean biomarker levels averaged over 72 hours based on lactate clearance quartile. The mean levels of pro-inflammatory markers interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-a (TNF-a), intercellular adhesion molecule-1 (ICAM-1), and high mobility group box-1 (HMGB-1); anti-inflammatory markers interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10); coagulation marker D-Dimer; and apoptosis marker Caspase-3 are significantly lower over 72 hours with higher lactate clearance quartiles.

sepsis and septic shock, it remains a robust surrogate marker for the development of multi-organ failure and poor outcome. Similar observations have been noted in other conditions of critical illness, including pediatric and adult cardiac surgery, the post-resuscitation period of cardiac arrest, trauma, general surgical, and liver surgery patients. A recurring theme in these studies is the inflammatory response plays a crucial mechanistic intermediate between lactate clearance and the development of multi-organ failure.

Evidence-based guidelines have recommended that an elevated lactate is sufficient to diagnosis shock, irrespective of hypotension. Sepsis with lactate level greater than or equal to 4 mmol/L is associated with high mortality and is an indication to initiate treatment protocols and care bundles. We previously reported a significant inverse relationship between lactate clearance (or resolution of global tissue hypoxia) during the first 6 hours and mortality in severe sepsis and septic shock. We have also shown that early goal-directed therapy targeting global tissue hypoxia to be more effective than standard care in decreasing lactate during the first six hours of intervention. In this study, we found a significant association between improving lactate clearance in the first 6 hours and a corresponding decrease in mean biomarker levels over 72 hours. This potential mechanistic link was also positively associated with improved organ dysfunction scores and decreased mortality.

The association between poor lactate clearance and the need for vasopressor therapy is consistent with observations that pathogenic but reversible correlates of outcome may be established in the first few hours of disease presentation. A limited course of vasopressor therapy indicates reversible tissue hypoxia; however, prolonged vasopressor usage for hemodynamic support is associated with worse lactate clearance and thus outcome. Additionally, lactate clearance has been shown to be significantly associated with improved microcirculatory flow. This provides supportive evidence for the mechanistic connection between prolonged vasopressor use, tissue ischemia, persistent lactate elevation, morbidity and mortality. Our results further support the notion that tissue hypoxia plays a crucial role in the early complex mechanisms leading to the endothelial response in severe sepsis and septic shock, rather than a terminal or irreversible event following inflammation and coagulopathy. Thus a goal-directed hemodynamic optimization strategy targeting the resolution of global tissue hypoxia, reflected by clearance of lactate, will likely reverse the diffuse endothelial and microcirculatory dysfunction in patients who most likely will benefit.

In-vitro models have shown that hypoxia induces the pro-inflammatory cytokines, IL-1, IL-6, IL-8, and TNF-α. These cytokines then increase the expression of intercellular adhesion molecules (ICAM-1) and further activation and migration of neutrophils. In humans, IL-6 and IL-8 elevations correlated significantly to lactate levels (as a measure of tissue hypoxia) in sepsis. Recently, combined serial lactate and cytokine levels (IL-1, IL-6, IL-10, and HMGB-1) in septic shock patients were shown to be useful indicators of clinical outcome. In our study, IL-1ra, IL-6, IL-8, IL-10, and TNF-α were measured due to their close association with the early pro- and anti-inflammatory response. HMGB-1 was chosen as a pro-inflammatory mediator that appears much later than the other cytokines after LPS stimulation. We have shown that the higher lactate clearance in the first 6 hours, the greater the decrease in all pro-inflammatory and anti-inflammatory cytokines measured over 72 hours.

Hematologic abnormalities (leukocytotosis, anemia and thrombocytopenia) are common in severe sepsis and septic shock. Alterations in the levels of various mediators of coagulation and fibrinolysis have been reported to be associated with disseminated intravascular coagulation (DIC) and mortality.[45] Patients with SIRS and sepsis having DIC were shown to have higher serial lactate levels over 4 days compared to those patients without DIC, suggesting a pathogenic link between tissue hypoxia and intravascular coagulation. While no single marker measured at hospital admission is sufficiently sensitive or specific in diagnosing DIC, we chose to measure D-Dimer as a marker of coagulation in this study as it is widely available, a correlate to the pro-inflammatory cytokine levels, and a valuable screening marker for organ failure and mortality. It also has been used previously as an indicator of response to therapies such as recombinant human activated protein C in severe sepsis. In our study, we showed that improvements in coagulation (reflected by a decrease in D-Dimer levels over 72 hours) corresponded with lactate clearance during the first 6 hours. Our results provide further evidence that tissue hypoxia may be a preceding or parallel event to the pro-coagulant state in severe sepsis and septic shock, and therapies targeting tissue hypoxia may play a crucial role in reversing this coagulopathy.

Cell death through apoptosis is a highly regulated process in the presence or absence of inflammation.[51] Apoptosis is initiated
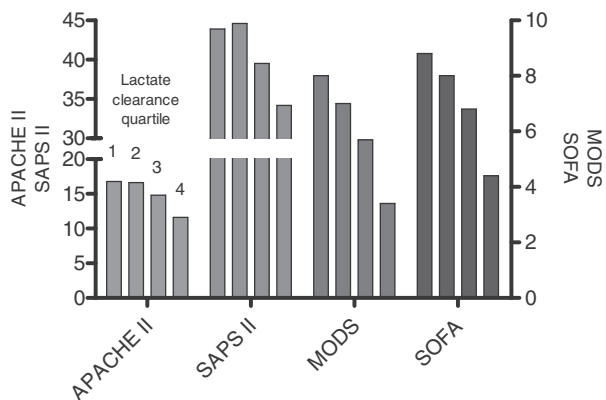
Figure 2. Mean organ dysfunction scores averaged over 72 hours based on lactate clearance quartile. The Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, Multiple Organ Dysfunction Score (MODS), and Sequential Organ Failure Assessment (SOFA) score are significantly lower over 72 hours with higher lactate clearance quartiles.

