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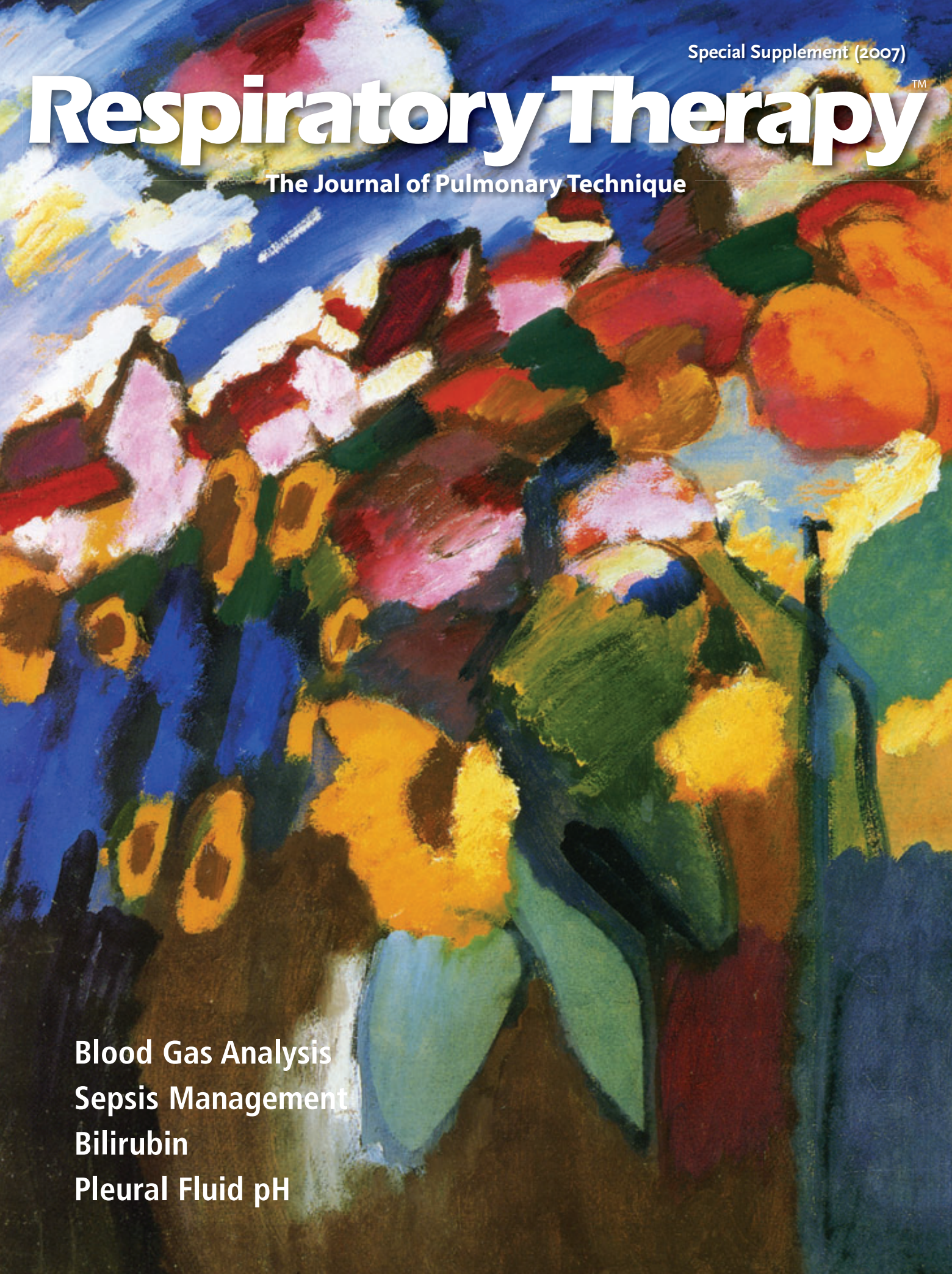
The Journal of Pulmonary Technique



Blood Gas Analysis
Sepsis Management
Bilirubin
Pleural Fluid pH

From Data to Actionable Information

Making a Difference in the Intensive Care Unit

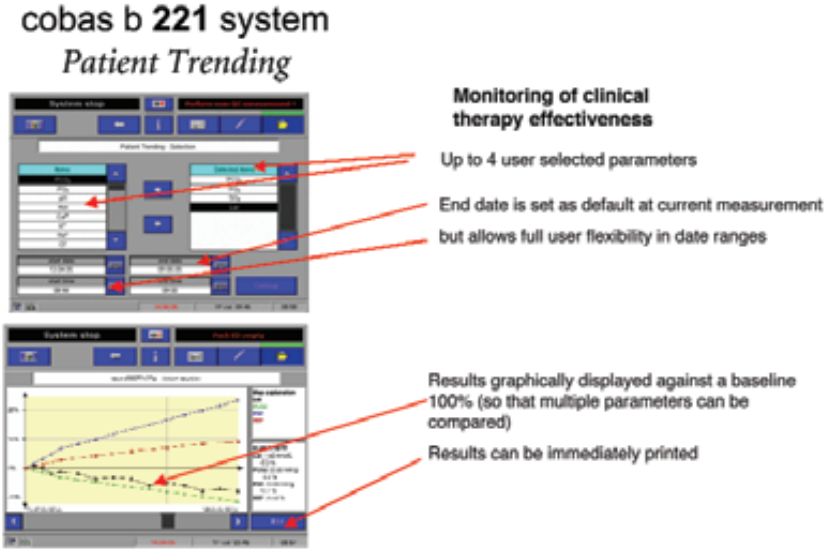
Thomas Klein, MD, MSc

A single measurement is like a snapshot: one moment frozen in time. However, in medical care the patient's condition is constantly changing, and only the tracking of individual measurements can produce the right picture—or rather, the right movie. The data of most patients in an ICU exhibit identifiable trends, and these are useful in making diagnoses and managing drugs, ventilation and other therapeutic factors. Putting together the individual data chunks can also help in differentiating between acute and chronic patient conditions.

At the core of this process is a data management and IT connectivity software solution which enables you to transform the data into meaningful information and which is tailored to the needs of an ICU. Automated acid-base trending, for example, results in a more precise diagnosis and therapy monitoring. Accurate, graphical mapping (a feature of the cobas b 221 from Roche) efficiently assists the healthcare professional in rapidly identifying metabolic and respiratory acid-base disturbances without needing a calculator. It also helps in monitoring the effectiveness of therapy.

The onboard patient-trending feature of the new cobas b 221 analyzer makes possible real-time and/or historical trending of any four test parameters simultaneously (PO2, PCO2, pH, glucose, lactate, BUN, co-oximetry, sodium, potassium, chloride and ionized calcium). Onboard patient trending helps healthcare providers to follow the progress of their patient's condition during the course of treatment. Respiratory therapists can trend any four blood gas and co-oximetry parameters.

In the ICU, a single set of data has very little predictive power unless it is set in context with other data. Only then can actionable information be derived. One of the burning issues in the ICU with regard to following a patient's trend and reacting immediately is tight glycemic control.



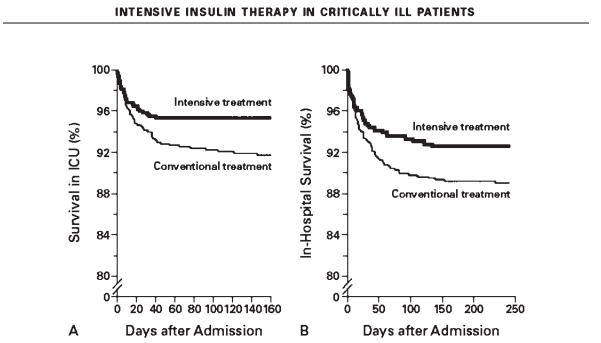


Figure 1. Kaplan–Meier Curves Showing Cumulative Survival of Patients Who Received Intensive Insulin Treatment or Conventional Treatment in the Intensive Care Unit (ICU).
Patients discharged alive from the ICU (Panel A) and from the hospital (Panel B) were considered to have survived. In both cases, the differences between the treatment groups were significant (survival in ICU, nominal P= 0.005 and adjusted P<0.04; in-hospital survival, nominal P=0.01). P values were determined with the use of the Mantel–Cox log-rank test.

In 2001 Greet Van den Berghe published a ground-breaking study, the first to clearly demonstrate the benefits of tight glycemic control in the ICU. This randomized controlled trial included 1548 patients in a mainly surgical intensive care unit receiving mechanical ventilation. The study compared mortality and morbidity in relation to intensive insulin therapy (IIT), aiming at a tight glucose control (TGC) (glucose level 80 - 110 mg/dl) with conventional treatment (insulin infusion if glucose > 215 mg/dl; maintenance glucose 180 - 200 mg/dl). Glucose was determined using a blood gas analyzer at 1- to 4-hour intervals.

The results were impressive: intensive insulin treatment resulted in a 42% reduction in mortality compared with conventional insulin treatment. The greatest reduction documented related to deaths due to multiple organ failure with a septic focus. Incidence of morbidity was unrelated to a history of diabetes or hyperglycemia. Intensive insulin treatment also significantly reduced the need for prolonged ventilatory support, renal replacement therapy, and prolonged use of antibiotics (lower rate of bacteremia). It also reduced the length of stay in the intensive care unit.

This study highlighted the value of TGC and hence of glucose determination on the spot for IIT. Rapidly available glucose results are a prerequisite for TGC, and they enable a more efficient use of intensive care resources. With a Roche blood gas analyzer, intensive care unit caregivers have convenient access to a self-contained glycemic control platform for measuring and tracking glucose results.

Note, Figure 1: The figure in this article is adapted from Intensive Insulin Therapy In Critically Ill Patients, by Greet Van Den Berghe, MD, PhD; Pieter Wouters, MSc; Frank Weekers, MD; Charles Verwaest, MD; Frans Bruyninckx, MD; Miet Schetz, MD, PhD; Dirk Vlasselaers, M; Patrick Ferdinande, MD, PhD; Peter Lauwers, MD; Roger Bouillon, MD, PhD, The New England Journal of Medicine, Volume 345 November 8, 2001 Number 19, downloaded from www.nejm.org at Hoffman LaRoche on March 23, 2006, © 2001 Massachusetts Medical Society.

