Getting Started

Education

The SSC leadership believes that continuing education is the most important factor for initial and ongoing SSC success. A variety of educational tools is available to institutions to support the learning process. Teaching tools include:

The survivingsepsis.org website will be updated as new offerings are available including webcasts, PowerPoint programs, videos, and other resources

SSC educational offerings at partner society's conferences

SSC guidelines poster 2012 guidelines

SSC pocket guide 2012 guidelines

Bundle badge cards

Surviving Sepsis Campaign lapel pins to show your team's commitment

For further assistance, please contact Stephen Davidow at the Society of Critical Care Medicine by phone at +1-847-827-7088 or by email at sdavidow@sccm.org.

Surviving Sepsis Campaign

Getting Started

The Surviving Sepsis Campaign In Your Institution: Getting Started

The Surviving Sepsis Campaign (SSC) partnered with the Institute for Healthcare Improvement (IHI) to incorporate its "bundle concept" into the diagnosis and treatment of patients with severe sepsis and septic shock. We believe that improvement in the delivery of care should be measured one patient at a time through a series of incremental steps that will eventually lead to systemic change within institutions and larger health care systems.

Local SSC implementation is the key to mortality reduction for severe sepsis and septic shock patients. Successful SSC adoption requires a hospital champion who can coordinate the LEADER steps outlined below.

L Learn about sepsis and quality improvement by attending local and national sepsis meetings.

E Establish a baseline in order to convince others that improvement is necessary and to make your measurements relevant. This should be done prior to formal improvement efforts. Start by collecting data on all severe sepsis patients in your intensive care unit (ICU) - you may see only one or two patients per day.

A Ask for buy-in from institutional leadership and seek initial support from the emergency department (ED) and ICU staff and directors, quality improvement personnel, nursing staff, and others. (You may want to watch the webcast "Administrative Buy-In: Key to Sepsis Care Improvement"

Form a sepsis team and bring all stakeholders to the table for input. Tell people what you are doing and why. You may not receive initial support across the board, but opinions often change when data start to become available.

Publicize the SSC with a formal kick-off event.

Highlight several physicians to speak about the effort and invite representatives from administration, medicine, nursing, respiratory therapy, and pharmacology. This commitment will provide early momentum and drive improvement efforts forward.

Surviving Sepsis Campaign

D Develop an institution-specific SSC protocol comprising all bundle elements.

Seek feedback and refine your protocol to the satisfaction of your team. Assign a "protocol owner" with the task of refining the protocol and patiently obtaining feedback from all stakeholders.

Invite comments and suggestions at regular team meetings. Publish refinements by scheduled deadlines and label each version with a date to ensure uniformity of use.

E Educate stakeholders in the ED and ICU and floors according to shift schedules. Post the SSC protocol in several prominent locations.

Familiarize staff with the bundles and your protocol. Explain the importance of the bundle tools. Tolerate failure and revise teaching as needed.

R Remediate errors and anticipate obstacles along the way.

Recount successes and failures every month. The SSC database can create graphs that benchmark your success and demonstrate powerful visuals of clinical targets where improvement is important. Everybody involved needs to see what is happening to drive the SSC effort forward. Identify critical failure modes as a team and redesign processes as needed while simultaneously measuring your results.

Getting Started

How To Improve – Forming The Team

To achieve the improvement goals, everyone involved with the care of the severe sepsis patient must be included, work processes must be carefully scripted and standardized, and awareness and commitment to this effort must be elevated. This must be a team effort that crosses disciplines and departments; it requires leadership and support from the entire organization and buy-in from all stakeholders involved with the care of these patients.

There are three different levels of participation in creating successful change:

Active working team responsible for daily planning, documenting, communication, education, monitoring, and evaluation of activities.

The working team must be multidisciplinary, with representation from all departments involved in the change processes — doctors, nurses, pharmacists, respiratory therapists and other staff with roles in the specific change process, such as clerks and technicians. Team members should be knowledgeable about the specific aims, the current local work processes, the associated literature, and any environmental issues that will be affected by these changes.

The leadership group or person who helps remove barriers, provides resources, monitors global progress, and gives suggestions from an institutional perspective is essential.

The working team needs someone with authority in the organization to overcome barriers that arise, and to allocate time and resources the team needs to achieve its aim. Leadership needs to understand both the implications of the proposed changes for various parts of the system and the remote, unintended consequences such a change might trigger.

Providers, including all stakeholders who have an interest in the change, must be engaged.

Procedures are needed to keep providers and other stakeholders informed, provide a hassle-free mechanism to receive their feedback, and assure them that their responses are respected and will influence the changes. This helps give them some ownership and facilitates implementation and utilization of the new processes

Getting Started

Examples Of Effective Teams

Example 1: Effective Work Team

Aim: Diagnose patients with severe sepsis or septic shock in the emergency department (ED) within 2 hours of triage

Core Working Team: The overall core team must be interdisciplinary and must include, at a minimum:

- ED physician
- Triage nurse
- Staff nurse
- Laboratory technician
- Laboratory supervisor
- Admissions clerk

Additional team members may include:

- Critical care medicine (CCM) physician
- House officer
- ICU charge nurse
- Infectious disease physician

Example 2: Effective Work Team

Aim: Ventilated septic patients will have tidal volumes near 6 ml/kg ideal body weight and plateau pressures less than 30 cm H_2O

Core Working Team: The overall core team must be interdisciplinary and must include, at a minimum:

- CCM physician
- Respiratory therapist
- Staff nurse
- Pharmacist

Additional team members may include:

- Private attending physician
- Surgeon
- ED physician
- Blood gas technician

Example 3: An Effective Leadership Team

- Aim: ED and CCM will join to implement best possible care for septic patients, using the known evidence that fits their institution.
- Core Leadership Team: The overall leadership team must be interdisciplinary and must include, at a minimum:
- Administrator over ED and CCM
- Critical care medicine physician
- ED physician
- CCM nurse manager
- ED nurse manager
- ED charge/triage nurse
- CCM charge nurse

Additional team members may include:

- Pharmacist
- Respiratory Therapy supervisor
- Process improvement facilitator
- Laboratory supervisor
- Technicians from ED

Getting Started

Establishing And Engaging Measures To Track Change

Process Measures

These measures tell you about how the process of change is unfolding as your improvement and clinical teams work to comply with the bundles. Are changes being translated into actual practice as you intended them to be?

Process measures will allow you to identify whether you have created a reliable system that follows the timing, sequence, and goals mandated in the Sepsis Bundles.

Outcomes Measures

These measures tell you whether changes are actually leading to the improvement you intended.

Faithful implementation of the Severe Sepsis Bundles, combined with an unwavering focus on the above process measures, will help you to achieve this goal at your institution

Data Collection

A hospital's improvement team is likely to use one of two methods to collect data for the measures described above. Whichever method is selected, that approach should be maintained from month-to-month in order to assess the degree of improvement over time accurately.

Concurrent Data Collection

Concurrent data collection is best suited to new improvement teams. That is, once a patient is placed on the hospital's severe sepsis protocol, data can be abstracted from the patient chart in real-time or, as most teams have found, at some point during the first 24 hours of admission so that data collection is semi-concurrent with the patient's admission. One convenient location for this effort is in the ICU where most patients will presumptively be admitted. There are two important advantages to this approach:

Concurrent collection of data serves as a prompt to execute the next phase of the bundles. Therefore, some teams may choose to begin the collection in the ED to encourage compliance.

Concurrent collection of data allows teams to segment their population carefully so that they focus their initial efforts on patients for whom they are most likely to succeed. For example, an improvement team may wish initially to segment their patient population to only those patients on a hospitalist-driven service to overcome resistance from multiple private practitioners. Over time as the institutional culture has matured to understand and accept the protocol, the sphere of care can be expanded.

Retrospective Chart Review

Retrospective Chart Review is suitable for advanced improvement teams, or teams that have demonstrated success with concurrent data collection. Using this strategy, teams identify charts for monthly review with the assistance of the health information services department based upon discharge diagnoses. As the clinical protocol is introduced and established, the success or deficiency of the improvement effort should be reflected in the results of the retrospective chart review. Advantages to this approach include:

- Obtaining a more accurate reflection of the state of sepsis care at the institutional level by reviewing charts coded by reviewers unaware of the protocol.
- The ability to use sampling to analyze only a portion of the charts coded as above. If there are a large number of charts, teams can select a reasonable sample to analyze, eg., 20 charts per month.

Getting Started

Setting Aims

The first step in improving the care of patients with severe sepsis and septic shock is making a solid commitment to improving that care. This commitment includes a strong and well-worded aim statement that sets an aggressive global aim. It is critical that the overall aim has a measurable objective and a specified time frame.

The original aim of the Surviving Sepsis Campaign was "a 25 percent reduction in sepsis mortality within the next 5 years (2009)" [Dellinger RP, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004;32(3):858-873].

In addition to the global aim, the sepsis work is divided into segments, each having its own specific aim, all of which contribute to achieving the global aim.

Each institution committed to this aim should have senior leaders involved in setting the specific aims, to ensure that these aims are aligned with the organization's strategic goals. When senior leaders approve the aims, they should also make a commitment to giving the team whatever support is needed to achieve them.

The following are specific aims, adopted from the Surviving Sepsis Campaign guidelines, that support the global aim of improving septic patient mortality. These aims break the work into smaller, measurable, achievable chunks for teams to tackle. Several teams may be working on specific aims simultaneously, with all reporting to the leadership team.

Examples of Effective Aim Statements:

- Time from ED triage to presumptive diagnosis of severe sepsis is less than 2 hours
- Time from ED triage to all patients' meeting severe sepsis criteria having a serum lactate is less than 3 hours
- Time from ED triage to appropriate antibiotics given is less than 1 hour
- If hypotensive or if lactate > 4.0 mmol, immediate fluid resuscitation is started (at least 30 mL/kg normal saline or lactated ringers solution within 1 hour)
- If MAP < 65 mmHg and not responsive to adequate (at least 30 mL/kg) fluid resuscitation, vasopressors are started immediately
- If blood pressure or serum lactate not responsive to fluid, a central venous pressure monitor is instituted within the first 6 hours

Getting Started

How To Improve – Setting Aims

Setting Aims

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Surviving Sepsis Campaign

Creating A Protocol and Educating Users

The Model for Improvement

The Model for Improvement, developed by Associates in Process Improvement, is a simple yet powerful tool for accelerating improvement. The model is not meant to replace change models that organizations may already be using, but rather to accelerate improvement. This model has been used very successfully by hundreds of health care organizations in many countries to improve many different health care processes and outcomes.

References

Langley GL, Nolan KM, Nolan TW, Norman CL, Provost LP. *The Improvement Guide: A Practical Approach to Enhancing Organizational Performance.*

The Plan-Do-Study-Act cycle was developed by W. Edwards Deming (Deming WE. *The New Economics for Industry, Government, Education.*).

Creating A Protocol and Educating Users

About Measures and Data Collection

Process Measures

These measures tell you about how the process of change is unfolding as your improvement and clinical teams work to comply with the bundles. Are changes being translated into actual practice as you intended them to be? Process measures will allow you to identify whether you have created a reliable system that follows the timing, sequence, and goals mandated in the Sepsis Bundle.