by two pathways: 1) a receptor activated, caspase-8 mediated (extrinsic) pathway; and 2) a mitochondrial initiated caspase-9 mediated (intrinsic) pathway. Either of these caspases can activate caspase-3 in the common pathway resulting in final cell death. Caspases are pro-apoptotic proenzymes that inactivate protective proteins and contribute to cell death by direct cellular disassembly via cell shrinkage (pyknosis) and nuclear fragmentation (karyorrhexis). The regulation of apoptosis in sepsis is complex, as the infecting pathogen may inhibit or induce apoptosis, involving both the extrinsic and intrinsic pathways, to enhance its damaging effects to the host. Caspase activation in apoptosis is an energy-dependent process. Hypoxia can induce apoptosis as long as cells have an adequate amount of adenosine triphosphate. Previously, apoptosis was believed to occur via the intrinsic pathway with cytochrome c release and caspase-9 activation in oxygen-deprived cells.[54] However, the extrinsic pathway may also play an important role in oxidative stress induced apoptosis.[53] In this study, caspase-3 as a marker of the final common pathway in apoptosis was shown to be elevated over 72 hours in patients with decreased lactate clearance, compared to lower caspase-3 in patients with higher lactate clearance. This finding supports the premise that tissue hypoxia in severe sepsis and septic shock is associated with increased apoptosis, suggesting that the ill effects resulting in cell death may be mitigated by resolution of global tissue hypoxia.
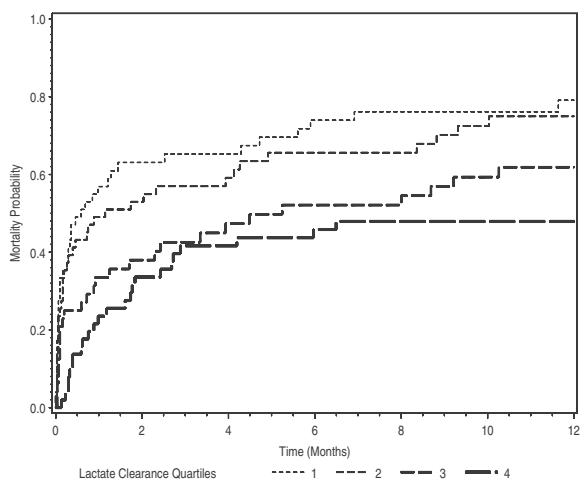
Figure 3. Kaplan-Meier 12-month survival analysis based on lactate clearance quartile. Lactate clearance quartile 1, 2, 3, and 4 have lactate clearance of -24.3±42.3, 30.1±7.5, 53.4±6.6, and 75.1±7.1%, respectively, during the first 6 hours in the emergency department (p<0.01).

Our results provide evidence that the design and interpretation of future clinical trials should consider the early stages of severe sepsis and septic shock. Previously, two studies failed to show significant outcome benefit with inhibition of TNF- and IL-1ra in severe sepsis and septic shock patients enrolled in the ICU. The association of lactate clearance with these targeted biomarkers shown in our study suggests that the severity of tissue hypoxia should be part of patient selection criteria in studies examining novel therapies that may alter its down stream effects. The failure to consider the magnitude, duration of tissue hypoxia and the timing of patient enrollment in clinical trials will likely result in some degree of hemodynamic heterogeneity confounding any treatment effect.

The results of our study do not confirm a causal relationship, but an association between lactate clearance in the first 6 hours and biomarker response over 72 hours. High lactate clearance quartiles had fewer patients in septic shock obviously requiring less vasopressor usage, but no difference in antibiotic and fluid administration. Lactate clearance over 6 hours may also depend on the patient's underlying comorbidities, such as liver disease, and the disease process rather than solely on the therapies themselves. However, baseline demographics, comorbidities, lactate and hemodynamic variables were similar in all quartiles. Thus the ability to clear lactate irrespective of the mechanism and its association with improved biomarkers suggests that further studies are needed to examine global tissue hypoxia as an inciting factor in the pathogenic pathways of severe sepsis and septic shock. Which of the three pathogenic pathways predominate as an association to tissue hypoxia cannot be discerned by this exploratory study. Nonetheless, our observation of a significant correlation of lactate clearance and decrease mortality is consistent with previous studies.

We have previously shown that early goal-directed therapy is significantly more effective than standard therapy in decreasing lactate (by 44% compared to 29%, p<0.01) during the first 6 hours, resulting in improved organ dysfunction and mortality. We further showed that global tissue hypoxia and early goal-directed therapy were associated with distinct biomarker patterns that were evident as early as 3 hours after intervention. The purpose of this study was to show that lactate clearance is associated with improved biomarkers and organ dysfunction scores. We a priori chose not to distinguish lactate clearance, biomarker responses, and organ dysfunction scores by resuscitation groups. While we have shown that lactate clearance is a mechanistic link in the early pathogenesis of sepsis, these findings do not support the substitution of lactate clearance as an independent alternative to an organized hemodynamic optimization strategy such as early goal-directed therapy.

Conclusions

This study showed a significant association between lactate clearance and biomarkers of pro- and anti-inflammation, coagulation, apoptosis; and further with multi-organ dysfunction and mortality in severe sepsis and septic shock. These findings support a growing body of evidence suggesting that global tissue hypoxia plays a crucial role in the complex mechanisms leading to the endothelial response in severe sepsis and septic shock rather than a terminal event. Future studies examining the pathogenic mechanisms or novel therapies for severe sepsis and septic shock should include lactate clearance as a measure of prognosis and therapeutic responses.

Lactate in Critical Illness: Implications for Monitoring

Karen Robinson RCP (NBRC), POCS; Gale L. Kongable, RN, MSN, FNP

Introduction

Under normal physiologic conditions, serum lactate levels are between 0.5 and 1 mEq/L, representing balanced lactate metabolism. Hyperlactatemia in critical illness is considered an adaptive response to anaerobic glycolysis[1] and levels are common during conditions of sepsis or trauma,[2,3,4] as accumulation exceeds the rate of clearance until hemodynamic stabilization.[5,6] While lactate levels at concentrations outside the reference range (< 2 mEq/L - 4 mEq/L) are tolerated in patients, higher levels have been found to be independently related to increased mortality[7] and call for intervention in the form of early goal-directed therapy.[8] In modern intensive care units (ICU) the frequent measurement of lactate using blood glucose analyzers is useful in identifying patients at increased risk of death and serve as an early marker of a potentially reversible state.[9] Outcomes may be improved by adapting resuscitation to serial lactate measurements. This review presents a brief discussion of the available evidence.