The Surviving Sepsis Campaign

Les Plesko

The Surviving Sepsis Campaign (SSC), an initiative of the European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine, has been developed to improve the management, diagnosis, and treatment of sepsis. The SSC aims to reduce mortality from sepsis via a multi-point strategy, primarily:

- Building awareness of sepsis
- Improving diagnosis
- Increasing the use of appropriate treatment
- Educating healthcare professionals
- Improving post-ICU care
- Developing guidelines of care
- Facilitating data collection for the purposes of audit and feedback

The website survivingsepsis.org provides information and resources for patients, healthcare professionals, and the general public.

Severe Sepsis Bundles

The SSC site has arranged its information for caregivers in so-called "bundles," whereby specific information can be searched quickly and handily. The Severe Sepsis Bundles are a distillation of the concepts and recommendations found in the practice guidelines. They are designed to allow teams to follow the timing, sequence, and goals of the individual elements of care, in order to achieve the goal of a 25% reduction in mortality from severe sepsis. Individual hospitals can use the bundles to create customized protocols and pathways specific to their institutions. However, the SSC notes that all of the elements in the bundles should be incorporated in those protocols. The addition of other strategies not found in the bundles is not recommended. The bundle forms the basis for the measurements that improvement teams can conduct to follow their progress.

To achieve the greatest results, hospitals are urged to incorporate two Severe Sepsis Bundles. Each bundle articulates requirements for specific timeframes. The Sepsis Resuscitation Bundle is for tasks that should begin immediately, but must be done within 6 hours for patients with severe sepsis or septic shock. The Sepsis Management Bundle is for tasks that should begin immediately, but must be done within 24 hours for patients with severe sepsis or septic shock.

The Concept

A "bundle" is defined as a group of interventions related to a disease process that, when implemented together, result in better outcomes than when implemented individually. The science behind the elements of the bundle is well-established as generally accepted practice. Bundle components can be easily measured as completed or not completed. As such, the overall bundle, all of the elements taken together, can also be measured as completed or not completed.

The SSC recommends that in general, teams should take the bundles and build protocols for use at their own institutions. The protocols should very closely mirror the bundles, but allow flexibility for logistical and other needs specific to the local hospital. It is important to accurately mirror the content of the bundles in any given approach because the measures used to assess progress are designed around the specifications contained in the bundle elements.

The severe sepsis bundles form the core of the implementation phase of the Surviving Sepsis Campaign. Bundle science is the result of an integration of medical science and improvement work. Several years ago, as a part of an Institute for Healthcare Improvement (IHI) initiative on care in the ICU, participants considered a small set of evidence-based interventions for patients on mechanical ventilation. These interventions were: DVT prophylaxis, peptic ulcer disease prophylaxis, elevation of the head of the bed, and sedation vacation. This set of four interventions is known as the ventilator bundle. Each of the teams measured the degree of compliance with the bundle, giving credit for medical contraindications. For each patient, a 1 or 0 was recorded, indicating whether or not all four elements of the bundle were implemented. A marked reduction in ventilator-associated pneumonia was noted when teams consistently implemented the bundle.

The use of the bundle prompted various disciplines in the ICU to reorganize their work. The results for ventilator-associated pneumonia were interesting and unexpected because for only two of the four elements in the bundle was there any scientific evidence that the element itself would reduce ventilator-associated pneumonia. This new method of clinical improvement, a bundle process that combines the best of medical science and improvement science, is developed in the following way:

1. Identify a set of four to six evidence-based interventions that apply to a cohort of patients with a common disease or a common location.
2. Develop the will in the providers to deliver the interventions every time they are indicated.
3. Measure compliance as "all" or "nothing."

Les Plesko is editor of Respiratory Therapy.

4. Redesign the delivery system to ensure the interventions in the bundle are delivered.
5. Measure related outcomes to ascertain the effects of the changes in the delivery system.

The sepsis bundles were developed in just such a manner, based on the experience of the ventilator bundle. The goal now is to motivate the providers to deliver the sepsis interventions every time they are indicated based on hospital policies. If the bundle elements are reliably performed the desired outcome of reducing sepsis-related deaths by 25% can be achieved.

The Bundle Elements

The sepsis bundles listed below distill the SSC practice guidelines into a manageable format for use at most institutions. They represent specific changes the campaign has identified as essential to the care of severely septic patients. Following the bundles will eliminate the piecemeal or inappropriate application of standards for sepsis care that characterizes most clinical environments today.

The bundles are not ready-made protocols for individual hospitals. Instead, hospitals should use them as a template to create customized protocols and pathways that will work well within their institutions. All of the elements in the bundles must be incorporated into those protocols. If all of the elements of the bundles are not incorporated into a customized protocol, performance on the measures will suffer.

Sepsis Resuscitation Bundle

Evidence-based goals must be completed within 6 hours for patients with severe sepsis, septic shock, and/or lactate > 4 mmol/L (36 mg/dL). For patients with severe sepsis, as many as seven bundle elements must be accomplished within the first 6 hours of presentation. Some items may not be completed if the clinical conditions described in the bundle do not prevail, but clinicians must assess for them. The goal is to perform all indicated tasks 100 percent of the time within the first 6 hours of identification of severe sepsis.

- Bundle Element 1: Measure serum lactate
- Bundle Element 2: Obtain blood cultures prior to antibiotic administration
- Bundle Element 3: Administer broad-spectrum antibiotic within 3 hours of ED admission and within 1 hour of non-ED admission
- Bundle Element 4: In the event of hypotension and/or serum lactate >4 mmol/L:
  a. Deliver an initial minimum of 20 mL/kg of crystalloid or an equivalent
  b. Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) >65 mm Hg
- Bundle Element 5: In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/L:
  a. Achieve a central venous pressure (CVP) of >8 mm Hg
  b. Achieve a central venous oxygen saturation ($ScvO_2$) > 70% or mixed venous oxygen saturation (SvO_2) > 65%

Sepsis Management Bundle

Evidence-based goals must be completed within 24 hours for patients with severe sepsis, septic shock and/or lactate > 4 mmol/L (36 mg/dl). For patients with severe sepsis, as many as four bundle elements must be accomplished within the first 24 hours of presentation. Some items may not be completed if the clinical conditions described in the bundle do not prevail, but clinicians must assess for them. The goal is to perform all indicated tasks 100 percent of the time within the first 24 hours from presentation:

- Bundle Element 1: Administer low-dose steroids for septic shock in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for low-dose steroids based upon the standardized protocol.
- Bundle Element 2: Administer recombinant human activated protein C (rhAPC) in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for rhAPC.
- Bundle Element 3: Maintain glucose control >70, but <150 mg/dL
- Bundle Element 4: Maintain a median inspiratory plateau pressure (IPP) <30 cm H20 for mechanically ventilated patients

Measuring and Documenting the Bundles

Using the SSC performance improvement database will help the team and hospital evaluate improvements necessary to consistently achieve specific bundle elements. Engaging PDSA (Plan, Do, Study, Act) cycles for each bundle element where performance is lower than desired, will assist the team to develop/alter protocols and order sets and put systems into place to correct deviations. The performance improvement database allows users to enter data directly from individual patient charts. In the background, the SSC database aggregates that information across units, institutions, or hospital systems gauging success with the SSC quality indicators. At the end of each month, or any time desired, the data is transformed into bundle compliance graphs. This offers the visual stimulation necessary to motivate the team toward positive change. Posting the graphs presents opportunities for discussions at meetings and in the unit or emergency department so that protocol adjustments, perhaps equipment purchases, or other implementation approaches can be acted upon. Entering data into the database concurrently will reveal in real time if the bundles were achieved or if policy was followed. Retrospective data collection is not ideal because all too often, the care memory can be lost. The campaign recommends that information is entered directly into the database not placed onto a paper tool first and then entered. This duplicative effort yields no benefit.

The Severe Sepsis Quality Indicators should be used in conjunction with the bundles to help improvement teams understand the measures that will be used to evaluate their progress in improving the care of severely septic patients.

The above information is adapted from the Surviving Sepsis Campaign website, © 2001-2007 Society of Critical Care Medicine. The Site is owned and operated by the Society of Critical Care Medicine, the International Sepsis Forum, and the European Society of Critical Care Medicine for the benefit of the goals of the SSC. All services, content, data, information and other materials on or directly accessible from the Site are owned by the three societies. The Site is protected by United States and international copyright and trademark laws. Another valuable resource is the Institute for Healthcare Improvement. The Institute for Healthcare Improvement (IHI) is a not-for-

profit organization leading the improvement of health care throughout the world. IHI was founded in 1991 and is based in Cambridge, Massachusetts. IHI's work is funded primarily through its own fee-based program offerings and services, and also through the support of a group of foundations, companies, and individuals.

Measuring Serum Lactate

The Surviving Sepsis Campaign offers the following guide for the measurement of serum lactate, as provided on its "bundle."

Hyperlactatemia is typically present in patients with severe sepsis or septic shock and may be secondary to anaerobic metabolism due to hypoperfusion. The prognostic value of raised blood lactate levels has been well established in septic shock patients,[1] particularly if the high levels persist.[2,3] In addition, blood lactate levels have been shown to have greater prognostic value than oxygen-derived variables.[4] Obtaining serum lactate is essential to identifying tissue hypoperfusion in patients who are not yet hypotensive but who are at risk for septic shock.

However, the interpretation of blood lactate levels in septic patients is not always straightforward. A number of studies have suggested that elevated lactate levels may result from cellular metabolic failure in sepsis rather than from global hypoperfusion. Elevated lactate levels can also result from decreased clearance by the liver.

Given the high risk for septic shock, all patients with elevated lactate > 4 mmol/L (36 mg/dl) will enter the early goal-directed therapy portion of the Severe Sepsis Resuscitation Bundle, regardless of blood pressure.

This approach is consistent with the trial that established the value of early goal directed therapies.[5]

Serum lactate must be available in your institution with rapid turnaround time (within minutes) to effectively treat severely septic patients. An arterial blood gas analyzer located in the clinical laboratories usually accomplishes this. However, any means of rapid turnaround time will be acceptable. It is essential for hospitals to invest in adequate equipment in order to meet present standards of care for septic patients.