Outcome Measures

These measures tell you whether changes are actually leading to the improvement you intended. The Surviving Sepsis Campaign suggests that you set as a goal a 25 percent reduction in overall mortality due to sepsis from the time you begin your work to your specified end date. Faithful implementation of the bundles, combined with an unwavering focus on the above process measures, will help your team achieve this goal at your institution.

Data Collection

A hospital's improvement team is likely to use one of two methods to collect data for the measures described above. Whichever method is selected, that approach should be maintained from month-to-month in order to assess the degree of improvement over time accurately.

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- Obtaining a more accurate reflection of the state of sepsis care at the institutional level by reviewing charts coded by reviewers unaware of the protocol.
- The ability to use sampling to analyze only a portion of the charts coded as above. If there are a large number of charts, teams can select a reasonable sample to analyze, eg., 20 charts per month.

Creating A Protocol and Educating Users

Testing Changes

The following are keys to successful implementation of protocols or care standards:

- When possible, base the protocol on firm evidence from the scientific literature.
- Design the protocol using a multidisciplinary team.
- Involve all stakeholders, using an information-feedback process to facilitate everyone's trust, confidence, and buy in.
- Test the protocol in the clinical environment using small Plan-Do-Study-Act (PDSA) cycles, modifying it as needed to make it unambiguous, safe, and acceptable to practitioners.
- Measure the protocol's impact on work processes and outcomes and feed back the information to the users.
- Test the protocol vigorously, using multiple small tests to reduce safety and compliance problems to a minimum before full implementation.

Using the Plan-Do-Study-Act (PDSA) Cycle

Example: Implement a process to ensure the early detection of severe sepsis.

Cycle 1: Set up a measuring system to collect data and use it in a retrospective chart review to establish how well we identify early patients with severe sepsis and septic shock within a 2-hour period.

Cycle 2: Develop a screening tool for the triage nurse and/or admitting clerk to use to identify potential severe sepsis and septic shock patients. Get buy-in from emergency room physicians.

Cycle 3: Have the emergency department admissions clerk and/or triage nurse prospectively flag potential severe sepsis and septic shock patients and measure any improvement in identifying these patients. Modify the screening tool as needed and retest.

Cycle 4: Establish a system to collect the physical and laboratory data automatically by protocol that is agreed upon by physicians, nurses, laboratory technicians, and unit clerks.

Cycle 5: Test the protocol on the next sepsis patient. Document problems. Modify the protocol as needed to eliminate ambiguity, work process objections, and non-protocol compliance.

Creating A Protocol and Educating Users

Cycle 6: Test the protocol on two or three more patients and measure the times until the information is available to make the diagnosis of severe sepsis or septic shock.

Cycle 7: Modify the screening and information gathering processes until the time to identification is less than 2 hours from emergency department admission.

Creating A Protocol and Educating Users

Enhancing Reliability

How will you know that your changes as intended are being faithfully implemented on the wards? Where are the bottlenecks? What steps can be taken to make the new clinical processes you have implemented function more reliably?

The Model for Improvement will be used in concert with Enhancing Reliability, an active approach to clinical process improvement that embeds steps to prevent, identify, and mitigate failures directly into the process itself. Reliability is a scientific method that evaluates, calculates, and improves the overall reliability of a complex system. It is a goal of consistently producing appropriate outcomes and preventing adverse events. The Enhancing Reliability methodology has three levels, as described below.

1. Stabilization (Prevention):

It is impossible to sustain improvement of a chaotic process. In general, any process that fails 1 time in 10 (functions less than 90 percent of the time as intended) is chaotic and unreliable. Efforts to stabilize the system prevent failures.

The first step in stabilizing a process is the establishment of a standardized approach. Therefore, a standardized protocol customized to your institution will be necessary to implement the sepsis bundle.

Next, measure the baseline reliability of the clinical processes you have created in your protocol. These are process measures. Each process being measured can be improved individually.

In the event that standardization is already in place but a particular process is functioning at less than 90 percent reliability, more work is necessary to stabilize that process. Some examples include building decision aids and reminders into the system and making the desired action the default strategy rather than an option.

2. Redundancy (Identification):

Once a process functions reliably 90 percent of the time or better, it is reasonable to pursue improvement in the next PDSA cycle toward the next threshold of reliability - 1 failure per every 100 opportunities, or 99 percent reliability. Redundancy of procedures helps to achieve this goal by identifying more instances when the process should be applied.

No effort to pursue this level of improvement in the course of a PDSA cycle should be undertaken for an unstable process. This is so because redundant efforts are, by definition, resource intensive. Implementing a redundant procedure in an unstable system is wasteful.

Effective redundancy steps function independently of the normal mechanism that triggers use of the clinical process. For example, the laboratory may have a procedure to contact physicians directly for routine labs that suggest acidosis, such as very low bicarbonate levels, which may indicate sepsis. A successful redundancy step may bring the number of missed cases below 10 percent and advance the process toward a 1 percent failure rate.

3. Failure Modes Analysis (Mitigation):

Once sufficient recovery of cases can be established to approach better than 90 percent reliability, further steps involve identifying the causes of failure and mitigating their effect.

Specific impediments to the functioning of reliable processes will be identified in the course of implementation. These represent failure modes that need to be eliminated or in some other way circumvented in subsequent PDSA cycles.

The particular impediment detected will drive your team to create a new level of customization to prevent further failures and to achieve increasingly reliable processes.

Severe Sepsis Bundles: Other Supportive Therapies

Reducing mortality due to severe sepsis requires an organized process that guarantees early recognition and consistent application of the evidence-based practices in the 2012 Surviving Sepsis Campaign guidelines.

The Severe Sepsis Bundles are a distillation of the concepts and recommendations found in the 2012 Surviving Sepsis Campaign guidelines. The bundles are designed to allow teams to follow the timing, sequence, and goals of the individual elements of care and collect the data to measure their improvement.

Individual hospitals should use the bundles to create customized protocols and pathways specific to their institutions. However, all of the elements in the bundles must be incorporated in those protocols. The addition of other strategies not found in the bundles is not recommended. The bundles will form the basis for the measurements that improvement teams will conduct to follow their progress as they make changes.

The Severe Sepsis Bundles are a series of evidence-based therapies that, when implemented together, will achieve better outcomes than if implemented individually.

Other selected therapies recommended by the 2012 Surviving Sepsis Campaign:

1. Blood Product Administration
2. Maintain Adequate Glycemic Control
3. Mechanical Ventilation of Sepsis-Induced Acute Respiratory Distress Syndrome (ARDS)
4. Sedation, Analgesia, and Neuromuscular Blockade
5. Deep Vein Thrombosis (DVT) and Peptic Ulcer Disease (PUD) Prophylaxis
6. Nutrition
7. Setting Goals of Care

The intention in applying the other selected therapies is to perform evidence-based treatments that will contribute to improving care of patients with severe sepsis and septic shock.

Surviving Sepsis Campaign

Severe Sepsis Bundles: Other Supportive Therapies

1. Blood Products Administration

Background

Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease, the 2012 Surviving Sepsis Campaign guidelines recommend that red blood cell transfusion occur when the hemoglobin concentration decreases to <7.0 g/dL to target a hemoglobin concentration of 7.0 to 9.0 g/dL in adults (Grade 1B).

Grading the Evidence

The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. "B" level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. The Grade 2 suggestion is a weaker recommendation for care based on a number of qualitative considerations. "D" level evidence generally reflects case series data or expert opinion.

The 2012 Surviving Sepsis Campaign guidelines suggest *not* using:

- Erythropoietin as a specific treatment of anemia associated with severe sepsis (Grade 1B)
- Fresh frozen plasma to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (Grade 2D)
- Antithrombin for the treatment of severe sepsis and septic shock (Grade 1B)

Although the optimum hemoglobin concentration for patients with severe sepsis has not been specifically investigated, the Transfusion Requirements in Critical Care trial suggested that a hemoglobin level of 7 to 9 g/dL, compared with 10 to 12 g/dL, was not associated with increased mortality in critically ill adults.[1] No significant differences in 30-day mortality rates were observed between treatment groups in the subgroup of patients with severe infections and septic shock (22.8 percent and 29.7 percent, respectively; p=0.36).

Although less applicable to septic patients, results of a randomized trial in patients undergoing cardiac surgery with cardiopulmonary bypass support a restrictive transfusion strategy using a threshold hematocrit of <24 percent (hemoglobin ≈8 g/dL) as equivalent to a transfusion threshold of hematocrit of <30 percent (hemoglobin ≈10 g/dL).[2] Red blood cell transfusion in septic patients increases oxygen delivery but does not usually increase oxygen consumption.[3-5] The transfusion threshold of 7 g/dL contrasts with early goal-directed resuscitation protocols that use a target hematocrit of 30 percent in patients with low $ScvO_2$ during the first 6 hours of resuscitation of septic shock.[6]

Severe Sepsis Bundles: Other Supportive Therapies

Administer Platelets Prophylactically

In patients with severe sepsis, administer platelets prophylactically when counts are $<10{,}000/mm^3$ ($10 \times 10^9/L$) in the absence of apparent bleeding. The 2012 Surviving Sepsis Campaign guidelines suggest prophylactic platelet transfusion when counts are $<20{,}000/mm^3$ ($20 \times 10^9/L$) if the patient has a significant risk of bleeding. Higher platelet counts of $\geq 50{,}000/mm^3$ ($50 \times 10^9/L$) are advised for active bleeding, surgery, or invasive procedures (Grade 2D).

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Content adapted extensively from:

- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*. 2013;41(2):580-637.

Severe Sepsis Bundles: Other Supportive Therapies

2. Maintain Adequate Glycemic Control

Background

Effective glucose control in the intensive care unit (ICU) has been shown to decrease morbidity across a large range of conditions and also to decrease mortality.

Hyperglycemia, caused by insulin resistance in the liver and muscle, is a common finding in ICU patients. Some have considered it to be an adaptive response, providing glucose for the brain, red blood cells, and wound healing. Traditionally, hyperglycemia has only been treated when blood glucose increases to >215 mg/dL (>12 mmol/L). Conventional wisdom in the ICU has been that some degree of hyperglycemia is beneficial and that hypoglycemia is dangerous and should be avoided. The extent of appropriate glucose control has been evaluated in recent years.

Initial Investigations: Intensive Insulin Therapy

An initial investigation by Van den Berghe and colleagues suggested that controlling blood glucose levels by intensive insulin therapy decreased mortality and morbidity in surgical critically ill patients.[2] The trial was a large single-center study of postoperative surgical patients. The design employed a continuous infusion of insulin to maintain glucose between 80 and 110 mg/dL (4.4–6.1 mmol/L). Exogenous glucose was begun simultaneously with insulin, with frequent monitoring of glucose (every 1 hour) and intensity of monitoring was greatest at the time of initiation of insulin. This protocol called for implementing a strategy to maintain normoglycemia with an insulin infusion while providing for normal intake of glucose (9 g/hour) and calories (19 kcal•kg^{-1}•day^{-1}).

A total of 35 of 765 patients (4.6 percent) in the intensive insulin group died in the ICU in Van den Berghe et al. study, compared with 63 patients (8.0 percent) in the conventional therapy group.