Lactate as an indicator of severity of illness

Early studies found that elevated venous lactate (≥ 4 mEq/L) was often present in shock patients on admission to the medical ICU and was associated with increased incidence of organ failure and mortality rates of greater than 30%.[2,3,7] More recently, not only the presence of hyperlactatemia on admission, but also subsequent development and duration of elevated lactate are reported to increase the risk of mortality in surgical and trauma ICU patients.[9]

Cerovic et al[10] postulated that blood lactate concentrations in injured patients on hospital admission might be an objective indicator of the patient's true condition and serve as an independent predictor of injury severity, morbidity and mortality. These researchers examined the correlation of the admission Injury Severity Score (ISS)[11] and Trauma Injury Severity Score (TRISS)[12] with lactate levels drawn at admission, twice daily for the first 2 days, and daily for a following 3 days. Lactate levels in non-survivors were significantly higher than those in survivors on admission (6.3 ± 5.9 vs 4.2 ± 3.3 mEq/L) and at 12 hours (6.1 ± 7.0 vs 3.2 ±1.9 mEq/L). Regression analysis demonstrated that

injury severity, as measured by the ISS can also be predicted from lactate concentration on admission, while actual or predicted survival, as measured by the TISS can be predicted from lactate concentration after 12 hours. In surviving patients, lactate showed a progressive decline over time, while levels remained high in non-survivors, from the 12 hour sampling until death.

More recently, in a retrospective observational study, Jansen et al[13] examined whether the level and duration of increased blood lactate (>2 mEq/L) was associated with daily Sequential Organ Failure Assessment (SOFA)[14] scores and organ subscores during the early and late phases of ICU stay. At 28 days, they found a 57% increased risk of death for every day lactate was elevated and every 1 mEq/L above 2 mEq/L. This clear association between lactate and SOFA score was strongest in the early phase of ICU care compared with later. This confirmed the relationship between blood lactate levels and injury severity and of the prognostic value of lactate clearance for survival of severely injured patients.

Mikkelsen et al,[15] determined that initial lactate levels were associated with mortality, independent of organ failure and shock. In this study of 830 patients admitted to the ED with severe sepsis, initial lactate was categorized as low (<2 mEq/L) intermediate (2-3.9 mEq/L) and high (≥ 4 mEq/L). Mortality at 28 days was 8.7%, CI of 4.9 - 14.2; 16.4%, CI 12.5-20.9; and 31.8%, CI 24.6-39.7 for the low, intermediate and high lactate levels in non-shock patients and 15.4%, CI 5.9-30.5; 37.3%,CI 25.0-50.8; and 46.9%, CI 36.8-57.3 in the low, intermediate and high lactate levels in patients with shock. A second important finding was related to the conventional lactate threshold of > 4 mEq/L and that some risk of death is associated with lactate levels that are deemed "normal."[15]

A recently published clinical study examining this association of "relative" hyperlactatemia, (< 2mEq/L), also found increased risk of hospital death to confirm these findings.[9] This retrospective observational study of prospectively collected data on 7155 consecutive critically ill patients admitted to the ICU examined the relationship of on admission, maximum, and time-weighted relative hyperlactatemia with hospital outcome. Findings concluded that even lactate concentrations >0.75 mEq/L can be used by clinicians to identify patients at higher risk of death. These findings suggest that the current reference range for lactate levels that trigger early goal-directed therapy in the critically ill may need to be reassessed.[9]

Lactate as a clinical marker for hypoxia

Jansen et al[16] studied lactate levels in septic patients versus other patients with hemorrhage or conditions generally associated with low-oxygen transport (LT) and in patients who were hemodynamically stable compared to those who were not. They found that a reduction in lactate concentration during the first 24 hours after ICU admission was associated with improved outcome in septic patients, but not in patients presenting with hemorrhage or LT, and that lactate on admission, not the reduction over time, predicted mortality in the hemorrhage and LT group. They hypothesized that the patients who experienced hemorrhage and LT and significantly higher lactate levels sustained a more severe insult and irreversible organ damage that would not respond to interventions designed to reduce lactate levels.[16]

Lactate as a predictor of mortality

Significantly higher lactate levels in non-survivors have been reported in several studies[16,17] demonstrating that hyperlactatemia adds mortality risk to all critically ill patient populations, regardless of admission diagnosis. In a study of 11,581 adult patients[16] admitted to 4 ICUs with serious medical, cardiac surgical, surgical and neuro/trauma conditions, the incidence of one episode of high lactate (> 2mEq/L) was present in 40% of patients and the average prevalence was 20 per 100 days of hyperlactatemia during the average ICU stay. The occurrence of hyperlactatemia varied significantly by admitting diagnostic category (p<0.001) with the highest cumulative incidence observed among the neuro/trauma patients, followed by the medical, then surgical, then cardiac surgical patient groups. Higher lactate levels were found in patients with higher Acute Physiology and Chronic Health Evaluation v.II (APACHE II) scores,[18] and increased with patient age. Among patients who did not have elevated lactate on admission, subsequent hyperlactatemia occurred in 6%. Mortality was highest among all patient groups with hyperlactatemia on admission, (20% vs 5%, p<0.001). This affected medical patients most (47%) followed by neuro/trauma (25%), surgical (15%) and cardiac surgical (13%) patients (p<0.001). After controlling for confounding variables, increasing levels of hyperlactatemia at presentation were independently associated with stepwise increased risk for subsequent ICU-related mortality. Lactate concentrations of 2-5 mEq/L conferred increased risk of death (Odds Ratio [OR], 95% CI; 1.94,1.62-2.32, while concentrations of 5-10 mEq/L (OR 3.38, 95% CI 2.64 to 4.33); 10-15 mEq/L (OR 4.41, 95% CI 2.99 to 6.50); 15-20 mEq/L (OR 7.58, 95% CI 3.93 to 14.60) and >20 mEq/L (OR 10.89, 95% CI 4.89 to 24.48) respectively.[16] Howell et al[17] reported that patients with a lactate level ≥ 4 mEq/L in the presence of normal blood pressure had a mortality rate of 15.0%, 6.0-24 (95% CI) while patients who had either septic shock or lactate ≥ 4 mEq/L had a mortality rate of 28.3% (21.3-35.3%), which was significantly higher than for those who had neither (2.5%, 1.6-3.4%). Additionally, patients with a lacate level of 2.5-4.0 mEq/L had adjusted odds ratio of death of 2.2 (1.1-4.2) and those with lactate ≥ 4 mEq/L had 7.1 (3.6-13.9) times the odds of experiencing death.[17] Jansen et al[19] also found that mortality was significantly higher in ED patients with lactate levels of ≥3.5 mEq/L compared to those with lactate levels below 3.5 mEq/L at first measure (T1) and on ED arrival (T2); T1: 41% vs. 12% and T2: 47% vs 15%).[19] These findings suggest that a clinical intervention for lactate concentration > 4 mEq/L may miss opportunities for preventing ICU death.