The technique of obtaining serum lactate by venipuncture typically carries a 24- to 48-hour turnaround time and will not be suitable to care for septic patients. This technique also requires special collection conditions, such as without the use of tourniquet, hindering clinical care.

Tips

- If serum lactate is not rapidly available in your institution, invest in equipment to make rapid assessment possible. This should be presented to hospital and laboratory administration as a present standard of care.
- Create a standardized protocol to manage severe sepsis that includes measurement of serum lactate.
- Include a prompt on arterial blood gas requisitions or physician order entry to prompt users to order lactate for suspected severe sepsis.

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5 Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. New England Journal of Medicine. 2001;345:1368–1377.

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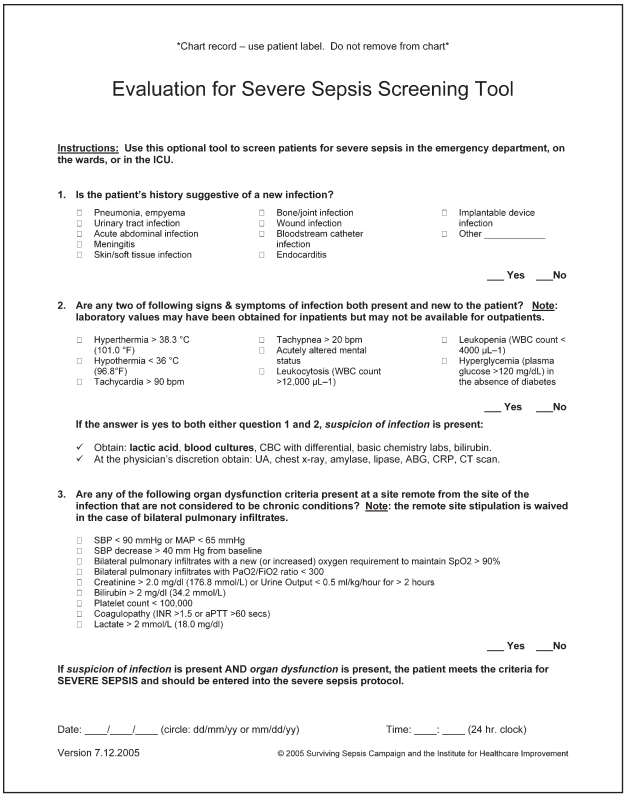

Chart record – use patient label. Do not remove from chart

Evaluation for Severe Sepsis Screening Tool

Instructions: **Use this optional tool to screen patients for severe sepsis in the emergency department, on the wards, or in the ICU.**

1. Is the patient's history suggestive of a new infection?

- ☐ Pneumonia, empyema
- ☐ Urinary tract infection
- ☐ Acute abdominal infection
- ☐ Meningitis
- ☐ Skin/soft tissue infection
- ☐ Bone/joint infection
- ☐ Wound infection
- ☐ Bloodstream catheter infection
- ☐ Endocarditis
- ☐ Implantable device infection
- ☐ Other _____

___ Yes ___No

2. Are any two of following signs & symptoms of infection both present and new to the patient? Note: laboratory values may have been obtained for inpatients but may not be available for outpatients.

- ☐ Hyperthermia > 38.3 °C (101.0 °F)
- ☐ Hypothermia < 36 °C (96.8°F)
- ☐ Tachycardia > 90 bpm
- ☐ Tachypnea > 20 bpm
- ☐ Acutely altered mental status
- ☐ Leukocytosis (WBC count >12,000 µL–1)
- ☐ Leukopenia (WBC count < 4000 µL–1)
- ☐ Hyperglycemia (plasma glucose >120 mg/dL) in the absence of diabetes

___ Yes ___No

If the answer is yes to both either question 1 and 2, *suspicion of infection* is present:

- ✓ Obtain: **lactic acid**, **blood cultures**, CBC with differential, basic chemistry labs, bilirubin.
- ✓ At the physician's discretion obtain: UA, chest x-ray, amylase, lipase, ABG, CRP, CT scan.

3. Are any of the following organ dysfunction criteria present at a site remote from the site of the infection that are not considered to be chronic conditions? Note: the remote site stipulation is waived in the case of bilateral pulmonary infiltrates.

- ☐ SBP < 90 mmHg or MAP < 65 mmHg
- ☐ SBP decrease > 40 mm Hg from baseline
- ☐ Bilateral pulmonary infiltrates with a new (or increased) oxygen requirement to maintain SpO2 > 90%
- ☐ Bilateral pulmonary infiltrates with PaO2/FiO2 ratio < 300
- ☐ Creatinine > 2.0 mg/dl (176.8 mmol/L) or Urine Output < 0.5 ml/kg/hour for > 2 hours
- ☐ Bilirubin > 2 mg/dl (34.2 mmol/L)
- ☐ Platelet count < 100,000
- ☐ Coagulopathy (INR >1.5 or aPTT >60 secs)
- ☐ Lactate > 2 mmol/L (18.0 mg/dl)

___ Yes ___No

If *suspicion of infection* is present AND *organ dysfunction* is present, the patient meets the criteria for SEVERE SEPSIS and should be entered into the severe sepsis protocol.

Date: ____/____/____ (circle: dd/mm/yy or mm/dd/yy) Time: ____: ____ (24 hr. clock)

Version 7.12.2005

Getting Our Priorities Straight: Treatment Of Severe Sepsis In The Emergency Setting

Laszlo Sandor

Is there any doubt that sepsis is a serious problem? Of course not. But unlike many conditions which offer problematic medical solutions, testing for, prevention of, and treatment for sepsis are all well within the bounds of the achievable.

According to an article in Critical Care,[1] published on BioMed Central, "Despite continuous advances in technologic and pharmacologic management, the mortality rate from septic shock remains high. Care of patients with sepsis includes measures to support the circulatory system and treat the underlying infection. There is a substantial body of knowledge indicating that fluid resuscitation, vasopressors, and antibiotics accomplish these goals."

The sepsis story begins, more often than not, in the emergency room, which has become the first line of care and even primary medical resource for so many Americans. According to the study, "National estimates of severe sepsis in US emergency departments,"[1] the ER often serves "as the first site for the recognition and treatment of patients with suspected severe sepsis." Authors Wang et al noted that out of 331.5 million emergency room visits, about 2.3 million were for sepsis. Severe sepsis patients account for 500,000 emergency visits each year, and patients spent about five hours per visit. "Nationally, few other disease groups have this collective size, morbidity, and mortality."

According to a recent study by Ngyuen et al, "patients suffering from severe sepsis or septic shock have a mortality rate of 20–54%. Among the 751,000 annual cases of severe sepsis in the United States, approximately 458,200 cases are first encountered in the emergency department."[3]

All the more reason that early identification and treatment for sepsis should be deemed a bulwark against the condition, insofar as identification and treatment can be readily accomplished in the ER or emergency department setting, and can improve long-term outcomes.

In the Wang study, over a four-year period, one of 33 patients presenting with infection was suspect for severe sepsis, with symptoms of fever, respiratory infection, or genitor-urinary infection. Patients also presented with hypotension and/or cardiovascular dysfunction. These conditions were severe enough that more than half the study group, drawn from a non-metropolitan, middle class area, arrived at the emergency room by ambulance.

Laszlo Sandor is a contributing editor to Respiratory Therapy.

Of course it makes sense that the emergency setting is where patients first show up with signs of sepsis, given its community-acquired nature. Yet, according to Wang and co-authors, "sepsis care has not received the public health attention given to patients suffering from other conditions. Efforts to improve the care of severe sepsis nationally offer hope if implemented in ways analogous to these other illnesses, with broader strategies to maximize public access to appropriate care." Given the crisis of emergency room overcrowding, the authors suggest that regional sepsis centers could offer the services currently offered by specialized trauma and stroke centers. But whatever the approach, guidelines need to be modified to accommodate early identification and treatment.

Bundle Up

One solution to the sepsis crisis is the implementation of so-called "sepsis bundles" in ER departments. The idea of bundles as treatment modalities has been refined by the "Surviving Sepsis Campaign," a national effort to implement quality care through a unique method of grouping treatment strategies.[2] A recent hallmark study by Nguyen et al examined how bundling could be effective employed as part of the emergency protocol. In the study, "Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality,"[3] researchers looked at how implementing a severe sepsis bundle provided "a quality indicator set with feedback to modify physician behavior related to the early management of severe sepsis and septic shock."

Ngyuen et al studied 330 emergency department patients admitted for severe sepsis or septic shock. The sepsis bundle applied the following treatment parameters: 1) initiate central venous pressure monitoring within two hours; 2) provide antibiotics within four hours; 3) initiate immediate therapy and complete therapy by six hours; 4) administer corticosteroids if appropriate; and 5) monitor for lactate clearance.

Quick Results

Using the sepsis bundle achieved quick results in many patients. According to Nguyen et al, "Bundle compliance increased from zero to 51.2% at the end of the study period. During the emergency department stay, patients with the bundle completed received more CVP/S_{CVO2} monitoring and more antibiotics compared with patients with the bundle not completed. Completion of early goal-directed therapy was significantly associated with decreased mortality. In-hospital mortality was less in patients with the bundle completed compared with patients with the bundle not completed… Patients with the bundle completed had higher percentage compliance of all

Continued on page 9…

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- Easily distinguish between compensatory responses and mixed acid-base disturbances
- Differentiate between acute and chronic patient conditions in complex environments such as the ED or ICU

Automated acid-base mapping on the cobas b 221 system creates a graphical representation of patient results.

Roche Diagnostics

Critical Care for Severe Sepsis

Assessing sepsis, and the right treatment, is not necessarily an easy task. In the excerpt below, published online by BioMed Central, several physicians hashed out possible treatment scenarios for a number of complex cases. The excerpt is only a partial summary for the complete summary, please type the title of the article into the BioMed Central search box.