Intensive insulin therapy halved the prevalence of:

- Bloodstream infections
- Prolonged inflammation
- Acute renal failure (ARF) requiring dialysis or hemofiltration
- Critical illness polyneuropathy
- Transfusion requirements

Patients receiving intensive insulin therapy were also less likely to require prolonged mechanical ventilation and intensive care.

Rigorous insulin treatment reduced the number of deaths from multi-organ failure with sepsis, regardless of whether there was a history of diabetes or hyperglycemia.

Surgical vs. Medical Patients

The same protocol used in the first Van den Berghe et al. trial for surgical patients was subsequently tested in medical patients.[3]

Patients who were considered to need intensive care for at least three days were enrolled in a prospective, randomized, single-center, controlled study. On admission, patients were randomly assigned to strict normalization of blood glucose levels (80 to 110 mg/dL [4.4 to 6.1 mmol/L]) with the use of insulin infusion or conventional therapy (i.e., insulin administered when the blood glucose level exceeded 215 mg/dL [12 mmol/L], with the infusion tapered when the level fell below 180 mg/dL [10 mmol/L]).

Intensive insulin therapy reduced blood glucose levels but did not significantly reduce in-hospital mortality (40.0 percent in the conventional treatment group vs. 37.3 percent in the intensive treatment group, p=0.33). However, morbidity was significantly reduced by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital.

Although length of stay in the ICU could not be predicted on admission, among 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapy. In contrast, among 767 patients who stayed in the ICU for three or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5 to 43.0 percent (p=0.009) and morbidity was also reduced.

The authors concluded that intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU. Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy.

Meta-Analyses and Severe Sepsis Specific Inquiries

A meta-analysis of 35 trials on insulin therapy in critically ill patients, including 12 randomized trials, demonstrated a 15 percent reduction in short-term mortality (relative risk 0.85, 95 percent confidence interval 0.75-0.97) but did not include any studies of insulin therapy in medical ICUs.[4]

A multi-center randomized control trial (VISEP) focusing on patients with severe sepsis failed to demonstrate improvement in mortality.[5] In VISEP, the investigators randomly assigned patients with severe sepsis to receive either intensive insulin therapy to maintain euglycemia or conventional insulin therapy. Of the 537 patients who could be evaluated, the mean morning

blood glucose level was lower in the intensive therapy group (112 mg/dL [6.2 mmol/L]) than in the conventional therapy group (151 mg/dL [8.4 mmol/L], p<0.001). However, at 28 days, there was no significant difference between the two groups in the rate of death or the mean score for organ failure.

Further, the VISEP investigators found that the rate of severe hypoglycemia (glucose level ≤40 mg/dL [2.2 mmol/L]) was higher in the intensive therapy group than in the conventional therapy group (17.0 percent vs. 4.1 percent, p<0.001), as was the rate of serious adverse events (10.9 percent vs. 5.2 percent, p=0.01). The trial was stopped earlier than planned for these reasons.

NICE-SUGAR Study

Based on the foregoing studies, most clinicians believed that there was a benefit to glucose control in terms of mortality and morbidity. However, the optimal target range for blood glucose in critically ill patients remained unclear.

The NICE-SUGAR study investigators [1] chose to evaluate whether there was a difference in mortality between subjects randomly assigned to either intensive glucose control, with a target blood glucose range of 81 to 108 mg/dL (4.5 to 6.0 mmol/L), or conventional glucose control, with a target of 180 mg or less per deciliter (10.0 mmol or less per liter). To be considered, patients were expected to require treatment in the ICU on 3 or more consecutive days.

Of the 6,104 patients who underwent randomization, 3,054 were assigned to undergo intensive control and 3,050 to undergo conventional control. A total of 829 patients (27.5 percent) in the intensive-control group and 751 (24.9 percent) in the conventional-control group died. Thus, the odds of dying with intensive control were 1.14 times greater than with conventional control (p=0.02). In addition, severe hypoglycemia (blood glucose level of 40 mg/dL [2.2 mmol/L]) was reported in 206 of 3,016 patients (6.8 percent) in the intensive-control group and in 15 of 3,014 patients (0.5 percent) in the conventional-control group (p<0.001). Thus, the incidence of hypoglycemia was lower in the conventional group.

With regard to morbidity and length of stay, NICE-SUGAR demonstrated that there was no significant difference between the two treatment groups in the median number of days in the ICU or hospital, or the median number of days of mechanical ventilation or renal-replacement therapy.

The NICE-SUGAR investigators concluded that intensive glucose control increased mortality among adults in the ICU and that a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.

Severe Sepsis Bundles: Other Supportive Therapies

Grading the Evidence

The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. “B” quality evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” quality evidence reflects well-done observational or cohort studies with controls. “D” quality evidence generally reflects downgraded controlled trials or expert opinion based on other experience.

The Surviving Sepsis Campaign formerly recommended in the 2008 Surviving Sepsis Campaign Guidelines that, following initial stabilization, patients with severe sepsis and hyperglycemia who are admitted to the ICU receive IV insulin therapy to reduce blood glucose levels (Grade 1B).

The Surviving Sepsis Campaign reviewed its specific recommendations and ranges for glucose control after publication of NICE-SUGAR and issued a statement on glucose control ranges for severely septic patients in June 2009:

> “There is insufficient information from randomized controlled trials to determine the optimal target range of blood glucose in the severely septic patient.[6] The NICE-SUGAR trial is the largest most compelling study to date on glucose control in ICU patients given its inclusion of multiple ICUs and hospitals, and a more general patient population. [1] Based on the results of this trial, we recommend against intravenous insulin therapy titrated to keep blood glucose in the normal range (80–110 mg/dL) in patients with severe sepsis. It is clear that attempts to normalize blood glucose with IV insulin during critical illness results in higher rates of hypoglycemia.[6-8] Until additional information is available, teams seeking to implement glucose control should consider initiating insulin therapy when blood glucose levels exceed 180 mg/dL with a goal blood glucose approximating 150 mg/dL as was observed in the beneficial arm of the NICE-SUGAR trial.”

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Severe Sepsis Bundles: Other Supportive Therapies

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TIPS

1. Create a standardized protocol that provides for continuous intravenous insulin infusion and nutritional support for cases of severe sepsis and septic shock.
2. Allow the protocol to be adjusted automatically by the nursing staff to accomplish tight glucose control safely with a reliable bedside presence.
3. Administer glucose or enteral feedings while the insulin infusion is active, with frequent glucose monitoring by finger stick.
4. Adopt a specific treatment plan for hypoglycemia.
5. Educate the nursing staff about the benefits of tight glucose control and relieve the fear of increasing the incidence of hypoglycemia. Tight glycemic control in patients can be so foreign to routine clinical practice that fear can defeat the success of the project.
6. Work closely with nursing in creating the protocols to make sure the increased burden of frequent glucose checks can be integrated into their workflow.

Severe Sepsis Bundles: Other Supportive Therapies

7. Setting Goals of Care

- Discuss goals of care and prognosis with patients and families (Grade 1B).
- Incorporate goals into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (Grade 1B).
- Address goals of care as early as feasible, but no later than within 72 hours of ICU admission (Grade 2C).

The majority of ICU patients receive full support with aggressive, life-sustaining treatments. Many patients with multiple organ system failure or severe neurologic injuries will not survive or will have a poor quality of life. Decisions to provide less-aggressive life-sustaining treatments or to withdraw life-sustaining treatments in these patients may be in the patient's best interest and may be what patients and their families desire.[1] Physicians have different end-of-life practices based on their region of practice, culture, and religion.[1]

Although the outcome of intensive care treatment in critically ill patients may be difficult to prognosticate accurately, establishing realistic treatment goals is important in promoting patient-centered care in the ICU.[2] Models for structuring initiatives to enhance care in the ICU highlight the importance of incorporating goals of care along with the prognosis into treatment plans.[3] Additionally, discussing the prognosis for achieving the goals of care and level of certainty of prognosis has been identified as an important component of surrogate decision making in the ICU.[4, 5] However, variations exist in the use of advanced care planning and integration of palliative and end-of-life care in the ICU, which can lead to conflicts that may threaten overall quality of care.[6, 7]

The use of proactive family care conferences to identify advanced directives and treatment goals within 72 hours of ICU admission promotes communication and understanding between the patient's family and the care team; improves family satisfaction; decreases stress, anxiety, and depression in surviv¬ing relatives; facilitates end-of-life decision making; and shortens length of stay for patients who die in the ICU.[8–12] Clinical practice guidelines for support of the ICU patient and family promote: early and repeated care conferencing to reduce family stress and improve consistency in communication; open flexible visitation; family presence during clinical rounds and resuscitation; and attention to cultural and spiritual support.[13] Additionally, the integration of advanced care planning and palliative care focused on pain management, symptom control, and family support has been shown to improve symptom management and patient comfort, and to improve family communication.[3, 9, 14, 15]

Severe Sepsis Bundles: Other Supportive Therapies

Grading the Evidence [See Ranking the Evidence]

The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. The Grade 2 suggestions are weaker recommendations for care based on a number of qualitative considerations. "B" level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. "C" level evidence reflects well-done observational or cohort studies with controls. "D" level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

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Severe Sepsis Bundles: Other Supportive Therapies

4. Sedation, Analgesia, and Neuromuscular Blockade

- Minimize continuous or intermittent sedation in mechanically ventilated sepsis patients, targeting specific titration endpoints (Grade 1B).
- When using neuromuscular blocking agents (NMBAs):
  - Avoid NMBAs if possible in the septic patient *without* ARDS due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with train-of-four monitoring of the depth of blockade should be used (Grade 1C).
  - Apply a short course of a NMBA (≤48 hours) for patients with early, severe sepsis-induced ARDS (Grade 2C).

A growing body of evidence indicates that limiting the use of sedation in critically ill ventilated patients can reduce the duration of mechanical ventilation and ICU and hospital lengths of stay.[1-3] While studies limiting sedation have been performed in a wide range of critically ill patients, there is little reason to assume that septic patients will not derive benefit from this approach.[3] The use of protocols for sedation is one method to limit sedation use, and a randomized, controlled clinical trial found that protocolized sedation compared with usual care reduced duration of mechanical ventilation, lengths of stay, and tracheostomy rates.[3] Avoidance of sedation is another strategy.

Grading the Evidence

The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. The Grade 2 suggestions are weaker recommendations for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

Severe Sepsis Bundles: Other Supportive Therapies

Decreasing Length of Stay on Ventilation

A recent observational study of 250 critically ill patients suggests that deep sedation is common in mechanically ventilated patients.[4] A randomized, controlled clinical trial found that patients treated with intravenous morphine boluses preferentially, with short-term propofol infusions for rescue therapy only, had significantly more days without ventilation, with shorter stays in the ICU and hospital, than patients who received propofol infusions in addition to bolus morphine.[5] However, agitated delirium was more frequently detected in the intervention group.