Early lactate clearance may decrease mortality

Early studies of lactate clearance demonstrated that lactate metabolism and the time needed to normalize lactate levels is also an important prognostic factor for survival in severely injured patients.[20] Serum lactate levels and oxygen transport were measured from admission up to 48 hours in 76 consecutive patients with multiple trauma. Patients were analyzed with respect to survival and lactate clearance to normal (≤ 2 mEq/L) by 24 and 48 hours. While there were no differences in interventions and severity scores, all patients whose lactate levels normalized in 24 hours survived. When lactate cleared to normal between 24 and 48 hours, the survival rate was 75%, and only 3 of the 22 patients who did not clear their lactate level at 48 hours survived, demonstrating that optimization of treatment of hypoxia and perfusion alone does not predict survival.[20]

Nguyen et al,[21] further examined the clinical implications of clearance of high lactate levels on presentation to the emergency department (ED). As the ED is frequently the initial point of care for patients with sepsis and shock, the hypothesis was that initiating early goal directed therapy to reduce lactate levels early in the course of therapy (prior to ICU admission) may improve outcomes from severe sepsis and septic shock. In this prospective observational study, therapy was initiated on recognition of sepsis in the ED and continued in the ICU. Survivors had a lactate clearance of 38.1 ± 34.6 mEq/L compared to 12.0 ± 51.6 mEq/L (p=0.005) in nonsurvivors. Multivariate logistic regression demonstrated lactate clearance had a significant inverse relationship with mortality (p=0.04). The investigators found an approximately 11% decrease likelihood of mortality for each 10% higher lactate clearance. Finally patients with a lactate clearance ≥ 10% had a lower 30 day and 60 day mortality rate when compared to patients with a <10% lactate clearance (37.5% vs. 67.7% and 42.5% vs. 71.0%) respectively, (p=0.004, p=0.007).[21] This is consistent with efforts emphasizing the importance of recognizing high lactate as a sign of tissue hypoperfusion and initiating treatment in the earliest hours of severe sepsis presentation.[8,22,23,24]

Lactate and early goal directed therapy

Early goal-directed therapy (EGDT)[8,23] and implementation of sepsis bundles[24] for the early management of severe sepsis and septic shock has become the standard of care in the ED and ICU. Rivers et al[8] demonstrated that interventions that adjusted cardiac perfusion to balance oxygen delivery with oxygen demand provided significant benefits with respect to outcome in patients with severe sepsis and septic shock. This study compared in-hospital mortality rates in patients randomized to EGDT or standard therapy in the first 6 hours of care. Parameters of central venous oxygen saturation, lactate concentration, base deficit and pH were monitored during the first 6 hours of resuscitation and the following interval (7-72 hours) to determine the efficacy of the two therapies and in-hospital mortality. The two patient groups were similar in risk factors at baseline (lactate levels, APACHE II scores, and perfusion parameters). During the interval from 7-72 hours, the patients assigned to early goal-directed therapy has a significantly improved central venous oxygen saturation (mean ± SD) 70.4 ± 10.7% compared to 65.3 ± 11.4% in the group assigned to standard care (p=0.009). EGDT was associated with a lowering of lactate concentration (3.0 ± 4.4 vs. 3.9 ± 4.4 mEq/L; a lowering of base deficit (2.0 ± 6.6 vs. 5.1 ± 6.7 mEq/L; and a higher pH (7.40 ± 0.12 vs. 7.36 ± 0.12 than patients receiving standard care. Additionally, during the same period, APACHE II scores were significantly improved, indicating less severe organ dysfunction in the patients assigned to EGDT than in those

assigned to standard therapy; (13.0 ± 6.3 vs. 15.9 ± 6.4, p<0.001).[8] Subsequently, guidelines for protocolized management of severe sepsis and septic shock have incorporated measurement of lactate as soon as possible on arrival, as a primary indicator of tissue hypoperfusion, and initiation of treatment when lactate is ≥ 4 mEq/L, even in patients who are not hypotensive. However, these authors state, "although lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation.[22,24]

Is lactate reliable?

While hyperlactatemia is thought to be an indication of the metabolic stress response, energy failure, and impaired organ perfusion, it can be present under stable oxygenation and hemodynamic conditions.[25,26] Additionally, elevated lactate concentrations can be found irrespective of the presence of lactic acidosis, and may precede clinical signs which appear at a critical stage.[25] In fact, elevated lactate may be the only indication of tissue hypoxia and anaerobic glycolysis when blood pressure, cardiac output, and urine output are within clinically acceptable ranges. Levraut et al[26] demonstrated that a combination of low lactate production and low clearance could mask abnormal lactate metabolism in septic patients with normal or near normal lactate levels. In this prospective observational study, the investigators found that when lactate levels were the same in survivors and non-survivors, production and clearance were higher in sepsis survivors at 28 days.[26] Under these circumstances, lactate production and low lactate clearance could be the expression of very different metabolic situations with opposing effects on prognosis.