Care of patients with sepsis includes measures to support the circulatory system and treat the underlying infection. There is a substantial body of knowledge indicating that fluid resuscitation, vasopressors, and antibiotics accomplish these goals. Recent clinical trials have provided new information on the addition of individual adjuvant therapies. Consensus on how current therapies should be prescribed is lacking. We present the reasoning and preferences of a group of intensivists who met to discuss the management of an actual case. The focus is on management, with emphasis on the criteria by which treatment decisions are made. It is clear from the discussion that there are areas where there is agreement and areas where opinions diverge. This presentation is intended to show how experienced intensivists apply clinical science to their practice of critical care medicine.[1]

One case presented a 56-year-old male with nausea, shortness of breath, and diaphoresis. Over the previous 2 days he had noted a productive cough, associated with midline chest pain, shaking chills, and diarrhea. He had no abdominal pain and no swelling or pain in the legs. Over the past 3 months he had lost 30 lb (approximately 13.6 kg) in weight and he sought medical attention for left shoulder pain. A bone scan was reportedly negative. Physical examination revealed normal temperature, tachycardia. His respirations were labored, at 26 breaths/min, and oxygen saturation was 89%. He was put on a nonrebreather mask, and his oxygen saturation increased to 98%. Breath sounds were diminished in the right upper lung zones.

The first physician taking part in the roundtable noted that the man's condition sounded like community-acquired pneumonia (CAP), possibly with an atypical pathogen. Perhaps the diarrhea was a red herring. Weight loss and left shoulder pain in a 53-year-old former smoker raises concern for lung cancer with possible postobstructive pneumonia. "This patient also has evidence of severe sepsis… He has respiratory failure… He is probably hemoconcentrated, and clinically we would expect him to be hypovolemic from diarrhea, high insensible losses, and poor oral intake.

The second doctor offered a different diagnosis: "I might disagree with you that this patient has severe sepsis. What if, after 2 or 3 l saline, his blood pressure, heart rate, and creatinine normalize? I think this illustrates one of the greatest triage challenges in this area, and that is differentiating infection with sepsis from another very common scenario—infection with dehydration and hypovolemia. I think the most important point is not to confuse sepsis with hypovolemia from any cause, including hemorrhage.

Other doctors in the roundtable added: The first steps in the care of patients like this should be very systematic. Once the tachycardia was assessed and assuming the chest radiograph confirms pneumonia, I would initiate prompt antibiotic therapy based on the most likely type(s) of infection; ensure adequate hemodynamic and respiratory support; try to identify the source of infection; identify and ascertain the extent of his organ dysfunction; and, based on that, develop an overall treatment plan… We need to treat this suspected infection. Although a chest radiograph is not initially available, there is a strong clinical suspicion for pneumonia, as a source of major infection, and empiric antibiotic coverage should be started.

The patient was given 2 l of normal saline and a chest radiograph was obtained. He was given a total of 18 mg adenosine with no response; and then 2.5 mg intravenous verapamil in three doses, with a decrease in heart rate to 110 beats/min. Atrial fibrillation was diagnosed. His blood pressure fell with these interventions. The chest radiograph showed a dense opacity in the right-upper lobe with patchy opacities in the right-lower lobe, the lingula, and left-upper lobe. There were no clear air bronchograms or lateral shift to suggest lobar collapse.

The doctors' diagnoses were as follows: There is no clear evidence of an endobronchial lesion or airway obstruction. This, along with the history of a recent negative bone scan, makes cancer less likely. Active tuberculosis is possible, and sputum should be sent for appropriate studies. With the complaint of midsternal pleuritic chest pain, there is concern of pericardial involvement. However, there are no suggestive changes on the ECG, and the heart size looks normal, somewhat narrow, and probably under-filled, which is consistent with hypovolemia… Do we need to consider any other diagnostic tests for CAP in a patient with severe sepsis?... The purist's goal is to try to establish a bacteriologic diagnosis, but the realization is that one must initially treat broadly because no single test has the sensitivity and specificity to allow one to treat narrowly… The initial approach should be to volume replete him aggressively and see whether the hemodynamics improve, and then address any persistent tachycardia only after he is volume replete. In this case, rate controlling agents may not be the first line of

therapy, given a strong suspicion for sepsis. If the need arises then support him with invasive or noninvasive ventilation and get him through this… If you think the patient is more at risk for death from severe sepsis than from demand ischemia, then your attention should be directed toward the interventions that are most likely to give the patient benefit. Because this patient had no prior history of coronary disease, the risk/benefit moves one step toward sepsis interventions rather than acute myocardial infarction interventions.

The above is a much-truncated sample of a longer more involved discussion, presented to highlight the particular and unique parameters that need to be assessed and addressed when dealing with cases of severe sepsis. However, as one doctor noted, the data often "make a case for early treatment in all respects. Early intervention of almost anything is better than later intervention. Given what we know of the sepsis cascade, the further it rolls on the worse it gets. For most of us who have been sepsis investigators for a long time, the generalized expectation is that the earlier we intervene the better the chances that one can interrupt the sepsis cascade."

The article concludes, "the analysis and commentary of the care provided to [the] patient with severe sepsis and septic shock highlight the challenges in assessing and managing critically ill patients. The participants provided their perspectives on the recognition of physiological instability and the definition of severe sepsis and septic shock; at what point a patient should be admitted to the ICU; the importance of early goal-directed resuscitation therapy and the choice of resuscitation fluid; when to consider intravascular monitoring; the use of low-dose corticosteroids and drotrecogin-alpha; and at what point an improving patient should leave the ICU. The… assessment of the patient begins with recognition of the signs and symptoms of a serious infection… Patients often present with tachycardia and electrocardiographic abnormalities that may reflect sepsis, infection with vasodilation and hypovolemia or cardiac ischemia. Distinguishing sepsis and an ineffective circulation from an acute coronary syndrome can be challenging. All of the participants agreed that, regardless, the most important effort should be directed toward restoring adequate intravascular volume. All agreed that the adequacy of volume resuscitation was best determined from cumulative data, including serial hemodynamic measurements, measurements of arterial and central venous oxygenation, and the response to volume infusion.

Source

1 Roundtable debate: Controversies in the management of the septic patient—desperately seeking consensus. Aaron Waxman, Nicholas Ward, Taylor Thompson, Craig Lilly, Alan Lisbon, Nicholas Hill, Stanley Nasraway, Stephen Heard, Howard Corwin, Mitchell Levy. © 2004 BioMed Central Ltd, Critical Care 2005, © 1999-2007 BioMed Central Ltd.

Priorities, *continued from page 6*

quality indicators. There was no difference in ED length of stay and hospital length of stay between patients with the bundle completed compared with patients with the bundle not completed." The study demonstrated that the use of antibiotics, therapy, administration of corticosteroids, and protein C and lung-protective strategies offered effective survival benefits. However, the authors noted, overall success in the treatment of severe sepsis must rely on effective sepsis management techniques, as well as the mapping of quality indicators to track results.

Implementation

In the Nguyen study, once patients met participation criteria, hemodynamic monitoring was begun, and mechanical ventilation started if necessary. Corticosteroid was given for vasopressor-dependent patients or those with suspected adrenal insufficiency. A repeat lactate level was obtained to assess for lactate clearance.

Nguyen's study suggests that the severe sepsis bundle "can be implemented as standard care through the use of compliance measurements and feedback. Using a stringent bundle and quality indicators, requiring CVP and S_{CVO2} monitoring, current compliance is also relatively higher than with other therapies for severe sepsis. Lung-protective strategies have been achieved only in 39% of patients on day 2 of acute lung injury. Tight glucose control was achieved in 19% of the time with routine insulin protocols. The administration of rhAPC was 14.3% in patients with bundle completed in this study. The bundle is unique in that it is applicable during the earliest hours of severe sepsis presentation. The items themselves are inherent quality indicators with supporting evidence associated with improved outcome. Most important, the bundle quality indicators were accepted by the implementing physicians as valid and feasible a priori bundle implementation."

The study concluded that the severe sepsis bundle could be successfully applied in the emergency department, using the basic model, with no need for additional staff, and that completion of the severe sepsis bundle program gave strong indicators associated with improved outcome.

Sources

1 National estimates of severe sepsis in United States emergency departments. Henry E. Wang, MD, MS; Nathan I. Shapiro, MD, MPH; Derek C. Angus, MD, MPH; Donald M. Yealy, MD. Copyright © 2007 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins.
2 For more, see the article on the Surviving Sepsis Campaign in this issue.
3 Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. H. Bryant Nguyen, MD, MS; Stephen W. Corbett, MD, PhD; Robert Steele, MD; Jim Banta, PhD, MPH; Robin T. Clark, BS; Sean R. Hayes; Jeremy Edwards; Thomas W. Cho, MD; William A. Wittlake, MD. Copyright © 2007 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins.

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Life needs answers

Why is a 1-minute bilirubin test especially important in the NICU?

Timely monitoring of critical newborns can reduce the risk of potentially life-threatening diseases and enhance neonatal care for hyperbilirubinemia.

Kernicterus is a serious condition that can occur in infants with elevated bilirubin levels (>20 mg/dL).[1] The **cobas b** 221 blood gas system can help reduce the risk of kernicterus by delivering fast, actionable bilirubin results in the NICU.

The cobas b 221 system delivers bilirubin results in 1 minute or less.

Roche Diagnostics

Accuracy of near-patient testing of bilirubin and haematocrit measurement With Omni S blood gas analyser

P K Dey[1], S Pattnayak[1], B Bewley[2], A MacDonald[2], A W Kelsall[1]

[1] NICU, Rosie Maternity, [2] Dept. of Clinical Biochemistry, Addenbrooke's Hospital, Cambridge

INTRODUCTION

Near-patient measurement of blood gases, electrolytes and bilirubin have been performed in neonatal intensive care units (NICU) [1, 2].

Advantages include:

- Multiple assays on smaller blood volumes
- Immediate access to results
- Less handling and trauma to babies
- Long-term reduction in blood transfusions
- Less risk of needle stick injury
- Less equipment

AIM OF THE STUDY

To compare bilirubin and haematocrit measurements from Omni S analyser with Bilimeter II and micro-haematocrit reader

METHODS

Blood samples were collected in heparinised capillary tubes (maximum 200 µL) for blood gas, bilirubin and haematocrit measurement using Omni S analyser.

Simultaneously blood samples were collected in 75 µL heparinsed capillary tubes & centrifuged for 3 minutes (Centurion Scientific instrument).

Bilirubin assays were performed with Bilimeter II (Pfaff Medical). Haematocrit measurements were done using Hawksley micro-haematocrit reader.