Intermittent vs. Continuous Sedation

Although not specifically studied in patients with sepsis, the administration of intermittent sedation, daily sedative interruption, and systematic titration to a predefined endpoint have been demonstrated to decrease the duration of mechanical ventilation.[3, 6-8] Patients receiving neuromuscular blocking agents (NMBAs) must be individually assessed regarding discontinuation of sedative drugs because the neuromuscular blockade must first be reversed. The use of intermittent vs. continuous methods for the delivery of sedation in critically ill patients has been examined in an observational study of mechanically ventilated patients that showed that patients receiving continuous sedation had significantly longer durations of mechanical ventilation and ICU and hospital lengths of stay.[8]

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Severe Sepsis Bundles: Other Supportive Therapies

3. Mechanical Ventilation of Sepsis-Induced Acute Respiratory Distress Syndrome

The 2012 Surviving Sepsis Campaign guidelines recommend:

- Target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced acute respiratory distress syndrome (ARDS) (Grade 1A, vs 12 mL/kg).
- Measure plateau pressures in patients with ARDS and that the initial upper limit goal for plateau pressures in a passively inflated lung be ≤30 cm H_2O (Grade 1B).
- Apply positive end-expiratory pressure (PEEP) to avoid alveolar collapse at end expiration (atelectotrauma) (Grade 1B). Apply strategies based on higher rather than lower levels of PEEP for patients with sepsis-induced moderate to severe ARDS (Grade 2C).
- Apply recruitment maneuvers in sepsis patients with severe refractory hypoxemia due to ARDS (Grade 2C).
- Maintain prone positioning in sepsis-induced ARDS patients with a PaO_2/FIO_2 ratio ≤100 mm Hg in facilities that have experience with such practices (Grade 2B).
- Elevate head of the bed between 30 and 45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (VAP) (Grade 1B).
- Use noninvasive mask ventilation (NIV) in that minority of sepsis-induced ARDS patients in whom the benefits of NIV have been carefully considered and are thought to outweigh the risks (Grade 2B).
- Mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria: a) arousable; b) hemodynamically stable (without vasopressor agents); c) no new potentially serious conditions; d) low ventilatory and end-expiratory pressure requirements; and e) low FIO_2 requirements which can be safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, extubation should be considered (Grade 1A).
- Use conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (Grade 1C).

Background

Patients with sepsis are at increased risk for developing acute respiratory failure, and most patients with severe sepsis and septic shock will require endotracheal intubation and

mechanical ventilation. Nearly 50 percent of patients with severe sepsis will develop acute respiratory distress syndrome (ARDS). Patients with lung injury will have bilateral patchy infiltrates on chest x-ray, low PaO_2:FIO_2 ratios (less than 300 for mild or less than 200 for moderate ARDS), and pulmonary capillary wedge pressure less than 18 cm H_20, although this last measure is often clinically not available.

High tidal volumes that are coupled with high plateau pressures should be avoided in ARDS. Clinicians should use as a starting point a reduction in tidal volumes over 1 to 2 hours to a "low" tidal volume (6 mL•kg^{-1}•lean body $weight^{-1}$) as a goal in conjunction with the goal of maintaining end-inspiratory plateau pressures of <30 cm H_2O.

Mortality Reduction

The largest trial of a volume- and pressure-limited strategy showed a 9 percent decrease of all-cause mortality in patients ventilated with tidal volumes of 6 mL/kg of estimated lean body weight (as opposed to 12 mL/kg) while aiming for a plateau pressure of <30 cm H_2O.[1]

The formal ARDSnet protocol for mechanical ventilation is encouraged for use in septic patients.

Permissive Hypercapnia

Hypercapnia (allowing $PaCO_2$ to increase above normal, so-called permissive hypercapnia) can be tolerated in patients with ARDS if required to minimize plateau pressures and tidal volumes.

Although an acutely elevated PCO_2 may have physiologic consequences that include vasodilatation and increased heart rate, blood pressure, and cardiac output, allowing modest hypercapnia in conjunction with limiting tidal volume and minute ventilation has been demonstrated to be safe in small, nonrandomized series.[2, 3] No upper limit for PCO_2 has been established. Some authorities recommend maintaining pH at >7.20–7.25, but this has not been prospectively established. The use of hypercarbia is limited in patients with pre-existing metabolic acidosis and is contraindicated in patients with increased intracranial pressure.[4] Sodium bicarbonate infusion may be considered in select patients to facilitate use of permissive hypercarbia.[1] Experimental models suggest that respiratory acidosis may confer protection against various forms of inflammatory injury.[6]

Positive End-Expiratory Pressure (PEEP)

Provide adequate supplemental oxygen to maintain a pulse oximetric saturation of ≥90 percent. A minimum amount of PEEP should be set to prevent lung collapse at end expiration. Setting PEEP based on severity of oxygenation deficit and guided by the FIO_2 required to maintain adequate oxygenation is one acceptable approach.

For patients supported by mechanical ventilation or who are appropriate candidates for a pressurized face mask, PEEP or continuous positive airway pressure may be used to increase mean and end-expiratory airway pressures, allowing the reduction of the oxygen concentrations below potentially toxic levels (FIO_2 <0.60).

Severe Sepsis Bundles: Other Supportive Therapies

Grading the Evidence

The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. The Grade 2 suggestions are weaker recommendations for care based on a number of qualitative considerations. "B" level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. "C" level evidence reflects well-done observational or cohort studies with controls. "D" level evidence generally reflects downgraded controlled trials or expert opinion based on other evidence.

- The 2012 Surviving Sepsis Campaign Guidelines recommend that clinicians target a tidal volume of 6 ml/kg (predicted) body weight in patients with ARDS (Grade 1A, vs 12 ml/kg). The Campaign also recommends that plateau pressures be measured in patients with ARDS and that the initial upper limit goal for plateau pressures in a passively inflated patient be ≤30 cm H_2O (Grade 1B).

  Over the past 10 years, several multi-center randomized trials have been performed to evaluate the effects of limiting inspiratory pressure through moderation of tidal volume.[1, 6-9] These studies showed differing results that may have been caused by differences between airway pressures in the treatment and control groups.[1, 10] The largest trial of a volume- and pressure-limited strategy showed a 9 percent decrease of all-cause mortality in patients with ARDS ventilated with tidal volumes of 6 mL/kg of predicted body weight (PBW), as opposed to 12 mL/kg, and aiming for a plateau pressure ≤30 cm H_2O.[1] The use of lung protective strategies for patients with ARDS is supported by clinical trials and has been widely accepted, but the precise choice of tidal volume for an individual patient with ARDS may require adjustment for such factors as the plateau pressure achieved, the level of positive end-expiratory pressure (PEEP) chosen, the compliance of the thoracoabdominal compartment and the vigor of the patient's breathing effort. Some clinicians believe it may be safe to ventilate with tidal volumes higher than 6 ml/kg PBW as long as the plateau pressure can be maintained ≤30cm H_2O.[11, 12]

  The validity of this ceiling value will depend on breathing effort, as those who are actively inspiring generate higher trans-alveolar pressures for a given plateau pressure than those who are passively inflated. Conversely, patients with very stiff chest walls may require plateau pressures >30 cm H_2O to meet vital clinical objectives. One retrospective study suggested that tidal volumes be lowered even with plateau pressures ≤30 cm H_2O.[13] An additional observational study suggested that knowledge of the plateau pressures was associated with lower plateau pressures; however, in this trial, plateau pressure was not independently associated with mortality rates across a wide range of plateau pressures that bracketed 30 cm H_2O.[14] The largest clinical trial employing a lung protective strategy coupled limited pressure with limited tidal volumes to demonstrate a mortality benefit.[1]

Severe Sepsis Bundles: Other Supportive Therapies

High tidal volumes that are coupled with high plateau pressures should be avoided in ARDS. Clinicians should use as a starting point the objective of reducing tidal volumes over 1 to 2 hours from its initial value toward the goal of a "low" tidal volume (≈6 mL per kilogram of predicted body weight) achieved in conjunction with an end-inspiratory plateau pressure less than or equal to 30 cm H_2O. If plateau pressure remains >30 after reduction of tidal volume to 6 ml/kg/PBW, tidal volume should be reduced further to as low as 4 ml/kg/PBW.

No single mode of ventilation (pressure control, volume control, airway pressure release ventilation, high frequency ventilation, etc.) has been consistently shown advantageous when compared with any other that respects the same principles of lung protection.

Allowing $PaCO_2$ to increase above its pre-morbid baseline, so-called permissive hypercapnia, may be allowed in patients with ARDS if needed to minimize plateau pressures and tidal volumes.

An acutely elevated $PaCO_2$ may have physiologic consequences that include vasodilation as well as an increased heart rate, blood pressure, and cardiac output. Allowing modest hypercapnia in conjunction with limiting tidal volume and minute ventilation has been demonstrated to be safe in small, nonrandomized series.[2, 3] Patients treated in larger trials that have the goal of limiting tidal volumes and airway pressures have demonstrated improved outcomes, but permissive hypercapnia was not a primary treatment goal in these studies.[1] The use of hypercapnia is limited in patients with preexisting metabolic acidosis and is contraindicated in patients with increased intracranial pressure. Sodium bicarbonate or tromethamine infusion may be considered in selected patients to facilitate use of permissive hypercarbia.[15, 16]

- The Surviving Sepsis Campaign recommends that positive end-expiratory pressure (PEEP) be set so as to avoid extensive lung collapse at end-expiration (Grade 1B).

  Raising PEEP in ARDS keeps lung units open to participate in gas exchange. This will increase PaO_2 when PEEP is applied through an endotracheal tube or a face mask.[17-19] In animal experiments, avoidance of end-expiratory alveolar collapse helps minimize ventilator-induced lung injury (VILI) when relatively high plateau pressures are in use. One large multi-center trial of the protocol-driven use of higher PEEP in conjunction with low tidal volumes did not show benefit or harm when compared to lower PEEP levels.[20] Neither the control nor experimental group in that study, however, was clearly exposed to hazardous plateau pressures. A recent multi-center Spanish trial compared a high PEEP, low-moderate tidal volume approach to one that used conventional tidal volumes and the least PEEP achieving adequate oxygenation. A marked survival advantage favored the former approach in high acuity patients with ARDS.[21] Two options are recommended for PEEP titration. One option is to titrate PEEP (and tidal volume) according to bedside measurements of thoracopulmonary compliance with the objective of obtaining the best compliance, reflecting a favorable balance of lung recruitment and overdistention.[22] The second option is to

titrate PEEP based on severity of oxygenation deficit and guided by the FIO_2 required to maintain adequate oxygenation.[1] Whichever the indicator — compliance or oxygenation — recruiting maneuvers are reasonable to employ in the process of PEEP selection. Blood pressure and oxygenation should be monitored and recruitment discontinued if deterioration in these parameters is observed. A PEEP >5 cm H_20 is usually required to avoid lung collapse.[23]

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TIPS

1. Create a standardized protocol that prompts users to use tidal volumes <6 ml/kg IBW and to maintain plateau pressures <30 cm H_20.
2. Make execution of an ARDSnet-like protocol the primary responsibility of the respiratory therapists, if possible.
3. Have stakeholders work in concert with the respiratory therapy department to create and deploy a clinical protocol for ARDS ventilation.
4. Avoid synchronized intermittent mandatory ventilation (SIMV) during the acute phase of illness. Instead, use mandatory modes of ventilation such as assist control (ACV) or pressure control (PCV) to prevent spontaneously large tidal volumes.
5. Do not allow peak pressures to govern ventilator management. The key value is the plateau pressure.
6. The weight for determining the Vt should be the ideal body weight. The ideal body weight is calculated from the patient's height.
7. Do not worry about the pCO_2 unless the pH is less than a threshold the clinical team cannot accept. Some intensivists are comfortable with pH as low as 7.10. Most clinicians like to see pH greater than 7.21. Some more conservative clinicians use pH in the range of 7.25 or 7.30. Where renal dysfunction prevents compensation, bicarbonate or tromethamine can be used to help maintain the pH. However, constant bicarbonate infusions can also contribute to CO_2 production. Tromethamine does not have this side effect.