This was evident in the study by Revelly et al,[6] evaluating the mechanisms leading to hyperlactatemia in patients with severe sepsis or cardiogenic shock. In these patients, elevated lactate levels were related to increased production from increased glucose turnover from concomitant hyperglycemia and not impaired lactate clearance. Therefore, treatment aimed at correction of hyperglycemia and tissue perfusion could result in decreased lactate levels and improved patient outcomes.[6,28]

Summary

Hyperlactatemia occurs in nearly half of all patients admitted to the ICU, and presentation with or development of hyperlactatemia is associated by significantly increased mortality. While there are multiple factors that may contribute to high lactate production or low lactate clearance, lactate levels have been found to increase the risk of death directly and proportionately. Currently, elevated lactate levels of ≥ 4 mEq/L, if recognized at any time, stimulates EGDT, but evidence suggests a lower lactate threshold should be established for resuscitation to be most effective. In modern intensive care units (ICU) the frequent measurement of lactate using blood glucose analyzers is useful in identifying patients at increased risk of death and serve as an early marker of a potentially reversible state. While lactate measurement as an optimal guide to the endpoint of resuscitation remains controversial, it is superior to other markers of resolution of tissue hypoxia and hypoperfusion. This evidence holds true for all patients with severe sepsis or shock regardless of the underlying pathology. Consideration for future research should be given to:

- whether the serum lactate threshold used to prompt EGDT be adjusted downward

- whether serum lactate should be measured prior to arrival to the ED to take advantage of the golden hours and optimize resuscitation

- whether serum lactate should be used to risk stratify patients in the ED and ICU to determine which patients would potentially benefit most from aggressive resuscitation strategies.

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change was not clinically significant.

The authors found that delay following sample collection does not substantially alter measured pH over one hour, though delays of four-plus hours produce clinically significant alterations. A 24 hour delay produced clinically significant inaccuracies in pH readings in over two-thirds of samples. A close correlation was observed between increase in pH and decrease in pleural fluid pCO_2 over 24 hours. Thus it may be suggested that the mechanism of pH change is related to CO_2 diffusing out of pleural fluid with time. The pO_2 level consistently increases in these samples over 24 hours, supporting the suggestion that constant gas exchange occurs between atmospheric air and pleural fluid, even in capped containers. Changes in pH over time may also be a result of metabolism of cells or bacteria in infected samples.

Pleural fluid glucose measurements are less susceptible to inaccuracy induced by the presence of air, lidocaine or heparin, except where the volume of additive is sufficient to cause a dilutional effect.

The authors noted: "This study highlights the need for a standardized protocol for pleural pH sampling and analysis, both for clinical practice and for future research studies… Clinicians must realize that although existing literature/guidelines often employs definitive thresholds of pH to guide management (eg, a cut-off pH 7.20 determines need for chest tube drainage of parapneumonic effusions), measurement of pH is vulnerable to variations in processing protocols… Decisions on clinical management should not be governed by pleural pH alone, and must be taken in conjunction with information from other investigations.

The authors stated, "In conclusion, pleural fluid pH measurements are subject to substantial variability during collection, which could be minimized by the systematic application of a simple collection protocol. Pleural fluid should be collected avoiding inclusion of air or other additives with the sample – particularly lidocaine – and analyzed in less than one hour using a blood gas analyzer. Pleural fluid glucose is an alternative to pH and its measurements are less vulnerable to changes in collection method."

Pleural Effusion

The American College of Chest Physicians offers the tutorial: Evaluation of the Patient with a Pleural Effusion, by Steven A. Sahn, MD, FCCP.*

The objectives of this article are to present information for understanding the diagnostic value of pleural analysis, and to appreciate the value of pleural pH in narrowing the differential diagnosis of the exudate.

Dr Sahn explains: Pleural effusions are a common occurrence in medicine, and there are about 1.5 million incidences each year in the US. Thoracentesis, the procedure to remove fluid from the space between the lining of the outside of the lungs (pleura) and the wall of the chest, is a simple diagnostic procedure that can be performed in the office, at the bedside, in the ICU, or in a dedicated procedure suite. Pleural fluid analysis by itself may result in only a small percentage of diagnoses with a high clinical likelihood that provides a strong argument for generating a prethoracentesis diagnosis. The author argues that if the clinician obtains a thorough history, performs a careful physical examination, orders appropriate blood tests, and interprets the chest images thoughtfully prior to thoracentesis, the likelihood of determining a likely clinical diagnosis is greatly enhanced. He presents a discussion of discriminating information from the pleural fluid analysis and addresses salient features of the history, physical examination, and radiographic imaging that should lead to a logical prethoracentesis differential diagnosis.

Background
Patients presenting with a pleural effusion may be symptomatic or asymptomatic. Diagnoses in which patients typically do not present with symptoms are: BAPE, hypoalbuminemia, nephrotic syndrome, peritoneal dialysis, rheumatoid effusion, trapped lung, urinothorax, and yellow tail syndrome. Half the patients with rheumatoid pleural effusion are asymptomatic, and 60 to 70% of patients with benign asbestos pleural effusion have no symptoms. Symptomatic conditions are: bacterial pneumonia, carcinomatous pleural effusion, congestive heart failure, lupus, malignant mesothelioma, PCSIS, and pulmonary embolism.

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* This article is based on information from: Evaluation of the Patient with a Pleural Effusion, by Steven A. Sahn, MD, FCCP, Professor of Medicine and Director, Division of Pulmonary, Critical Care Allergy and Sleep Medicine, Medical University of South Carolina, Charleston, SC. The article appears in Disorders of the Pleura, Pleural Effusions, CME, PCCSU Volume 22. The PCCSU series is published by the American College of Chest Physicians, copyright ACCP. Permission to reprint information granted by ACCP.

Patients exhibiting the foregoing almost always have symptoms in association with their pleural effusions.

Patients with pleural effusion most commonly have the symptoms, dyspnea and chest pain. Patients with a small pleural effusion and normal lungs may have no noticeable symptoms. The author notes, "In contrast, patients may present with a massive pleural effusion associated with contralateral mediastinal shift, leading to dyspnea at rest." Chest pain is the main symptom of pleural inflammation and is typically accompanied by a pleural effusion. The level of pain varies with the intensity of the inflammation. Patients have described pleuritic chest pain as "stabbing," "shooting," or having a "stitch in the side." The pain is exacerbated by deep inspiration, cough, or sneezing. Pleuritic chest pain may be focused over the inflammation or may be referred. In the case of costal pleural inflammation, the pain tends to be localized directly over the site of pleural involvement and the area will be tender if pushed, and the skin will be hypersensitive. When the lateral, anterior, and portions of the posterior diaphragm are inflamed, the pain is felt over the lower thorax, back, and abdomen. On the other hand, inflammation of the central portion of the diaphragmatic pleura doesn't result in local pain; instead pain is referred to the ipsilateral posterior neck, shoulder, and trapezius muscle. The author notes, "Central diaphragmatic pleural inflammation causes referred pain because the sensory fibers of the phrenic nerve enter the spinal cord at the C4 level, which is the usual entry point of sensation from the shoulder."