(No additional blood samples were taken)

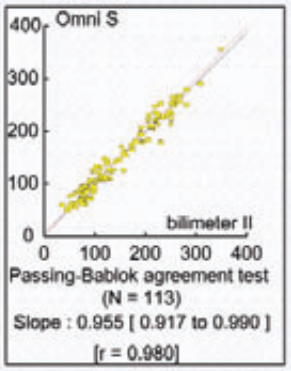
Statistical analysis was performed using method validator software.

Fig1 Omni S analyzor

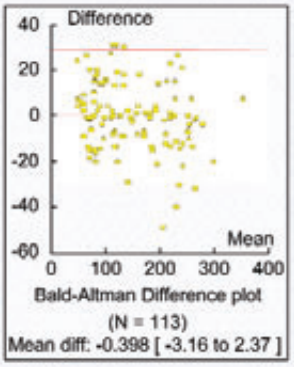
Fig2 Tests Omni S can perform

RESULTS

Fig 3 & Fig 4 show comparisons of bilirubin measurements between Bilimeter II & Omni S

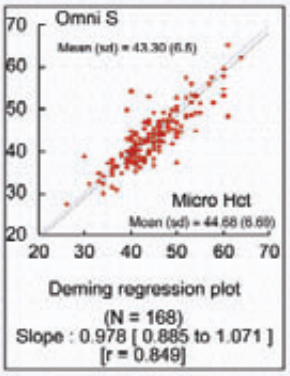


Passing-Bablok agreement test
(N = 113)
Slope : 0.955 [0.917 to 0.990]
[r = 0.980]

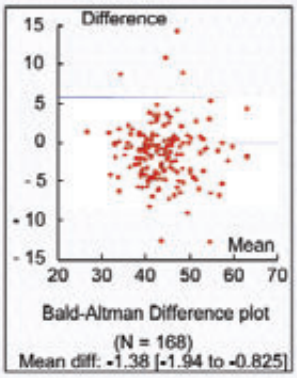


Bald-Altman Difference plot
(N = 113)
Mean diff: -0.398 [-3.16 to 2.37]

Fig 5 & Fig 6 show comparisons of haematocrit measurements between micro-haematocrit reader & Omni S



Deming regression plot
(N = 168)
Slope : 0.978 [0.885 to 1.071]
[r = 0.849]



Bald-Altman Difference plot
(N = 168)
Mean diff: -1.38 [-1.94 to -0.825]

CONCLUSIONS

Bilirubin & haematocrit assays can be successfully measured from single blood sample using the Omni S analyser. This system results in reduced blood sampling and simplified equipment requirements on NICU.

REFERENCES

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2. Laterza et al. Accurate direct spectrophotometric bilirubin measurement combined with blood gas analysis. Clinica Chemica Acta 2002;323(115–120).

Sepsis-Induced Hypoperfusion

The following is an edited version of the article, Hemodynamic Optimization of Sepsis-Induced Tissue Hypoperfusion by Sergio L. Zanotti Cavazzoni and R. Phillip Dellinger, with the Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Camden, NJ, reprinted from BioMed Central, Critical Care 2006, 10 (Suppl 3):S2, © 2006 BioMed Central Ltd.

Severe sepsis and septic shock are among the most important causes of morbidity and mortality in patients admitted to the intensive care unit. Sepsis is associated with a spectrum of cardiovascular derangements that may lead to development of tissue hypoperfusion.

The hemodynamic profile of severe sepsis and septic shock is characterized by components of hypovolemic, cardiogenic, and distributive shock. In the early phases, increased capillary leak and increased venous capacitance will result in a decrease in venous return to the heart. Cytokines released as a result of the host response to sepsis may also cause direct myocardial depression. The end result of these changes is a decrease in stroke volume and ejection fraction, leading to a compensatory tachycardia, increased ventricular compliance, and a decrease in arteriolar resistance. Fluid therapy and administration will modify this hemodynamic profile. In the early stages of sepsis, prior to fluid therapy, patients may present with a decreased cardiac output. Fluid therapy will usually result in a hyperdynamic state with a high normal or elevated cardiac output. After adequate restoration of left ventricular preload, hypotension – if present – is dependent on the degree of decreased systemic vascular resistance and on impairment of contractility.

Even with restoration of adequate blood pressure and normal or supranormal cardiac output, signs of tissue hypoperfusion may persist. This distributive shock may be related to maldistribution of blood flow at the regional or microvascular level and/or a cellular inability to utilize oxygen despite adequate oxygen delivery. It is believed that early intervention with aggressive hemodynamic support can limit the damage of sepsis-induced tissue hypoperfusion and limit or prevent the development of endothelial injury. Support for this hypothesis is offered by the results of the early goal-directed therapy (EGDT).

Septic shock has traditionally been utilized to conceptualize the clinical syndrome of persistent sepsis-induced tissue hypoperfusion. Blood pressure alone is unlikely to be sufficient in identifying the presence or absence of tissue hypoperfusion in patients with sepsis; patients with sepsis-induced hypoperfusion can present with normal blood pressures. It is therefore important to recognize other signs. Markers of tissue hypoperfusion can be classified into two groups: indices of global hypoperfusion and indices of regional hypoperfusion. A recent International Sepsis Definitions Conference recommended expanding the diagnostic criteria for sepsis. Many of these criteria, including altered mental status, organ dysfunction parameters, acute oliguria, hyperlactatemia and decreased capillary refill or motling, suggest the presence of tissue hypoperfusion. It is clinically important that tissue hypoperfusion be recognized, despite what may appear to be normal blood pressures, and should trigger timely and aggressive hemodynamic support interventions.

Patients with evidence of sepsis-induced tissue hypoperfusion should be treated in a monitored area, preferably an intensive care unit. Noninvasive monitoring with continuous electrocardiography and pulse oximetry should be initiated. Arterial pressure monitoring with an indwelling arterial catheter can provide accurate and continuous blood pressure measurements. This is especially useful in patients with very low blood pressures, in whom noninvasive blood pressure measurements may be inaccurate, or in patients on vasopressors, in whom sudden changes in blood pressure may occur. The radial artery is preferred, although the femoral artery is also commonly utilized.

Central venous pressure has been used for many years as a monitor of central venous blood volume. Normal CVP is approximately 2–8 mmHg. It is commonly accepted that a very low CVP is indicative of low intravascular volumes and supports the administration of crystalloids or colloids for volume expansion and improvement in tissue hypoperfusion. However, an elevated CVP does not always correlate with adequate intravascular volume.

Despite the ongoing debate surrounding use of the pulmonary artery catheter, it is still utilized and when used appropriately it can provide important information to assist in choosing hemodynamic interventions in patients with sepsis. The PAC allows measurements of intracardiac pressures, determination of cardiac output and mixed venous oxygen saturation. Information obtained from the PAC can be useful in diagnosing different causes of shock as well as monitoring disease progression and response to therapeutic interventions. The pulmonary artery occlusion pressure, as a reflection of left ventricular end-diastolic pressure, is presumed to correlate with left ventricular end-diastolic volume. Although clinicians assume that a high PAOP represents a high intravascular volume, many patients with elevated PAOP may still require higher intravascular volumes to ensure that there is adequate CO in patients with decreased ventricular compliance. Changes in PAOP in relation to intravascular volume are strongly influenced by myocardial compliance. It is important to recognize this relationship and appreciate that myocardial compliance may be different from patient to patient and may also change in an individual patient through the course of critical illness. It is useful to utilize the information provided by the PAC in a dynamic way, assessing changes in PAOP and their impact on CO as hemodynamic interventions are instituted.

SvO_2 can be measured in patients using a PAC. The determinants of SvO_2 include CO, oxygen demand, hemoglobin, and arterial oxygen saturation. Normal SvO2 is 70–75%. In sepsis SvO_2 may be elevated secondary to maldistribution of flow. However, patients with sepsis may also present with a low or normal SvO_2. Values of SvO_2 must be interpreted within the overall context of the hemodynamic profile. Although a normal or high SvO_2 does not always indicate adequate resuscitation, a low SvO_2 should trigger aggressive interventions to increase oxygen delivery to the tissues and minimize sepsis-induced tissue hypoperfusion.

Recently, continuous measurement of central venous oxygen saturation using a central venous catheter has garnered increasing attention. But monitoring techniques do not directly

affect outcome. It is the proper use of this information to guide clinical interventions that potentially has an impact on patient outcomes. Current recommendations for hemodynamic management of septic shock include arterial canulation for monitoring of blood pressure and assessment of cardiac filling pressures.

The principal goals of hemodynamic support in patients with sepsis are restoration of effective tissue perfusion and normalization of cellular metabolism. In order to facilitate hemodynamic optimization targets for treatment include intravascular volume, blood pressure, and CO.

Restoration of adequate intravascular volume should be the first goal in resuscitation. Adequate intravascular volume should be determined by achieving filling pressures associated with maximal increases in CO. In patients who are not undergoing invasive monitoring, establishing goals for clinical markers of perfusion such as heart rate, mean arterial pressure, and urine output is appropriate. However, in many patients these markers may be unreliable as sepsis-induced tissue hypoperfusion may occur even with normal values. Changes caused by positive pressure ventilation in systolic arterial pressure or pulse arterial pressure can predict which patients will respond to fluid loading with an increase in their CO. The degree of change observed in systolic arterial pressure or pulse arterial pressure during the respiratory cycle correlates directly with the response in terms of CO augmentation that a patient will have to a predetermined fluid challenge.

Blood flow to vital organs is usually preserved at a relatively constant rate by autoregulatory mechanisms when mean arterial pressure is maintained between 60 and 120 mmHg. When MAP drops below 60 mmHg hypoperfusion can occur. It is important to appreciate that in patients with chronic hypertension the relationship between MAP and organ perfusion might be shifted to the right. This means that patients with chronic hypertension might need a higher MAP to ensure that there is adequate organ flow to vital organs. Current guidelines recommend the maintenance of a MAP of 65 mmHg or greater as an endpoint for resuscitation. It is important to supplement this end-point with other markers of perfusion as well as clinical considerations.

Most patients with sepsis will have adequate CO after aggressive fluid resuscitation. However, in early unresuscitated sepsis and in a subgroup of patients later in the disease process and after adequate resuscitation, there is evidence of low or inadequate CO. The CO can be measured using thermodilution measurements with PACs and echocardiographically derived measurements. In addition, the measurement of SvO_2 or $ScvO_2$ can be utilized as a surrogate for adequate CO. As a general rule one should aim for a cardiac index (CO [l/min]/body surface area [m2]) of 3.0 l/min per m2 or greater. A SvO_2 of at least 65% or a $ScvO_2$ of at least 70% can be used as targets of adequate oxygen delivery.