3-Hour Bundle

1. Measure Lactate Level

Background

Hyperlactatemia is typically present in patients with severe sepsis or septic shock and may be secondary to anaerobic metabolism due to hypoperfusion or other complex factors. 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 a lactate level is essential to identifying tissue hypoperfusion in patients who are not yet hypotensive but who are at risk for septic shock.

Limitations

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. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation.

Implications

Given the high risk for septic shock, all patients with elevated lactate >4 mmol/L (36 mg/dL) enter the early goal-directed therapy portion of the 6-Hour Septic Shock Bundle, regardless of blood pressure. Mortality is high in septic patients with both hypotension and lactate ≥4 mmol/L (46.1 percent). Mortality is also increased in severely septic patients with hypotension alone (36.7 percent) and lactate ≥4 mmol/L alone (30 percent).[5] This approach is consistent with the trial that established the value of early goal-directed therapies.[6]

Turnaround Time

Lactate levels 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 satisfies this requirement. However, any means of rapid turnaround time is acceptable. In some cases, it will be essential for hospitals to invest in adequate equipment in order to meet present standards of care for septic patients.

The technique of obtaining 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, which will likely hinder proper clinical care.

Arterial vs. Venous Lactate

The question has been raised several times as to whether an arterial or venous lactate sample is required. While there is no consensus of settled literature on this question, an elevated lactate of any variety is typically abnormal and must be explained. Either collection is appropriate for bundle compliance. Lactate elevations may be influenced by other conditions such as a variety of medications, hepatic insufficiency, or hyperlactatemia due to primarily cardiac causes of hypoperfusion.

Grading the Evidence

- The use of lactate as a method to detect severe sepsis and septic shock and as a rationale for further therapies was evaluated as part of the larger recommendation on initial resuscitation in the 2012 Surviving Sepsis Campaign Guidelines. There, the guidelines committee recommended the protocolized, quantitative resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration equal to or greater than 4 mmol/L).

Evidence Grade 1C: This is a strong recommendation for care based on a number of qualitative considerations. "C" level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies.

- The strategy of clearing lactate to normal values was also assessed in the 2012 Surviving Sepsis Campaign Guidelines. The Campaign suggests targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.

Evidence Grade 2C: This is a suggestion for care based on a number of qualitative considerations. "C" level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies [7].

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- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*. 2013 Feb;41(2):580-637.

TIPS

1. 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.
2. Create a standardized protocol to manage severe sepsis that includes measurement of lactate.
3. Include a prompt on arterial blood gas requisitions or physician order entry to prompt users to order lactate for suspected severe sepsis.

3-Hour Bundle

2. Obtain Blood Cultures Prior to Administration of Antibiotics

Related Measures

Timing of Blood Cultures

Background

The incidence of sepsis and bacteremia in critically ill patients has been increasing in the past two decades.[8,9] Thirty percent to 50 percent of patients presenting with a clinical syndrome of severe sepsis or shock have positive blood cultures. Therefore, blood should be obtained for culture in any critically ill septic patient.

Collecting blood cultures prior to antibiotic administration offers the best hope of identifying the organism that caused severe sepsis in an individual patient. Failure to check blood cultures prior to antibiotic infusion will perhaps affect the growth of any blood borne bacteria and prevent a culture from becoming positive later.

Collection Strategy

Two or more blood cultures are recommended with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently inserted (<48 hours).[1,2] In patients with suspected catheter-related infection, a pair of blood cultures obtained through the catheter hub and a peripheral site should be obtained simultaneously. Cultures of other sites (preferably quantitative, where appropriate), such as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection should also be obtained before antimicrobial therapy.[2] If the same organism is recovered from both cultures, the likelihood that the organism is causing the severe sepsis is enhanced. In addition, if the culture drawn through the vascular access device is positive much earlier than the peripheral blood culture (i.e., >2 hours earlier), it may offer support that the vascular access device is the source of the infection.[3] Volume of blood may also be important.[4]

Indications

Fever, chills, hypothermia, leukocytosis, left shift of neutrophils, neutropenia, and the development of otherwise unexplained organ dysfunction (e.g., renal failure or signs of hemodynamic compromise) are specific indications for obtaining blood for culture. Blood cultures should be taken as soon as possible after the onset of fever or chills.

While it remains difficult to predict bacteremia in patients with sepsis[5], a number of clinical and laboratory parameters are independently correlated with the presence of bacteria in the blood of patients when infection is suspected. These include chills, hypoalbuminemia, the development of renal failure, and a diagnosis of urinary tract infection[5,6]; other criteria are new fever, hypothermia, leukocytosis and left shift of neutrophils, neutropenia, and signs of hemodynamic compromise.[7] Peaking fever appears to be more sensitive than leukocytosis to predict bacteremia[8]; however, fever and low-grade bacteremia can be continuous, such as in endocarditis.

Grading the Evidence

The 2012 Surviving Sepsis Campaign Guidelines recommend obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay in antibiotic administration.

Evidence Grade 1C: This is a strong recommendation for care based on a number of qualitative considerations. The quality of the evidence generally derives from well-done observational or cohort studies with controls.

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TIPS

1. Create a standardized protocol to manage severe sepsis that includes reminders to draw blood cultures before administering antibiotics.
2. Place prompts in locations near antibiotic storage querying staff regarding whether blood cultures have been drawn.
3. Store first dose antibiotics in automated dispensing system on unit.

3-Hour Bundle

3. Administer Broad Spectrum Antibiotics

Related Measures

Timing of Antibiotics

Background

Once severe sepsis is identified, antibiotics must be started rapidly to treat the underlying infection. Although early antibiotic administration seems to be an intuitive approach, administration of effective therapies is often delayed. Evidence supports that for patients with septic shock, the duration of hypotension prior the administration of antibiotics is a critical determinant in the survival of septic shock.[1]

The balance of evidence unwaveringly suggests that early administration of appropriate antibiotics reduces mortality in patients with Gram-positive and Gram-negative bacteremias. Some of the evidence supporting early administration is based on the assumption that patients who fail to receive appropriate antibiotics essentially represent a set of patients for whom delay has occurred in antibiotic delivery. Several studies have confirmed the mortality benefit associated with appropriate antimicrobials in patients with severe infections due to Gram-negative and Gram-positive bacteria.[2-4]

In addition, the major sources of infection in severe sepsis or shock are pneumonia and intra-abdominal infections [5,6] and other sources generally account for <5 percent of cases. The prevalence of pneumonia as a cause of sepsis lends support to the case for treating severe sepsis with early antibiotic administration. In a study of ventilator-acquired pneumonia, patients with significant organ dysfunction (required criteria for severe sepsis) who received antibiotics later had far greater ICU mortality: 37 percent vs. 7 percent (p=0.006); hospital mortality: 44 percent vs. 15 percent (p=0.01).[7]

Choice of Antibiotics

The choice of antibiotics should be guided by the susceptibility of likely pathogens in the community and the hospital, as well as any specific knowledge about the patient, including drug intolerance, underlying disease, the clinical syndrome. The regimen should cover all likely pathogens since there is little margin for error in critically ill patients. There is ample evidence that failure to initiate appropriate therapy promptly (i.e., therapy that is active against the causative pathogen) has adverse consequences on outcome.[2-4]

Although restricting the use of antibiotics, and particularly broad spectrum antibiotics, is important for limiting superinfection and for decreasing the development of antibiotic resistant pathogens, patients with severe sepsis or septic shock warrant broad spectrum therapy until the causative organism and its antibiotic susceptibilities are defined.

Surviving Sepsis Campaign

Availability

Establishing a supply of premixed antibiotics in an emergency department or critical care unit for such urgent situations is an appropriate strategy for enhancing the likelihood that antimicrobial agents will be infused promptly. Staff should be cognizant that some agents require more lengthy infusion time, whereas others can be rapidly infused or even administered as a bolus.

48- to 72-Hour Re-evaluation

Once the causative agent and antibiotic susceptibilities have been identified, restriction of the number of antibiotics and narrowing the spectrum of antimicrobial therapy is an important and responsible strategy for minimizing the development of resistant pathogens and for containing costs.

The antimicrobial regimen should always be reassessed after 48 to 72 hours on the basis of microbiological and clinical data, with the aim of using a narrow-spectrum antibiotic to prevent the development of resistance, to reduce toxicity, and to reduce costs. Empiric combination therapy should not be administered for more than 3 to 5 days.[12-16] Once a causative pathogen is identified, there is no evidence that combination therapy is more effective than monotherapy. The duration of therapy should typically be 7 to 10 days and guided by clinical response. Longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia.[17]

Dosing

All patients should receive a full loading dose of each antimicrobial. However, patients with sepsis or septic shock often have abnormal renal or hepatic function and may have abnormal volumes of distribution due to aggressive fluid resuscitation. The ICU pharmacist should be consulted to ensure that serum concentrations are attained that maximize efficacy and minimize toxicity.[8-11]

Grading the Evidence

The Grade 1 recommendations below reflect strong evidence for care based on a number of qualitative considerations. The Grade 2 suggestions below are weaker recommendations for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects case series data or expert opinion. “UG” level evidence is ungraded.

- Administer effective intravenous antimicrobials within the first hour of recognition of septic shock (Grade 1B) and severe sepsis without septic shock (Grade 1C) as the goal of therapy.
- Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (Grade 1B) should be employed.
- Antimicrobial regimen should be reassessed daily for potential deescalation (Grade 1B).

- Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (Grade 2C).
- Combination empirical therapy for neutropenic patients with severe sepsis (Grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as Acinetobacter and Pseudomonas spp. (Grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for P. aeruginosa bacteremia (Grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic Streptococcus pneumoniae infections (Grade 2B).
- Empiric combination therapy should not be administered for more than 3 to 5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (Grade 2B).
- Duration of therapy is typically 7 to 10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia (Grade 2C).
- Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (Grade 2C).
- Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

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TIPS

1. Establish a standardized clinical protocol that includes the empiric administration of antibiotics in severe sepsis within 1 hour of presentation.
2. Establish a pre-mixed quantity of broad spectrum antibiotics available in the emergency department and ICU, in order to avoid delays involving pharmacy acquisition of the antibiotic.
3. Infuse antibiotics through multiple lines as available in order to speed delivery of agents.
4. Cover both Gram-positive and Gram-negative organisms.
5. Consider specific knowledge about the patient's past organism burden, if available (including fungal infection); the setting from which the patient arrived in the emergency department (e.g., another institution that may harbor resistant organism); and community and hospital resistance patterns in making choices.