There are fewer drugs associated with pleural disease than those that are thought to cause parenchrymal lung disease, but drugs should be considered as possible causes of pleural effusion or fibrosis, particularly if the etiology of the effusion is hard to trace.

Some of the drugs that have been associated with a pleural effusion include bromocriptine, cyclophosphamide, dantrolene, isotretinoin, mesalamine, methotrexate, mitomycin, nitrofurantoin, practolol, procarbazine, and valproic acid.

Examination for a Pleural Effusion
Because pleural fluid separates the lung from the chest wall, it interferes with sound transmission from the lung to the stethoscope. Observable signs of a pleural effusion depend on the volume of pleural fluid and the degree of lung compression. The status of the underlying lung and the patency of the bronchial tree will effect the physical findings. The examination

results will be seen as normal when the fluid volume is below 250 mL. If pleural fluid volume is at 500 mL, typical physical findings will include dullness to percussion, decreased fremitus, and vesicular breath sounds of decreased intensity compared with the contralateral side. Pleural fluid volume of more than 1,000 mL results in egophony (E to A) at the upper level of the effusion.

Standard chest radiography can provide further diagnostic insight before thoracentesis. If the chest radiograph shows a solitary pleural effusion or is associated with another abnormality, diverse differential diagnoses should be considered. With a single pleural effusion, infectious causes like a tuberculous pleural effusion, viral pleurisy, or a limited bacterial pneumonia should be considered. Lupus pleuritis and rheumatoid pleurisy are more likely to result in an observation of an isolated pleural effusion. Metastatic cancer to the pleura, non-Hodgkin lymphoma, and leukemia can also present as a solitary pleural effusion. A massive effusion, with opacification of the entire hemithorax, and contralateral mediastinal shift, signals a diagnosis of non-lung carcinoma. Without the contralateral mediastinal shift, lung cancer of the ipsilateral main stem bronchus and malignant mesothelioma are most likely. Solitary effusions are connected with with diseases below the diaphragm, including hepatic hydrothorax, nephrotic syndrome, urinothorax, peritoneal dialysis and exudates from acute and chronic pancreatitis, chylous ascites, and abscesses or infarcts of the liver and spleen.

Bilateral effusions are connected with congestive heart failure, nephrotic syndrome, hypoalbuminemia, and constrictive pericarditis. The cardiac silhouette is enlarged in congestive heart failure but may be of normal size with nephrotic syndrome and constrictive pericarditis. Bilateral pleural effusions with a normal heart size are related to malignancy from a non-lung primary but can also occur with lupus pleuritis, rheumatoid pleurisy, hepatic hydrothorax, and hypoalbuminemia.

A chest radiograph with interstitial infiltrates can raise the differential diagnosis of congestive heart failure, rheumatoid disease, asbestos pleuropulmonary disease, lymphangitic carcinomatosis, lymphangioleiomyomatosis, viral and mycoplasma pneumonia, sarcoidosis, and *Pneumocystis carinii* pneumonia. Pleural effusions associated with multiple pulmonary nodules most commonly suggest cancer, Wegener granulomatosis, rheumatoid disease, septic pulmonary emboli, sarcoidosis, or tularemia.

Almost all patients with a newly discovered pleural effusion should undergo thoracentesis to confirm a diagnosis, except those who have typical congestive heart failure with a clinical diagnosis that doesn't raise suspicion for an alternative diagnosis, or a very small pleural effusion. Observation is warranted if the clinical situation worsens or is atypical, and then a thoracentesis should be performed without delay. In a prospective study of 129 patients with pleural effusion published 20 years ago, thoracentesis provided a definitive diagnosis in only 18% and a presumptive diagnosis in 55%. In the balance of 27% of patients, the pleural fluid findings weren't helpful because the values were compatible with two or more clinical possibilities. In a number of these patients, though, the findings excluded possible diagnoses, such as empyema. Since that study, healthcare professionals have become better educated about pleural fluid analysis, so this should enable a definitive or confident presumptive diagnosis in close to 95% of patients.

Diseases that can be definitely established by pleural fluid analysis are: acute pancratitis, biliopleural fistula, cholesterol effusion, chylothorax, complicated parapneumonic effusion, duropleural fistula, empyema, esophageal rupture, EVM of CVC, fungal effusion, glycinothorax, hemothorax, lupus pleuritis, malignancy, pancreaticopleural fistula, perintoneal dialysis, rheumatoid pleurisy, tuberculous effusion and urinothorax. The first diagnostic step is to examine the pleural fluid as it is aspirated from the pleural space, noting the color, character, and odor of the fluid. Clear, straw-colored fluid suggests a transudate, but a paucicellular exudate cannot be excluded. Sanguinous fluid is not helpful diagnostically when it is grossly bloody; the differential diagnosis can then be narrowed to malignancy, BAPE, postcardiac injury syndrome, or pulmonary infarction in the absence of trauma. A hemothorax is usually due to chest trauma but may also occur from invasive procedures, anticoagulation with a hemorrhagic pulmonary infarction, and catamenial hemothorax.

Aspiration of a white or milky fluid is from the pleural space signals a chylothorax or a cholesterol effusion, and an empyema may simulate this appearance. Centrifugation of the fluid will separate a lipid effusion from an empyema. A yellow-green fluid suggests rheumatoid pleurisy, and green pleural fluid signals a biliopleural fistula. If a central venous catheter has migrated into the mediastinum, the pleural fluid will be similar to the infusate.

If pus is aspirated, an empyema is established. Pus with a putrid odor confirms an anaerobic infection. If the pleural fluid contains debris, rheumatoid pleurisy with exfoliation of rheumatoid nodules from the visceral pleural surface into the pleural space is probably the cause. If pleural fluid smells like ammonia, the diagnosis is urinothorax. The next deductive step is to determine if the effusion is an exudate or transudate. Transudative effusions have normal pleurae and limited diagnostic possibilities. Rare causes of transudates develop from an extravascular origin and include urinothorax, duropleural fistula, peritoneal dialysis, and extravascular migration of a central venous catheter with saline infusion. Exudative effusions have a more extensive differential diagnosis, since these effusions are caused by inflammation, infection, malignancy, and lymphatic abnormalities.