The Surviving Sepsis Campaign recommends that the following end-points of resuscitation be targeted: CVP 8-12 mmHg (higher in mechanically ventilated patients); MAP at least 65 mmHg; urine output at least 0.5 ml/kg per hour; and $ScvO_2$ or SvO_2 of at least 70%.

Therapy

The initial step is aggressive fluid resuscitation. There is, however, controversy over the optimal type of fluid, crystalloids versus colloids. Meta-analyses of clinical studies performed in general critical care patient populations have demonstrated no difference in clinical outcomes between patients fluid resuscitated with crystalloids and those receiving colloids, so extrapolation of these results to patients with sepsis-induced tissue hypoperfusion is difficult. In patients with septic shock targets of resuscitation can be achieved with both types.

Patients with sepsis-induced tissue hypoperfusion often present with significant intravascular volume deficits. It is important to initiate aggressive resuscitation as soon as possible. The first step should be an adequate volume challenge with at least 20 cc/kg of crystalloids or an equivalent amount of colloids. Resuscitation should continue until end-points of CVP, MAP, and CO are met with the administration of fluid challenges. Once end-points are met it is important to re-evaluate tissue perfusion continuously to determine the need for further volume expansion.

Blood transfusions have been associated with immunosuppression, and there are concerns regarding the ultimate ability of stored red blood cells to carry and deliver oxygen. It is probably appropriate to target hemoglobin of 8–10 g/dl in patients with sepsis, recognizing that some patients with altered oxygen transport will likely benefit from blood transfusions targeted at achieving a $ScvO_2$ or 70% or more.

Some patients may remain hypotensive despite adequate fluid replacement. In these patients vasopressor agents to increase MAP should be utilized. Catecholamines have traditionally been used to raise blood pressure in patients with septic shock. The ideal vasopressor has been a subject of unresolved discussion. Important factors to consider in choosing a vasopressor include other hemodynamic effects, individual patient characteristics, and potential effects of vasopressors on regional vascular beds.

Vasopressors should be utilized in patients who remain hypotensive after volume expansion or during volume resuscitation in the presence of life-threatening hypotension. Vasopressor therapy should be targeted to maintain a MAP of 65 mmHg or greater. Norepinephrine or dopamine should be used as first-line agents to correct hypotension in patients with sepsis. Epinephrine and phenylephrine are recommended in patients who do not respond to initial vasopressors. Finally, vasopressin is not recommended as a first-line agent. It can be used as hormone replacement, given at low doses 24 hours after the onset of shock, in cases refractory to other vasopressors.

Cardiac function is impaired in most patients with sepsisinduced hypotension after fluid resuscitation. Myocardial dysfunction in sepsis is complex and usually characterized by ventricular dilation, decreased ejection fraction, and impaired contractile response to fluid resuscitation. In patients with low CO despite fluid administration, it is recommended that inotropic agents be utilized to increase CO. The agent of choice is dobutamine, which at doses ranging from 2 to 28 µg/kg per min results in increased cardiac index, stroke volume, and heart rate in patients with sepsis. In patients with hypotension, dobutamine should be used in conjunction with a vasopressor agent. Dopexamine has also been proposed, but it is not currently approved for use in the US. The use of inotropes to

achieve supranormal or supraphysiologic CO in sepsis is not recommended. Current recommendations strongly emphasize that strategies to increase oxygen delivery beyond normal values should not be implemented in patients with sepsis.

Although we have much to learn regarding this very important aspect of sepsis, it is important to recognize tissue hypoperfusion as a medical emergency. As such it is essential to implement therapeutic interventions. The initial intervention should be administration of crystalloids or colloids. For patients who require vasopressors, norepinephrine or dopamine should be utilized as first-line agents. Some patients may require dobutamine to increase low CO. Implementation of hemodynamic interventions targeting predefined end-points is a time-sensitive therapy that has a significant impact on decreasing morbidity and mortality from sepsis.

BLOOD GAS ROUNDTABLE

Roche Diagnostics

Larry Healy
Larry Healy is Marketing Manager, Point of Care Diagnostics, Roche Diagnostics

Has your equipment facilitated results reporting through the hospital information systems, and if so, which systems interface effectively with your equipment?
Roche Diagnostics offers specific IT and Data Management solutions with the cobas b 221 system to help hospitals maximize workflow efficiency and result reporting for Respiratory Therapy, the Laboratory and POC. For example, DataCare software enables staff to effectively manage patient data for all areas. OMNILink Instrument Manager software offers command and control of decentralized blood gas systems, and Axeda protected remote access provides virtual onsite technical support to help maximize instrument uptime. In the centralized setting of the laboratory, interfacing with the LIS/HIS through existing Middleware connections can significantly reduce the cost and set-up time for blood gas connectivity. And with RALS-Plus data management software from MAS, POC Coordinators have a single IT solution for both blood gas and glucose.

What features (ie data storage) assist you when preparing for lab inspections from JCAHO, CAP, FDA etc?
Roche offers a full suite of blood gas, IT and Web-based solutions that help simplify regulatory compliance for healthcare facilities. With 20 GB of onboard data storage, the cobas b 221 system maintains an average of five years worth of QC, calibration and patient data for review and reporting, to support users with limited or no LIS capabilities. OMNILink software allows remote screen sharing of decentralized systems and immediate access to QC, calibration, and maintenance logs from these systems. RALS-Plus and DataCare data management software reporting functions generate the necessary documentation to meet compliance standards. And eQAP offers real-time peer review of QC to help ensure system proficiency.

What do you see as an emerging trend in blood gas technology?
With the trend of managing patient health outcomes through standards of care, healthcare professionals need blood gas systems to do more in less time. As a result, blood gas systems are beginning to offer expanded menus with whole blood analysis and rapid turnaround time, which is especially beneficial in high-cost areas like the ICU and the ED.

Is point of care blood gas testing becoming widely accepted? If so, what are the benefits?
Recent market research indicates that blood gas testing is moving to the decentralized areas of the ICU, NICU, OR and ED. This trend toward point-of-care testing can offer several benefits to the healthcare facility and its patients. For example, POC blood gas testing with the cobas b 221 system can help reduce turnaround time for results and give the clinician immediate access to actionable information that can help in diagnosis, treatment decisions, monitoring the patient's condition and evaluating response to treatment.

What barriers to implementation have you seen when a POC Coordinator, RT director, lab manager or medical director decides to purchase point of care systems?
The specific barrier depends on the person's role, of course, but the most common concerns include ease of use, maintaining command and control, and making the "paradigm shift" to do testing at the point of care. Current blood gas technology offers several capabilities that help overcome those barriers, though. For example, Roche's cobas b 221 system has a multi-user interface that makes it easier for all operators to use. Staff with command and control concerns—like the POC Coordinator, RT Director and Lab Manager—have the ability to direct, monitor and report the activities of all their decentralized blood gas systems with OMNILink Instrument Manager software. And having immediate access to actionable information can make it easier to gain the medical staff's acceptance of point-of-care blood gas testing.

Compare the blood gas technology of the past with today's standard as it relates to your hospital.
Blood gas technology has evolved to match changing standards of patient care. Today, blood gas systems need to maintain a high state of readiness, deliver results faster, provide comprehensive test menus that are driven by disease states, and offer information technology solutions.

To maintain immediate readiness and ensure operator safety, most systems today are self-calibrating, without gas tanks, and have programmable onboard AutoQC. Smaller sample sizes and independent sample paths also help some systems deliver rapid turnaround on results. And analyzers like the cobas b 221 system offer additional features like continuous self-monitoring, which provides updates on pending maintenance, to increase instrument uptime.

Because test menu parameters today are driven primarily by disease states, on some systems they now go beyond basic blood gas profiles to include electrolytes, metabolites, COOX and bilirubin. The systems must have flexible sample inputs for syringes and capillaries and the ability to run whole blood, serum plasma, body fluids and dialysate. Measurement ranges have been expanded too, as a result of new cardiovascular procedures and IV therapies.

The biggest change in blood gas technology, though, is in the IT area. Information solutions like data and instrument management software, protected remote access and HIS/LIS connectivity have resulted in a true information paradigm shift in blood gas technology and in its relationship to other point-of-care testing areas.

Pleural Fluid pH Analysis in the Blood Gas Laboratory

This article is specifically addressing the role of the Respiratory Care Practitioner (RCP) in the role of body fluid analysis and specifically pleural fluid pH. Before we take an in depth look at this analyte we must first look at the pathophysiology of this pneumonic process.