3-Hour Bundle

4. Administer 30 mL/kg Crystalloid for Hypotension or Lactate ≥4 mmol/L

In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or lactate ≥4 mmol/L (36 mg/dL):

- Measure central venous pressure (CVP)*
- Measure central venous oxygen saturation ($ScvO_2$)*

**Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $ScvO_2$ of ≥70 percent, and lactate normalization.*

Background

Patients with severe sepsis and septic shock may experience ineffective arterial circulation due to the vasodilatation associated with infection or impaired cardiac output. Poorly perfused tissue beds result in global tissue hypoxia, which is often found in association with an elevated serum lactate level. A serum lactate value greater than 4 mmol/L (36 mg/dL) is correlated with increased severity of illness and poorer outcomes even if hypotension is not yet present. As such, patients who are hypotensive or have a lactate greater than 4 mmol/L (36 mg/dL) require intravenous fluids to expand their circulating volume and effectively restore perfusion pressure.

Initial Fluid Administration

The Severe Sepsis 3-Hour Resuscitation Bundle calls for an initial administration of 30 mL/kg of crystalloid as a fluid challenge in cases of suspected hypovolemia or actual cases of serum lactate greater than 4 mmol/L (36 mg/dL).

Fluid resuscitation should be commenced as early as possible in the course of septic shock (even before intensive care unit admission). Requirements for fluid infusion are not easily determined so that repeated fluid challenges should be performed.

The targets for quantitative resuscitation provided in the guidelines are CVP of ≥8 mm Hg, $ScvO_2$ of ≥70 percent, and normalization of lactate.

Fluid Challenge vs. Increase in Maintenance Fluids

An increase in maintenance fluid administration must be distinguished from fluid challenge. Fluid challenge is a term used to describe the initial volume expansion period in which the response of the patient to fluid administration is carefully evaluated. During this process, large amounts of fluids may be administered over a short period of time under close monitoring to evaluate the patient's response.

Fluid challenges require the definition of four components: 1) the type of fluid to be administered; 2) the rate of fluid infusion (e.g., 500 mL to 1,000 mL over 30 minutes); 3) the end points (e.g., mean arterial pressure of >65 mm Hg, heart rate of <110 beats per minute); and 4) the safety limits (e.g., development of pulmonary edema). Maintenance fluid increases typically alter only the rate of administration of continuous fluids.

Crystalloid vs. Colloid

Although prospective studies of choice of fluid resuscitation in patients with septic shock only are lacking, a prospective, controlled, randomized, double-blind study comparing 4 percent human albumin solution with 0.9 percent sodium chloride (saline) in critically ill patients requiring fluid resuscitation (SAFE study) has been completed. The results of this study showed identical mortality rates in patients receiving albumin or 0.9 percent sodium chloride. Subgroup analysis revealed that albumin might have some (albeit not statistically significant) benefit in patients with severe sepsis.[1]

In addition, meta-analyses of clinical studies comparing crystalloid and colloid resuscitation in general and surgical patient populations indicate no clinical outcome difference between colloids and crystalloids and would appear to be generalizable to sepsis populations.[2-4] As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same goals and results in more edema.

End Points of Fluid Resuscitation

For the Severe Sepsis 3-Hour Resuscitation Bundle, a minimum fluid challenge is defined in an effort to avoid hypotension. The bundle does not restrict additional fluids. If, however, the patient should enter the early goal-directed phases of the 6-Hour Septic Shock Bundle, either for hypotension not responding to fluid challenges or a lactate ≥4 mmol/L (36 mg/dL), targets for central venous pressure as well as central and mixed venous oxygen saturation have been defined. These targets are not arbitrary. They are based on specifications defined in the best available literature[5], and a recent analysis supporting a 65 percent SvO_2 saturation as similar to a 70 percent $ScvO_2$.[6]

In Rivers et al., hospital mortality was 30.5 percent in the group assigned to early goal-directed therapy, compared with 46.5 percent in the standard therapy group (p=0.009).[5] Rivers et al. used restoration of a central venous oxygen saturation of >70 percent as one of their goals, and this was met in 95 percent of the early goal-directed group, compared with just 60 percent of the standard treatment group (p<0.001). Patients in the early goal-directed treatment groups received more fluids (5 vs. 3.5 L, p<0.001) and more were given red cell transfusions (64 vs. 18.5 percent, p<0.001) in the first 6 hours than in the standard treatment group, emphasizing the importance of early and adequate fluid resuscitation in patients with severe sepsis.

However, considerable debate remains on these thresholds largely because of problems in monitoring the regional microcirculation and oxygenation. Changes may persist at a local level while systemic hemodynamic and oxygenation variables seem to have stabilized. Each end point must be considered in its context, and the combination of clinical variables (mean arterial pressure, urine output, apparent skin perfusion, level of consciousness) along with serum lactate values may be helpful to the clinician despite a lack of randomized trials to establish this point.

Safety Margins

Patients should be carefully observed for evidence of pulmonary and systemic edema during fluid resuscitation. The degree of intravascular volume deficit in patients with severe sepsis varies. With venodilation and ongoing capillary leak, most patients require continuing aggressive fluid resuscitation during the first 24 hours of management. Input is typically much greater than output, and input/output ratio is of no utility to judge fluid resuscitation needs during this time.

Grading the Evidence

The Grade 1 recommendations below are based on strong evidence for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence. “UG” level evidence is ungraded.

- The 2012 Surviving Sepsis Campaign Guidelines recommend fluid resuscitation with crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (Grade 1B). The absence of any clear benefit following the administration of colloid solutions compared to crystalloid solutions, together with the expense associated with colloid solutions, supports a high-grade recommendation for the use of crystalloid solutions in the initial resuscitation of patients with severe sepsis and septic shock.
- The Surviving Sepsis Campaign recommends fluid resuscitation initially target a CVP of at least 8 mm Hg (12 mm Hg in mechanically ventilated patients). Further fluid therapy is often required (Grade 1C).
- The Surviving Sepsis Campaign recommends that a fluid challenge technique be applied, wherein fluid administration is continued as long as the hemodynamic improvement (e.g., arterial pressure, heart rate, urine output) continues (UG). The Surviving Sepsis Campaign recommends fluid challenge in patients with suspected hypovolemia be started with at least 30 mL/kg of crystalloids (a portion of this may be albumin equivalent) over 30 minutes. More rapid administration and greater amounts of fluid may be needed in patients with sepsis-induced tissue hypoperfusion (Grade 1C). The Surviving Sepsis Campaign recommends the rate of fluid administration be reduced substantially when cardiac filling pressures (CVP or pulmonary artery balloon-occluded pressure) increase without concurrent hemodynamic improvement (Grade 1D).

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6-Hour Bundle

Revised November 22, 2013

1. Apply Vasopressors (for Hypotension That Does Not Respond to Initial Fluid Resuscitation) to Maintain a Mean Arterial Pressure (MAP) ≥65 mm Hg

Background

Adequate fluid resuscitation is a prerequisite for the successful and appropriate use of vasopressors in patients with septic shock. In general, the end points of fluid resuscitation are the same as those for the use of pharmacologic hemodynamic support (i.e., MAP ≥65 mm Hg). Sometimes, fluid resuscitation alone may suffice.

When an appropriate fluid challenge fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be started. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not been resolved or when a fluid challenge is in progress.

Cautions

Although all the vasopressor agents generally result in an increase in blood pressure, concerns remain in clinical practice about their potentially inappropriate or detrimental use.

- The most obvious of these relates to the inadequately volume-resuscitated patient, in whom vasopressor use may worsen already inadequate organ perfusion.
- Even when volume resuscitation has been performed, discussion continues as to whether vasopressor agents may raise blood pressure at the expense of the perfusion of vulnerable organs, most particularly the kidneys and the gut.
- A further concern relates to the possibility that overenthusiastic use, especially if an unnecessarily high blood pressure is targeted, may increase left ventricular work to an unsustainable degree and so worsen cardiac output and end-organ perfusion. This may be especially harmful in patients with pre-existing heart disease.

Monitoring

Because hypotension is a primary feature of septic shock and improving blood pressure is a therapeutic goal, accurate and continuous measurement of blood pressure is essential. It is therefore customary to use an arterial catheter to enable continuous invasive blood pressure monitoring. The radial artery is the site most frequently chosen, but the femoral artery is also often used. It is important to note that there may be marked differences in the blood pressure recordings at the two sites, especially in patients who are in shock, receiving vasopressors, and still hypovolemic.

Choice of Vasopressors

Norepinephrine (through a central venous catheter as soon as placement is possible) is the first choice vasopressor agent to correct hypotension in septic shock (Grade 1B).

Epinephrine (added to and potentially substituted for norepinephrine) may be used when an additional agent is needed to maintain adequate blood pressure (Grade 2B).[1-3]

Phenylephrine should not be used as a first-line vasopressor as part of the treatment of septic shock. Phenylephrine was reported to reduce splanchnic blood flow and oxygen delivery in septic shock patients.[4]

Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors. Pending the outcome of ongoing trials, it is not recommended as a replacement for norepinephrine or dopamine as a first-line agent.

Dopamine

Dopamine may be used as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., a patient with low risk of tachyarrhythmias and absolute or relative bradycardia). Dopamine increases mean arterial pressure primarily by increasing cardiac index with minimal effects on systemic vascular resistance. The increase in cardiac index is due to an increase in stroke volume and, to a lesser extent, to increased heart rate.[5,6]

Splanchnic perfusion and the integrity of the gut mucosa may play an important role in the pathogenesis of multiple organ failure. The effect of dopamine on gastric tonometric and splanchnic variables has been evaluated with mixed results. At low doses, dopamine increases splanchnic oxygen delivery by 65 percent but splanchnic oxygen consumption by only 16 percent. Despite this, dopamine may decrease pH, perhaps by a direct effect on the gastric mucosal cell. The effects of dopamine on cellular oxygen supply in the gut remain incompletely defined.

Studies have shown that dopamine may alter the inflammatory response in septic shock by decreasing the release of a number of hormones, including prolactin.[7] Other potentially harmful endocrine effects have been demonstrated in trauma patients.[8-11] In a study of 12 stable mechanically ventilated patients, Dive et al. used intestinal manometry to demonstrate that dopamine resulted in impaired gastroduodenal motility.[12] Concerns remain that these and other poorly understood biological effects of dopamine might potentially have harmful effects in patients with septic shock.