It is important to distinguish between a transudate and an exudate. The detection of an exudative pleural effusion warrants additional diagnostic testing to determine the underlying cause. On the other hand, the patient's clinical presentation is usually sufficient to determine the cause of a transudative effusion without further testing.

An exudative effusion is defined by the presence of a high concentration of large, molecular weight proteins. The two tests that have the highest specificity and sensitivity are the pleural fluid-to-serum total protein ratio and the pleural fluid LDH (lactate dehydrogenase) compared with the upper limits of the normal serum LDH. The total protein ratio can be used because the pleural fluid and serum values are related. But since there is no correlation between pleural fluid and serum LDH, the previously mentioned ratio should be used instead. If the pleural fluid-to-serum total protein ratio is >0.50 or the pleural fluid LDH is >0.67 of the upper limit of normal serum LDH, the fluid is most likely an exudate. If both total protein and LDH ratios

are ≤0.50 and 0.67, the fluid is most likely a transudate. However, the closer the values are to the cut-point, the fluid is likely to be either a transudate or an exudate, while the further the value, the more likely the fluid is to be a transudate or an exudate.

Treatment of the patient may affect pleural fluid values; for example, in patients with congestive heart failure treated with diuretics, either the protein or LDH ratio may be increased from the transudative range prior to diuresis to the exudative range following diuresis. The test with the highest sensitivity and specificity for separating transudates and exudates was a pleural fluid LDH, compared with the upper limit of the normal serum LDH ratio of 0.82 (AUC = 0.89); this higher ratio decreases the incidence of false exudates.

The absolute concentrations of total protein and LDH may be of some diagnostic value. A tuberculous pleural effusion rarely has a total protein concentration less than 4.0 g/dL, while total protein concentrations in malignancy and parapneumonic effusions have a wide range. A total protein concentration greater than or equal to 7.0 g/dL suggests Waldenström macroglobulinemia, multiple myeloma, or a cholesterol effusion. A pleural fluid LDH concentration greater than three times the upper limit of normal for the serum LDH is usually seen only in complicated parapneumonic effusions or empyema, rheumatoid pleurisy, or pleural paragonimiasis. The total nucleated cell count is rarely diagnostic but may provide useful information. Most exudates have >1,000 nucleated cells/µL, while transudates have a few hundred cells per microliter. Pleural fluid nucleated cell counts >10,000/µL are commonly seen with parapneumonic effusions, acute pancreatitis, subdiaphragmatic abscesses, liver, hepatic and splenic abscesses, and splenic infarction. This cell count can also occur with pulmonary infarction, PCIS, and lupus pleuritis. When the nucleated cell count is >50,000/µL, the differential is limited to a complicated parapneumonic effusion and empyema and rarely with acute pancreatitis and pulmonary infarction. Chronic exudates typically have nucleated cell counts <5,000/µL. When pus is aspirated from the pleural space, the nucleated cell count may be as low as a few hundred cells.

The predominant cell population is determined by the type of pleural injury and the timing of thoracentesis in relation to the pleural injury. The acute response to any pleural injury is the attraction of neutrophils to the pleural space, initiated by the chemotaxin interleukin-8. Within three days following the cessation of acute pleural injury, mononuclear cells enter the pleural space from the peripheral blood and become the predominant cells. This macrophage predominance is then replaced by lymphocytes in effusions that persist for more than 2 weeks. As such, a neutrophil-predominant exudate is the rule when the patient presents shortly after the onset of symptoms, *ie*, acute bacterial pneumonia, acute pulmonary embolism with infarction, and acute pancreatitis. In contrast, with the insidious onset of disease, as with malignancy and tuberculosis, a lymphocyte-predominant exudate is found. Transudative effusions are never neutrophil-predominant, and when the neutrophil percentage is 10 to 15%, a second diagnosis is likely. Transudative effusions are mononuclear-cell-predominant.

When the lymphocyte population is >80% of the total nucleated cells, the differential diagnosis of the exudate is narrowed to acute lung rejection, chylothorax, lymphoma, postcoronary artery bypass, rheumatoid pleurisy, sarcoidosis, tuberculous effusion or yellow nail syndrome. In contrast to lymphoma, only

about 60% of patients with metastatic carcinoma to the pleura have a majority of lymphocytes, usually 50 to 75% of the total nucleated cell count. A lymphocyte-predominant exudate is the most appropriate indication for percutaneous pleural biopsy, which is the most sensitive diagnostic test for a tuberculous pleural effusion, with the exception of thoracoscopy.

Pleural fluid eosinophilia is defined as a pleural fluid eosinophil count >10% of the total nucleated cell count.

Causes of PFE are BAPE, carcinoma, Churg-Strauss syndrome, drug-induced, fungal disease, hemothorax, lymphoma, parasitic disease, pneumothorax, pulmonary embolism, sarcoid or tuberculous effusion. The most common causes are pneumothorax and hemothorax. Eosinophilic pleuritis is a common, early finding in patients requiring thoractomy or thoracoscopy for treatment of spontaneous pneumothorax. Eosinophils don't appear in the pleural space for 1 to 2 weeks following hemothorax. PFE is also associated with peripheral blood eosinophilia following trauma that does not clear until the pleural fluid resolves. About 30% of patients with BAPE have PFE, involving 50% of the nucleated cells. Recent studies show that the prevalence of malignancy is similar in both eosinophilic and noneosinophilic pleural effusions.

Pleural fluid macrophages, originating from the blood monocyte, are of no diagnostic value. Although common in transudative effusions and some exudates, mesothelial cells are rarely found in tuberculous pleural effusion. The scarcity of mesothelial cells is also the typical finding in other inflammatory processes, such as empyema, chemical pleurodesis, rheumatoid pleuritis, and chronic malignant effusions.