Pleural effusion is the accumulation of fluid in the chest between the lung and the chest cavity. Normally there is no space between the parietal pleura, which covers the chest wall, and the visceral pleura, which covers the lung. The normal fluid that is present facilitates the mechanics of ventilation that maintains a negative intrapleural pressure therefore allowing the lungs to remain expanded. For a diagnosis of pleural effusion, 75% of those patients will have a diagnosis made at the onset of the clinical findings presented. 25% of those patients will have a positive cytology or positive culture of the aspirate analyzed. Fifty percent of those patients have a presumptive diagnosis prior to the laboratory findings. Fifteen to 20% of the patients will not have a diagnosis made prior to diagnostic studies. The history and physical (H & P) exam are critical in guiding the evaluation of the pleural effusion and it is imperative that an extensive H & P be obtained from the patient. Chest examination demonstrates dullness to percussion and diminished breath sounds, which may be, but are not necessarily gravity dependent. Confirmation of a pleural effusion may include an Anterior-Posterior radiograph, lateral decubitus whereby the patient lays on their side, and/or CT of the chest and abdomen. The interpretive physician is looking for clear radiographic findings that suggest a pleural space infiltrate. The definitive diagnosis is a thoracentesis whereby the physician performs a needle aspirate to a local anesthetized area of the chest wall and inserts the needle into the pleural space now occupied by an infiltrate. The sample must be obtained under anaerobic conditions, iced, and analyzed within two hours preferentially through the "gold standard" Blood Gas Analyzer (BGA). If the sample is not iced, in vitro glycolysis will occur resulting in a false low pH. If the sample is exposed to room air, then a false high pH will occur due to gas equilibration. The sample, by most clinical standards of medical practice, should include a diagnostic order for LDH, Protein, Glucose, Amylase, Cell Count, Cytology, and cultures in addition to pH analysis. There are about 1 million cases per year of pleural effusions and primarily are subcategorized as transudate (movement of fluid into the pleural space due to imbalance of hydrostatic and oncotic pressures) or exudative (caused by inflammation of the lung or pleura) effusions. Trasudative effusions normally have a pH 7.40-7.55 and exudative effusions normally have a pH less than 7.45. Categorically, most of the effusions are by congestive heart failure, malignancy, infections, and pulmonary emboli, requiring urgent evaluation and treatment. It is interesting to note that 25% of the pleural effusions are resolved within 48 hours with aggressive diuretic therapy. Cirrhosis, pulmonary embolus, infection, malignancy, immunologic disorders, lymphatic abnormalities, non-infectious inflammation and nephritic syndrome are other common etiologies of transudative pleural effusions. Decreased glucose in the pleural fluid may indicate a malignancy, empyema, and a complicated parapneumonic effusion, or tuberculosis to name just a few disease entities. Normal pH of pleural fluid is 7.60. American College Chest Physicians (ACCP) and the British Thoracic Society agree that pH values less than 7.20 are a critical value with a parapneumonic infection and will require immediate drainage via chest tube insertion. 20-25% of pneumonia patients have a parapneumonic infection and will resolve with aggressive antibiotic therapy. Decreased glucose with a decreased pH signals the possible diagnosis of a malignant pneumonic process. A pH less than 7.28, with a malignant pneumonic process, has a 39% mortality after 3 months. Two negative cytologys with a low pH indicate possible tuberculosis or rheumatoid pleurisy.

Several analytical methods have historically been performed over the years. The methods that have been and currently are being utilized are the pH meter, pH indicator strips, and the Blood Gas Analyzer (BGA). In studies reported in Chest (1998), pH meters and pH indicator paper reported significantly higher mean pH than the BGA; therefore the clinical and research findings as stated earlier in this article were that the BGA is the gold standard for pleural fluid pH analysis. Blood Gas Laboratories must meet regulatory standards as set forth by CLIA and other regulatory agencies such as College of American Pathologists (CAP). The method of testing falls into three CLIA classifications of waived, moderately complex, and highly complex categories. The BGA fall into either the moderately complex or high CLIA complexity category depending upon whether the BGA has undergone 510K FDA clearance for analyzing pleural fluid pH. It is each laboratory's responsibility to determine if their BGA has met the FDA clearance for analyzing pleural fluid pH. If your instrument is 510 K FDA cleared, then CLIA recognizes this instrument's analyte as a moderately complex instrumentation. If the BGA is not FDA cleared which is referred to as "off-label," then the analyte is considered to be reported from high complexity instrumentation and must meet the 6 point high complexity CLIA category. Pleural fluid pH analyte reported from a moderate complex BGA has less regulatory requirements from CLIA as opposed to an "off-label" BGA that must meet more CLIA regulations. CLIA does not recognize the waived category for pleural fluid pH so to use litmus paper you must meet CAP guidelines of proficiency testing, daily QC, method validation, and personnel training and competency validations. The use of litmus paper is compromised by the fact that the test results cannot be reported in hundredths (X.XX) and the accuracy needs to be reported to this mathematical expression, as accuracy is the critical factor in reporting pleural pH. Litmus paper relies on colorimetric determinations and has a falsely reportable high value as previously mentioned in Chest. PH meters expose the anaerobic sample to room air and have falsely high reportable pH as well. Pleural fluid samples when analyzed through the BGA should be cautiously analyzed with the addition of a clot catcher between the syringe and the BGA sample inlet port or an internal clot catcher as the pleural sample presents a small risk of BGA clotting contaminates much like other blood samples introduced into a BGA such as neonatal or patients with polycythemia.

cobas®

Life needs answers

Why use a blood gas system with FDA 510(k) clearance for pleural fluid pH testing?

The College of American Pathologists and articles in *Chest* cite blood gas analyzers as the "method of choice" for measuring pleural fluid pH,[1,2] and only one analyzer is FDA-cleared to help you achieve regulatory compliance: The **cobas b** 221 blood gas system.

Pleural fluid pH can be a clinically useful tool for managing patients with pleural effusions—and can be especially important in critical care environments such as the ED.

Only the cobas b 221 blood gas system is FDA 510(k)-cleared for pleural fluid pH testing.

Roche Diagnostics

Critical values must be determined to meet CAP standards and documented like any other critical value in your laboratory. We have established any value less than 7.20 as a critical result and must be called and read back to the ordering physician to meet CLIA, CAP, JCAHO, and other accreditation standards.

Body fluids must meet proficiency testing just like any other analyte and can be ordered from the CAP web site. These are performed twice a year and reported using similar proficiency testing methodologies.

In summary, pH pleural fluid testing provides the physician with a valuable diagnostic test that complements the clinical decisions necessary to provide excellence in patient outcomes. Not only does the diagnostic testing provide a diagnostic tool, but also from the financial aspect it is a revenue stream within your departmental operations.

Bilirubin Determination Using the cobas b 221 (OMNI S) Point-of-Care Analyzer

Information for this article appeared in another format in Point of Care Volume 4, Number 1, March 2005, © 2005 Lippincott Willliams & Wilkins. The authors are Boris Rolinski, MD; Anthony Okorodudu, PhD; Gerald Kost, MD; Markus Roser, MD; Jiaxi Wu, MD, PhD; Ada Goerlach-Graw, PhDk; and Helmut Kuester, MD. The article was provided for publication in Respiratory Therapy by Roche Diagnostics.

According to the Symposium Article, "Evaluation of Total Bilirubin Determination in Neonatal Whole Blood Samples by Multiwavelength Photometry on the cobas b 221 (OMNI S) Point-of-Care Analyzer," jaundice is a common finding in healthy and diseased neonates. Because of early discharge, the risk of kernicterus is a reemerging problem in the US. Precise and accurate determination of plasma total concentrations is indispensable for proper management of jaundiced infants. In their multicenter study, Rolinski, et al investigated the analytical performance of the cobas b 221 (OMNI S) blood gas analyzer for measurement of total bilirubin from neonatal whole blood using a multiple-wavelength photometric method. Results were compared to other results from routine clinical chemistry methods and another device. Four hundred and ninety-six heparinized blood samples were drawn from newborns of 39 days or less. An aliquot of the whole-blood sample was measured on the cobas b 221 (OMNI S) and on the Radiometer ABL 735. Plasma bilirubin concentrations covered the diagnostic relevant range up to 23.7 mg/dL. There was good agreement between the bilirubin concentrations measured in whole blood on the cobas b 221 (OMNI S) and Radiometer ABL 735 and between the comparison routine analyzers. Correlation coefficients were above 0.94, and the slope of the regression lines ranged from 0.971 to 1.172. The mean biases ranged from –0.3 to 1.4 mg/dL, and the differences between comparison methods were less than those reported in proficiency testing. Direct spectrophotometric measurement of bilirubin in neonatal whole-blood samples gave results that compared well with those obtained using routine chemistry methods. Noted advantages were the very small volume of blood and the short turnaround time. The authors of the study concluded that the cobas b 221 (OMNI S) analyzer represents a suitable method for monitoring neonatal jaundice at the point of care.

BACKGROUND

In the newborn, hyperbilirubinemia is due to an increased hemoglobin turnover along with immature hepatic glucuronidation. Neonatal jaundice is a common finding insofar as about 60% of infants become clinically jaundiced in the first week of life, and about 33% of breastfed infants have total bilirubin levels above 12 mg/dL. Plasma bilirubin concentrations in neonates can range as high as 40 mg/dL. Newborn jaundice is usually considered benign, with hyperbilirubinemia resolving within the first week, but in rare cases, higher concentrations of bilirubin may cause kernicterus. While the condition is considered rare due to prompt postnatal medical care, reports have shown an increasing frequency. Because phototherapy or exchange transfusions may be required to lower bilirubin concentration, therapeutic decisions must rely on determining plasma bilirubin concentration. As such, babies with jaundice are typically monitored for bilirubin levels from four hours a day to every other day. Thus, it's desirable to employ methods that come up with quick and reliable results, using small volumes of whole blood. Recently, the cobas b 221 (OMNI S) blood gas analyzer was equipped with the same feature as the first instrument to provide total bilirubin determination in whole blood, manufactured by Radiometer.

MULTICENTER STUDY

The study was conducted in four hospitals with NICUs, in California, Texas and Germany. Four hundred ninety-six heparinized blood samples were analyzed, using samples from 353 newborns ranging in age up to 39 days, with a median age of 4 days. An aliquot of whole blood was measured on the cobas b 221 (OMNI S) or the Radiometer ALB 735, and plasma was prepared from the remaining sample. Total bilirubin in plasma was measured by wet chemistry, and a total of ten sets of comparison data were obtained. One set of samples was also measured for direct bilirubin and for serum indices by direct photometry. Various methods were used to assess imprecision, inaccuracy and recovery, and heparinized whole-blood samples were obtained from healthy volunteers. The hematocrit was measured on the cobas b 221 (OMNI S) and the plasma volume calculated. The samples were centrifuged, and a portion of plasma supernatant was replaced by an equal volume of bilirubin stock solution to provide desired plasma concentrations of 6, 24 and 48 mg/dL, after which samples were re-dispersed and used for immediate bilirubin measurement on the cobas b 221 (OMNI S). Fresh samples were prepared daily. Control samples were prepared by dilution in albumin solution or bovine serum albumin fraction V, or in human pool plasma with low bilirubin concentrations to give final bilirubin concentrations of 0,2,10 and 20 mg/dL and 0.8, 2.8, 10.8 and 20.8 mg/dL for albumin-based and plasma-based samples, respectively. The samples were aliquoted and stored until analysis. Recovery on the cobas b 221 (OMNI S) was investigated at two sites with a set of 10 accuracy controls ranging from 1 to 13 mg/dL bilirubin.

RESULTS

Plasma bilirubin concentrations ranged from 0.2 to 23.7 mg/DL, which covered the range for proper diagnostic decisions. Hemoglobin concentrations varied from 10 to 23.6 g/dL.