Norepinephrine

Norepinephrine is a potent α-adrenergic agonist with some β-adrenergic agonist effects. Norepinephrine therapy usually causes a statistically and clinically significant increase in mean arterial pressure due to the vasoconstrictive effects, with little change in heart rate or cardiac output, leading to increased systemic vascular resistance.[13-15]

In open-label trials, norepinephrine has been shown to increase mean arterial pressure in patients with hypotension resistant to fluid resuscitation and dopamine. In the past, there was concern that norepinephrine may have negative effects on blood flow in the splanchnic and renal vascular beds, with resultant regional ischemia. This meant that in the past norepinephrine was commonly reserved for use as a last resort, with predictably poor results. However, recent experience with the use of norepinephrine in patients with septic shock suggests that it can successfully increase blood pressure without causing the feared deterioration in organ function. Norepinephrine seems to be more effective than dopamine at reversing hypotension in septic shock patients.[16]

Concern is frequently expressed with regard to the effect of norepinephrine on the kidney. In patients with hypotension and hypovolemia during hemorrhagic shock, for example, norepinephrine and other vasoconstrictor agents may have severe detrimental effects on renal hemodynamics. Despite the improvement in blood pressure, renal blood flow does not increase, and renal vascular resistance continues to rise.[17] However, in hyperdynamic septic shock, during which urine flow is believed to decrease mainly because of lowered renal glomerular perfusion pressure, the situation is different.[18] Norepinephrine markedly improves mean arterial pressure and glomerular filtration. This is particularly true in the high-output, low-resistance state of many septic shock patients. After restoration of systemic hemodynamics, urine flow reappears in most patients and renal function improves. This fact supports the hypothesis that the renal ischemia observed during hyperdynamic septic shock is not worsened by norepinephrine infusion and even suggests that this drug may be effective in improving renal blood flow and renal vascular resistance.[19-22]

Combination Therapies

The effects of dopamine on cellular oxygen supply in the gut remain incompletely defined, and the effects of norepinephrine alone on splanchnic circulation may be difficult to predict.[23-25] The combination of norepinephrine and dobutamine seems to be more predictable and more appropriate to the goals of septic shock therapy than norepinephrine with dopamine or dopamine alone.[26, 27]

Grading the Evidence

The Grade 1 recommendations below are based on strong evidence for care based on a number of qualitative considerations. "B" level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. "C" level evidence reflects well-done observational or cohort studies with controls. "D" level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

- The 2012 Surviving Sepsis Campaign Guidelines recommend mean arterial pressure (MAP) be maintained ≥65 mm Hg (Grade 1C).

  Vasopressor therapy is required to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not yet been resolved. Below a certain mean arterial pressure, autoregulation in various vascular beds can be lost, and perfusion can become linearly dependent on pressure. Thus, some patients may require vasopressor therapy to achieve a minimal perfusion pressure and maintain adequate flow.[28, 29] The titration of norepinephrine to as low as MAP of 65 mm Hg has been shown to preserve tissue perfusion.[29] In addition, pre-existing comorbidities should be considered as to most appropriate MAP target. For example, a MAP of 65 mm Hg might be too low in a patient with severe uncontrolled hypertension, and in a young previously normotensive patient, a lower MAP might be adequate. Supplementing end points such as blood pressure with assessment of regional and global perfusion, such as blood lactate concentrations and urine output, is important. Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock, and should ideally be achieved before vasopressors and inotropes are used, but using vasopressors early as an emergency measure in patients with severe shock is frequently necessary. When that occurs great effort should be directed to weaning vasopressors with continuing fluid resuscitation.

- The Surviving Sepsis Campaign also recommends norepinephrine as the first choice vasopressor agent to correct hypotension in septic shock, administered through a central catheter as soon as one is available (Grade 1B).

The Grade 2 suggestions below are weaker recommendations for care based on a number of qualitative considerations. "D" level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence. "UG" level evidence is ungraded.

- The Surviving Sepsis Campaign suggests that epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (Grade 2C). Vasopressin 0.03 units/minute may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone (UG). The Surviving Sepsis Campaign suggests that epinephrine be the first chosen alternative agent in septic shock that is poorly responsive to norepinephrine (Grade 2B).

  There is no high-quality primary evidence to recommend one catecholamine over another. Much literature exists that contrasts the physiologic effects of choice of vasopressor and combined inotrope/vasopressors in septic shock. Human and animal studies suggest

some advantages of norepinephrine and dopamine over epinephrine (the latter with the potential for tachycardia as well as disadvantageous effects on splanchnic circulation and hyperlactemia) and phenylephrine (decrease in stroke volume). There is, however, no clinical evidence that epinephrine results in worse outcomes, and it should be the first chosen alternative to dopamine or norepinephrine. Phenylephrine is the adrenergic agent least likely to produce tachycardia, but as a pure vasopressor would be expected to decrease stroke volume. Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Either may be used as a first-line agent to correct hypotension in sepsis. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function, but causes more tachycardia and may be more arrhythmogenic.[30] It may also influence the endocrine response via the hypothalamic-pituitary axis and have immunosuppressive effects.

Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state.[31] Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors, and may have other potential physiologic benefits.[32-37] Terlipressin has similar effects but is long lasting.[38] Studies show that vasopressin concentrations are elevated in early septic shock, but with continued shock, concentration decreases to normal range in the majority of patients between 24 and 48 hours.[39] This has been called “relative vasopressin deficiency” because in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. The recent VASST trial, a randomized, controlled trial comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 units/minute showed no difference in outcome in the intent to treat population. An *a priori* defined subgroup analysis showed that the survival of patients receiving less than 15 µg/min norepinephrine at the time of randomization was better with vasopressin. It should be noted however that the pre-trial rationale for this stratification was based on exploring potential benefit in the 15 µg or greater norepinephrine requirement population. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia and should be reserved for situations where alternative vasopressors have failed.[40] Cardiac output measurement to allow maintenance of a normal or elevated flow is desirable when these pure vasopressors are instituted.

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TIPS

1. Include the use of vasopressors on a standardized protocol for the treatment of hypotension not responding to fluid administration.
2. Be sure that emergency department and intensive care nurses and staff are familiar with the appropriate dosing of dopamine, dobutamine, and norepinephrine.
3. Do not wait to start vasopressors until a fluid challenge or bolus of intravenous fluid is completed before using vasopressor agents if severe hypotension is present.
4. If you are unable to wean vasopressors, consider other diagnoses such as depressed cardiac function, adrenal insufficiency, tension pneumothorax, or cardiac tamponade, etc.

6-Hour Bundle

2. In the Event of Persistent Arterial Hypotension Despite Volume Resuscitation (Septic Shock) or Initial Lactate ≥4 mmol/L (36 mg/dL):

a. Maintain Adequate Central Venous Pressure

In the event of persistent hypotension despite fluid resuscitation (septic shock) or lactate ≥4 mmol/L (36 mg/dL) measure central venous pressure (CVP). (The target for CVP is >8 mm Hg.)

Related Measures

Central Venous Pressure Goal

Background

Early goal-directed therapy represents an attempt to predefine resuscitation end points to help clinicians at the bedside to resuscitate patients in septic shock. The end points used vary according to the clinical study, but attempt to adjust cardiac preload, contractility, and afterload to balance systemic oxygen delivery with demand.

Two essential features of early goal-directed therapy include: 1) maintaining an adequate central venous pressure (CVP) to carry out other hemodynamic adjustments; and 2) maximizing mixed or central venous oxygen saturation ($ScvO_2$) [see bundle element 2b].

Following the bundle, once lactate is ≥4 mmol/L (36 mg/dL), or hypotension has been demonstrated to be refractive to an initial fluid challenge with 30 mL/kg of crystalloid, patients should then have their CVP maintained at ≥8 mm Hg.

Of note, in adhering to this strategy, patients receive the initial minimum 30 mL/kg fluid challenge *prior to placement of a central venous catheter and attempts to maximize CVP*. This recommendation is consistent with the methods used in Rivers et al.[1]

Maintaining CVP

Techniques to maintain an appropriate CVP include placing a central venous catheter and delivering repeated fluid challenges until the target value is achieved. Fluid challenges are distinct from an increase in the rate of maintenance fluid administration.

Consider Blood Products

In carrying out early goal-directed therapy, one key aim is central venous pressure, but it is also imperative to maintain central or mixed venous oxygen saturation targets. If a patient is both hypovolemic and anemic with a hematocrit less than 30 percent of blood volume, it is appropriate to transfuse packed red blood cells. This may have the dual advantage of increasing oxygen delivery to ischemic tissue beds and keeping central venous pressure ≥8 mm Hg for longer periods than fluids alone.

Special Considerations

In mechanically ventilated patients, a higher target central venous pressure of 12–15 mm Hg is recommended to account for the presence of positive end expiratory pressure and increases in intrathoracic pressure.

Similar consideration to the above may be warranted in circumstances of increased abdominal pressure.

Although the cause of tachycardia in septic patients may be multifactorial, a decrease in elevated pulse with fluid resuscitation is often a useful marker of improving intravascular filling.

Early Goal-Directed Therapy Study Protocol

Rivers, et al. performed a randomized, controlled, predominantly blinded study in an 850-bed tertiary referral center over a three-year period.[1] This study was performed in the emergency department of the hospital and enrolled patients presenting with severe sepsis or septic shock who fulfilled two of the four systemic inflammatory response syndrome criteria in association with a systolic blood pressure of <90 mm Hg after a 20–30 mL/kg crystalloid challenge or a blood lactate concentration of ≥4 mmol/L (36 mg/dL).

The patients were randomized to receive six hours of standard therapy or six hours of early goal-directed therapy before admission to the intensive care unit. Clinicians who were subsequently involved in the care of these patients were blinded to the treatment arm of the study.

The control group's care was directed according to a protocol for hemodynamic support. The aims of this protocol were to ensure that the patients had a central venous pressure of between 8 and 12 mm Hg, a mean arterial pressure of ≥65 mm Hg, and a urine output of ≥0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$. These goals were targeted with the use of 500 mL boluses of crystalloid or colloid and vasopressor agents as necessary. The patients assigned to the early goal-directed therapy group received a central venous catheter capable of measuring $ScvO_2$. Their treatment aims were then the same as the control groups, except that they also had to achieve a $ScvO_2$ of ≥70 percent.

The patients assigned to the early goal-directed therapy group received a central venous catheter capable of measuring $ScvO_2$. Their treatment aims were then the same as the control groups, except that they also had to achieve a $ScvO_2$ of ≥70 percent. This was achieved first by the administration of transfused red blood cells, then with positive inotropic therapy, and if this goal was then not achieved, by sedation and mechanical ventilation to reduce oxygen demand.

The study enrolled 263 patients equally between the two groups. There were no significant differences between the two groups at baseline. During the initial 6 hours of therapy, the early goal-directed therapy group received more intravenous fluid (5.0 vs. 3.5 L, p<0.001), red cell transfusions (p<0.001), and inotropic therapy (p<0.001). During the subsequent 66 hours, the control group received more red cell transfusions (p<0.001), more vasopressors (p=0.03), and had a greater requirement for mechanical ventilation (p<0.001) and pulmonary artery catheterization (p=0.04). This in part reflects the fact that the control group patients were relatively under-resuscitated initially, and this was noticed and thus acted on by clinicians later on in their treatment course. In-hospital mortality was significantly higher in the control group than in the early goal-directed therapy group (46.5 percent vs. 30.5 percent, p=0.009). These differences were maintained through to 28 (p=0.01) and 60 days (p=0.03).