A large number of plasma cells in pleural fluid suggests pleural involvement with multiple myeloma. When basophils represent >10% of the nucleated cells, leukemic involvement of the pleura is likely. A limited number of diagnoses are associated with pleural fluid acidosis, which is defined as a pleural fluid pH <7.30 measured with a blood gas analyzer. The diseases revealed by this analysis are complicated parappneumonic effusion, empyema, esophageal rupture, rheumatoid pleurisy, malignant effusion, lupus pleuritis, tuberculous effusion, hemothorax, pancreaticopleural fistula, pulmonary infarction, and diaphragmatic hernia with bowel infarction.

The presence of a low pleural fluid pH is diagnostically helpful and has prognostic implications. In the only study of acid-base characteristics of normal human pleural fluid, the pleural fluid pH was measured at 7.64, 0.23 pH units greater than the simultaneously measured blood pH. The authors of this study and others have measured an alkaline pH of about 7.60 in normal animals. It seems a bicarbonate gradient between pleural fluid and blood explains the alkaline pH of normal pleural fluid. Human transudative effusions have a pleural fluid pH ranging from 7.45 to 7.55. Most exudative effusions have pH values that range from 7.45 to 7.30, while a small number are associated with pleural fluid acidosis (pH <7.30).

Pleural fluid pH provides prognostic information and helps guide therapy for parapneumonic and malignant effusions. A metaanalysis found that the pleural fluid pH was lower in patients who had a complicated course and required pleural space drainage. The main studies recommend various cut-points for a complicated effusion that from 7.10 to 7.30. While no single

pH value can be used as a definitive cut-point for classifying patients as having complicated or uncomplicated parapneumonic effusions, the pleural fluid pH serves as information that should be combined with the clinicians' judgment in determining the need for pleural space drainage.

A low pleural fluid pH (<7.30) is seen in approximately a third of patients presenting with a malignant pleural effusion. A low pleural fluid pH under these circumstances suggests that the patients will have positive cytologic findings on initial testing, a shorter survival time, and a poorer response to chemical pleurodesis. Finding a low pH is not an absolute contraindication to pleurodesis but should be considered in the decision when contemplating treatment.

In the normal physiologic state, pleural fluid and blood glucose concentrations are equivalent. The same diseases associated with low pleural fluid pH also have a low pleural fluid glucose concentration, which is defined as <60 mg/dL or a pleural fluid/serum glucose ratio of <0.5. The only diagnoses associated with a glucose of 0 mg/dL are chronic rheumatoid pleurisy and empyema.

An increased pleural fluid amylase level, defined as either a value greater than the upper limits of normal serum or a pleural fluid/serum amylase ratio >1.0, is found with pancreatic disease, esophageal rupture, and malignancy. Acute pancreatitis and a pancreaticopleural fistula can cause an amylase-rich pleural effusion. An increased pleural fluid amylase concentration occurs in 10 to 14% of patients with a malignant pleural effusion. The amylase in these malignant effusions is virtually all salivary-type. Adenocarcinoma of the lung is the most common malignancy associated with a salivary amylase-rich pleural effusion followed by adenocarcinoma of the ovary. Esophageal rupture is also characterized by the presence of pleural fluid salivary isoamylase.

There are two types of lipid pleural effusions, chylothorax and a cholesterol effusion, also called a chyliform effusion or pseudochylothorax. A chylothorax represents leakage of chyle into the pleural space from the thoracic duct or one of its major tributaries. The most common cause of a chylothorax is lymphoma, typically non-Hodgkin lymphoma. A cholesterol effusion is a chronic form of lung entrapment that is most commonly associated with rheumatoid pleurisy and tuberculosis. The diagnosis of chylothorax is likely when the pleural fluid triglyceride concentration is >110 mg/dL and unlikely if the triglyceride concentration is under 50 mg/dL.

Pleural fluid cytology has a widely variable diagnostic yield, ranging from 40 to 90% of patients with a known malignancy. Flow cytometry can be helpful in the diagnosis of lymphoma of the pleura and can specifically define lymphocyte surface markers. As such, it can define clonality of a population of lymphocytes to determine whether the cells are from T- or B-cell lineage. Flow cytometery is most helpful in patients with a lymphocyte-predominant pleural effusion when lymphoma is in the differential diagnosis.

Summary

The authors state, "For pleural fluid analysis to be most valuable, the clinician must have a solid prethoracentesis diagnosis based on a patient's history, physical examination, laboratory findings, and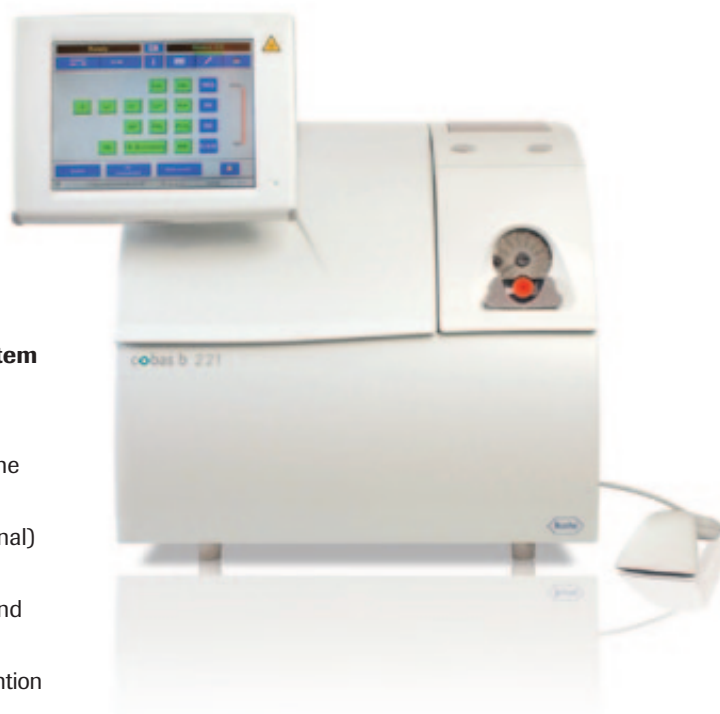 radiographic imaging. With a presumptive clinical diagnosis in concert with a good working knowledge of pleural fluid analysis, a definitive or confident clinical diagnosis can be determined in 95% of patients. Without this approach, the clinician may be left with an unacceptable number of problematic or undiagnosed pleural effusions."

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