Agreement was good between bilirubin concentrations measured in whole blood on the cobas b 221 (OMNI S) and measured from comparison methods. The mean correlation coefficient was 0.966 +/- 0.015 and the mean slope of the regression lines was 1.047 +/- 0.052, with mean intercept of –0.065 +/- 0.523. Mean bias was 0.41 +/- 0.51 mg/dL.

The authors observed a slight offset between the same Roche 2,5-DPD method in two of the German settings, with recorded values slightly higher and lower, respectively than those of the OMNI S. The difference remained unexplained, but evaluation showed that the Roche DPD method fit correctly with the cobas b 221 (OMNI S). The rest of the wet chemistry methods also correlated well with the cobas b 221 (OMNI S), except for the neonatal bilirubin run in Munich. The method is a direct photometric reading from the sample diluted in buffer at two wavelengths, with recorded values about 10% lower than those obtained with DPD. According to the authors, the method suffers from interference by hemolysis and turbidity more than methods based on reaction with diazo dyes. As such, according to Rolinski, et al, direct photometry at two wavelengths is inferior to all other methods tested in the study, and discrepancies can be attributed to this problem rather than to methods employed. Dry chemistry bilirubin correlated closely with the cobas b 221 (OMNI S) whether compared with values obtained with TBIL or BIL slides. Comparison of the cobas b 221 (OMNI S) with the Radiometer ABL 735 showed an offset of 1 mg/dL between the instruments, which the authors found odd insofar as both instruments rely on direct multiwavelength photometry. It was surmised that the discrepancies may have occurred in the calibration process, from the calculation algorithm, or from differences in compensating the hemoglobin interference.

Outliers defined as a relative bias of >21% were observed, with the highest number at one of the German sites. It was speculated that perhaps the Roche analyzer employed at that site was less reliable than the others, but it wasn't possible to repeat the measurement due to sample limitations. However, differences between methods were found to be minor and much less than differences typically reported in daily routine or proficiency testing surveys.

Results of quality control studies revealed that precision and accuracy were well within the specified ranges of the instruments. Precision and bias for whole-blood controls were less accurate, but sample preparation would have contributed significantly to the imprecisions noted. Recovery of the 10 commercial accuracy controls based on plasma matrix was good, with a bias from –0.13 to 1.23 mg/dL. No difference was observed between the control materials.

The authors note that quality control is a difficult issue for methods using whole-blood samples, and, until now, the problem of matrix conformity of quality-control material had been unresolved. This is why different matrices were used in the study. The Auto Trol material used for the cobas b 221 (OMNI S) is a photometer control based on dyes in aqueous solution and doesn't contain bilirubin. The researchers used commercial and in-house quality-control material based on serum matrix, with the advantage that this material contains the real analyte and is stable for within-day experiments. Whole-blood controls were also used but had to be prepped daily, which increases imprecision and isn't feasible for clinical routine.

CONCLUSIONS

According to the authors, "Measurement of bilirubin is know as one of the most unreliable tests in clinical chemistry." Until recently, no accepted reference method existed and no standardization between assays of different reagent suppliers had been achieved. As such, there have been no true values to rely on for comparison studies or for the care of patients, and target values for control materials may vary widely, depending on the assay. Rolinski et al conclude, "Taking this into consideration, our study clearly demonstrates that the accuracy and precision of the cobas b 221 (OMNI S) analyzer meets the expectations for routine laboratory method and allows for the reliable determination of bilirubin concentrations in neonatal whole-blood samples. Advances in laboratory medicine are often driven by the need to obtain more information from a smaller sample at a faster time than previously possible. Especially for monitoring hyperbilirubinemia in the newborn, direct photometry of neonatal whole-blood samples in a blood gas analyzer provides fast yet reliable results from very small sample volumes, enabling bilirubin measurement at the point of care."

Pleural Fluid pH

The following information is based on the article "Prognostic Value of Pleural Fluid pH in Malignant Epithelial Mesothelioma after Talc Poudrage" by Yossef Aelony, Janis Yao and Randel King. Aelony and King are with the Department of Internal Medicine, Kaiser Permanente, Harbor City, CA. Yao is with the Southern California Permanente Medical Group, Pasadena, CA. Information for the article is redacted from "Prognostic Value of Pleural Fluid pH in Malignant Epithelia Mesothelioma after Talc Poudrage," Respiration 2006;73:334–339, Copyright © 2006 S. Karger AG, Basel, Switzerland, E-Mail karger@karger.ch Accessible online at: Rancho Palos Verdes, CA 90275 (USA) www.karger.com, www.karger.com/res. Information provided to Respiratory Therapy by Roche Diagnostics.

According to a recent article in Respiration (see above), current staging schemes for malignant mesothelioma are inadequate. The most accurate staging may require pneumonectomy. The authors note, "Low pleural pH (ppH) has long been correlated with poor outcome in patients with malignant pleural effusion. The mechanism of low ppH in advanced malignant disease is believed to be related to increased metabolism by pleural cells, decreased glucose transport into the pleural fluid, and a diffusion block of CO_2 efflux out of the pleural space. Under these conditions, lactic acid and hydrogen ions accumulate in the pleural fluid. This lower ppH has been directly correlated with the extent of tumor visualized thoracoscopically and with shorter survival."

The study by Aelony et al determines that ppH predicts survival in neomesotheliomatous malignant pleural effusions, suggesting that this noninvasive test might be useful for prognostication in malignant mesothelioma. Aeolony's study was to determine whether baseline ppH correlates with survival in malignant epithelial pleural mesothelioma. The authors reviewed survival data in patients treated with thoracoscopic talc pleurodesis where the final diagnosis was epithelial malignant pleural mesothelioma and charting recorded a ppH determination performed just before thoracoscopy. The authors monitored 26 patients, of whom 25 ultimately died, identifying cutoff ppH values that discriminate best for survival. The mean follow-up

time was 19 ± 14 months, mean ppH was 7.30 ± 0.09, and median ppH was 7.32. ppH 7.32 was associated with the greatest survival value. Patients with ppH less than 7.32 lived a median of 21.2 months after diagnosis compared with patients who had ppH ≤ 7.32 and lived a median of 13.4 months. The baseline ppH correlated with survival in epithelial mesothelioma patients treated palliatively with pleurodesis by thoracoscopic talc poudrage. The authors recommended that this noninvasive ppH test should be included when staging patients with malignant mesothelioma.

BACKGROUND

Little data exists on ppH and malignant mesothelioma. Patients were typically diagnosed by closed needle biopsy, and pathologists considered the amount of specimen obtained to be inadequate for reaching a definite diagnosis. Limitations on information garnered (low rate of confirmed diagnoses, inadequate tissue typing) resulted in a lack of adequate association between ppH and survival. Aelony and Yao had previously reported treatment results of palliative thoracoscopic talc poundage, though the results weren't statistically significant. The current study was designed to determine if the pathoracoscopic ppH in a combined group of 26 patients from Aelony and Yao's study correlated with duration of survival after the procedure.

For more than 20 years, Kaiser patients with recurrent symptomatic pleural effusion had received thoracoscopy for diagnostic biopsy, talc pleurodesis, or both. These patients' medical data were incorporated into a prospective database. A review of these data formed the basis for this study. Measurement of ppH was considered noninvasive because it is derived from fluid that would be sampled in any event. Baseline ppH was measured in fresh pleural fluid under anaerobic conditions, obtained before the induction of the pneumothora, prior to thoracoscopy. The ppH was measured using an AVL Scientific blood gas analyzer. Pleuroscopy with a parietal pleural biopsy and talc insufflation was performed using a rigid telescope with a single-puncture technique. Microscopic analysis was performed by our own pathologists and confirmed by the US-Canadian mesothelioma panel.

To identify a cutoff ppH value that defined a warning level for survival in the data, the researchers used the 18-month follow-up data, which provided sufficient information. Adjusted ROC curves were recursively run using the same ppH cutoff values and were adjusted by age and side of lung affected.

ppH VALUES AND SURVIVAL

Results indicated that ppH values were significantly associated with survival. Associations of either side of the lung affected and age with survival were borderline significant. The median survival for patients with ppH >7.32 was 21.2 months versus 13.4 months for ppH ≤ 7.32. The study revealed that ppH was the only significant factor.

Patients were treated by the same approach, using thoracoscopic talc pleurodesis as the primary palliative modality of care. Three patients were subsequently treated with chemotherapy and radiation therapy and survived a mean of 10.5 ± 3.1 months. After receiving talc poudrage, the patient with ppH 7.26 survived 12.5 months, the patient with ppH 7.27, 14.6 months, and the patient with ppH 7.19, 4.5 months. The other 23 patients received no antineoplastic treatment before or after receiving pleurodesis.

As this series demonstrates, the relation of ppH to survival in patients with malignant effusion also applies to patients with epithelial malignant mesothelioma when the main treatment is palliative thoracoscopic talc pleurodesis. Management was basically the same for all patients. Overall survival in this group of patients was relatively good compared to other approaches.

Aelony et al noted that the ppH prognostic factor is likely to be important regardless of the type of subsequent treatment received, but because the sample size in this study was small, the optimal ppH cutoff point might not be representative, and suggested that a multicenter study would be necessary to collect a large enough series to achieve statistical significance for less frequent subtypes of mesothelioma.

All patients in this study had large effusions (>1,000 ml). Staging proposals could not be applied using a retrospective record review and current surgical staging seems inapplicable for thoracoscopy patients. Recent editorials have decried the unavailability of uniform, effective staging schemes in mesothelioma.

The authors noted that prospective studies with multivariate analysis are needed to determine whether ppH functions independently of these other factors, and awaited information from the European Organization of Research and Treatment of Cancer and the Cancer and Leukemia Group B staging programs which could then be combined with ppH, PET scan intensity and tumor necrosis grading, leading to prospective studies showing correlation with survival.

The authors concluded, "Research efforts should now focus on incorporating ppH into disease staging for all mesothelioma patients. Ideally, controlled studies would always be conducted comparing various modalities of treatment… and including a control group of patients receiving best supportive care. Notwithstanding those studies, improved staging is essential to allow prognostication for the patient, to permit better comparisons between phase II studies, and to facilitate selection of patients for future prospective trials."

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