Grading the Evidence [See Ranking the Evidence]

The Grade 1 recommendations below are based on strong evidence for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

- The 2012 Surviving Sepsis Campaign Guidelines recommend the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission. During the first 6 hours of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol (Grade 1C):
  - Central venous pressure (CVP) 8-12 mm Hg
  - Mean arterial pressure (MAP) ≥65 mm Hg
  - Urine output ≥0.5 mL•kg^{-1}•hr^{-1}
  - Central venous (superior vena cava) or mixed venous oxygen saturation ≥70 percent or ≥65 percent, respectively

  Early goal-directed resuscitation has been shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single-center study.[1] Resuscitation directed toward the previously mentioned goals for the initial 6-hour period of the resuscitation was able to reduce 28-day mortality rate. The consensus panel judged use of central venous and mixed venous oxygen saturation targets to be equivalent. Either intermittent or continuous measurements of oxygen saturation were judged to be acceptable. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation. In mechanically ventilated patients or patients with known pre-existing decreased ventricular compliance, a higher target CVP of 12-15 mm Hg is recommended to account for the

impediment to filling.[2] Similar consideration may be warranted in circumstances of increased abdominal pressure or diastolic dysfunction.[3]

Elevated central venous pressures may also be seen with pre-existing clinically significant pulmonary artery hypertension. Although the cause of tachycardia in septic patients may be multifactorial, a decrease in elevated pulse rate with fluid resuscitation is often a useful marker of improving intravascular filling. Observational studies have demonstrated an association between good clinical outcome in septic shock and MAP ≥65 mm Hg as well as central venous oxygen saturation ($ScvO_2$, measured in superior vena cava, either intermittently or continuously) of ≥70 percent.[4] Many studies support the value of early protocolized resuscitation in severe sepsis and sepsis-induced tissue hypoperfusion.[5-10] Studies of patients with shock indicate that SvO_2 runs 5 percent to 7 percent lower than central venous oxygen saturation ($ScvO_2$)[11], and that an early goal-directed resuscitation protocol can be established in a non-research general practice venue.[12]

There are recognized limitations to ventricular filling pressure estimates as surrogates for fluid resuscitation.[13,14] However, measurement of CVP is currently the most readily obtainable target for fluid resuscitation. There may be advantages to targeting fluid resuscitation to flow and perhaps to volumetric indices (and even to microcirculation changes).[15-18] Technologies currently exist that allow measurement of flow at the bedside.[19, 20]

The Grade 2 suggestion below is a weaker recommendation for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

- Following the Rivers protocol[1], if during the first 6 hours of resuscitation of severe sepsis or septic shock, $ScvO_2$ or SvO_2 of 70 percent or 65 percent respectively is not achieved with fluid resuscitation to the CVP target, then transfusion of packed red blood cells to achieve a hematocrit of ≥30 percent and/or administration of a dobutamine infusion (up to a maximum of 20 $\mu g \bullet kg^{-1} \bullet min^{-1}$) be utilized to achieve this goal.

  The protocol used in the study targeted an increase in $ScvO_2$ to ≥70 percent. [1] This was achieved by sequential institution of initial fluid resuscitation, then packed red blood cells, and then dobutamine. This protocol was associated with an improvement in survival. Based on bedside clinical assessment and personal preference, a clinician may deem either blood transfusion (if Hct is less than 30 percent) or dobutamine to be the best initial choice to increase oxygen delivery and thereby elevate $ScvO_2$ when fluid resuscitation is believed to be already adequate. The design of the aforementioned trial did not allow assessment of the relative contribution of these two components (i.e., increasing O_2 content or increasing cardiac output) of the protocol on achievement of improved outcome.

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- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*. 2013;41:580-637
- Rhodes A, Bennett ED. Early goal-directed therapy: An evidence-based review. *Critical Care Medicine*. 2004;32(Suppl):S448-S450.

TIPS

1. Create a standardized protocol that includes a goal CVP >8 mm Hg for patients with lactate ≥4 mmol/L (36 mg/dL) or hypotension not responding to initial fluid resuscitation (septic shock).
2. Stress the importance of prioritization: initial fluid challenge as defined, followed by central line placement, followed by assessment of CVP; if CVP is low, the addition of PRBCs is appropriate if hematocrit is less than 30 percent and MAP remains <65 mm Hg, followed by further fluid challenges to keep CVP >8 mm Hg.
3. If your emergency department does not commonly perform these techniques, provide in-service training to emergency department personnel regarding CVP monitoring and the importance of leveling equipment relative to the patient's heart.
4. Do not wait for transfer to the ICU to initiate CVP monitoring.

6-Hour Bundle

2. In the Event of Persistent Arterial Hypotension Despite Volume Resuscitation (Septic Shock) or Initial Lactate ≥4 mmol/L (36 mg/dL):

b. Maintain Adequate Central Venous Oxygen Saturation

In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate ≥4 mmol/L (36 mg/dL) measure central venous oxygen saturation ($ScvO_2$). (The target is ≥70 percent.*)

**Mixed venous oxygen saturation (SvO_2) ≥65 percent is an acceptable alternative.*

Related Measures

Central Venous Oxygen Saturation Goal

Background

Goal-directed therapy represents an attempt to predefine resuscitation end points to help clinicians at the bedside to resuscitate patients in septic shock. The end points used vary according to the clinical study but attempt to adjust cardiac preload, contractility, and afterload to balance systemic oxygen delivery with demand.

Two essential features of early goal-directed therapy include: 1) maintaining an adequate central venous pressure (CVP) to carry out other hemodynamic adjustments [see bundle element 2a]; and 2) maximizing mixed or central venous oxygen saturation ($ScvO_2$).

Following the bundle, once lactate is ≥4 mmol/L (36 mg/dL), or hypotension has been demonstrated to be refractive to an initial fluid challenge with 20 mL/kg of crystalloid or colloid equivalent, patients should then have their central venous pressure (CVP) maintained at ≥8 mm Hg and central venous oxygen saturation ($ScvO_2$) should be maintained at ≥70 percent.

These recommendations are consistent with Rivers, et al., the only trial to demonstrate a mortality benefit in early goal-directed therapy using $ScvO_2$ as one of its major end points.[1]

Importance of Early Therapies

The resuscitation of severely septic individuals with lactate ≥4 mmol/L (36 mg/dL) or who are in septic shock must start early. The longer the resuscitation is delayed, the less likely a beneficial effect will occur. This makes sense, as the purpose of resuscitating a patient is to prevent further organ dysfunction and failure. If the resuscitation is delayed until after cellular dysfunction and cell death are present, then strategies designed to provide the cells with more oxygen are unlikely to be helpful. It is unclear, however, when the transition from reversible cellular dysfunction to irreversible cellular dysfunction occurs. At present, the only effective strategy is to provide the resuscitation at the earliest stage possible.

Maintaining $ScvO_2$

Techniques to maintain $ScvO_2$ include two principal strategies. In carrying out early goal-directed therapy, if a patient is both hypovolemic and the hematocrit is less than 30 percent, it is appropriate to transfuse packed red blood cells provided that the fluid resuscitation has achieved a CVP ≥8 mm Hg. If CVP ≥8 mm Hg has not been achieved, additional fluid challenges are needed. Once the decision to use blood products has been made, this may accomplish the dual purpose of 1) increasing $ScvO_2$ due to increased oxygen delivery to ischemic tissue beds, and 2) keeping the central venous pressure ≥8 mm Hg for longer periods than fluids alone.

The second strategy involves attempting to improve the patient's hemodynamic profile with inotropes. Provided that the patient has been adequately resuscitated and the CVP is ≥8 mm Hg, cardiac output may remain insufficient to meet metabolic needs of certain tissue beds despite an adequate circulating volume. In some cases, cardiac output itself may be diminished due to sepsis-induced cardiac dysfunction. In these cases, dobutamine infusion (up to a maximum of 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) should be given to increase oxygen delivery to the periphery and prevent further organ dysfunction due to hypoperfusion and ischemia. If dobutamine infusion results in hypotension, norepinephrine should be used to counteract the vasodilatory effects of dobutamine.

Special Considerations

Evidence is not conclusive on attempting to maximize a patient's cardiac index to surpranormal levels to overcome increased oxygen demand, abnormalities in oxygen extraction, and myocardial depression associated with sepsis.[2, 3] Therefore, a strategy of increasing cardiac index to achieve an arbitrarily predefined elevated level is not recommended.

Before attempting to use inotropes to maximize central venous oxygen saturation in mechanically ventilated patients, a higher target central venous pressure of 12–15 mm Hg is recommended to account for the presence of positive end expiratory pressure and increases in intrathoracic pressure.

Similar consideration to the above may be warranted in circumstances of increased abdominal pressure.

Early Goal-Directed Therapy Study Protocol

It is impossible to determine from the study which particular facet of the protocol was beneficial for the patients, so the protocol as a whole must be recommended.

Rivers, et al. performed a randomized, controlled, predominantly blinded study in an 850-bed tertiary referral center over a three-year period.[1] This study was performed in the emergency department of the hospital and enrolled patients presenting with severe sepsis or septic shock who fulfilled two of the four systemic inflammatory response syndrome criteria in association with a systolic blood pressure of <90 mm Hg after a 20–30 mL/kg crystalloid challenge or a blood lactate concentration of ≥4 mmol/L (36 mg/dL).

The patients were randomized to receive six hours of standard therapy or six hours of early goal-directed therapy before admission to the intensive care unit. Clinicians who were subsequently involved in the care of these patients were blinded to the treatment arm of the study.

The control group's care was directed according to a protocol for hemodynamic support. The aims of this protocol were to ensure that the patients had a central venous pressure of between 8 and 12 mm Hg, a mean arterial pressure of ≥65 mm Hg, and a urine output of ≥0.5 $mL \bullet kg^{-1} \bullet min^{-1}$. These goals were targeted with the use of 500 mL boluses of crystalloid or colloid and vasopressor agents as necessary. The patients assigned to the early goal-directed therapy group received a central venous catheter capable of measuring $ScvO_2$. Their treatment aims were then the same as the control groups, except that they also had to achieve a $ScvO_2$ of ≥70 percent.

The patients assigned to the early goal-directed therapy group received a central venous catheter capable of measuring $ScvO_2$. Their treatment aims were then the same as the control groups, except that they also had to achieve a $ScvO_2$ of ≥70 percent. This was achieved first by the administration of transfused red blood cells, then with positive inotropic therapy, and if this goal was then not achieved, by sedation and mechanical ventilation to reduce oxygen demand.

The study enrolled 263 patients equally between the two groups. There were no significant differences between the two groups at baseline. During the initial 6 hours of therapy, the early goal-directed therapy group received more intravenous fluid (5.0 vs. 3.5 L, $p<0.001$), red cell transfusions ($p<0.001$), and inotropic therapy ($p<0.001$). During the subsequent 66 hours, the control group received more red cell transfusions ($p<0.001$), more vasopressors ($p=0.03$), and had a greater requirement for mechanical ventilation ($p<0.001$) and pulmonary artery catheterization ($p=0.04$). This in part reflects the fact that the control group patients were relatively under-resuscitated initially, and this was noticed and thus acted on by clinicians later on in their treatment course. In-hospital mortality was significantly higher in the control group than in the early goal-directed therapy group (46.5 percent vs. 30.5 percent, $p=0.009$). These differences were maintained through to 28 ($p=0.01$) and 60 days ($p=0.03$).

Grading the Evidence

The Grade 1 recommendations below are based on strong evidence for care based on a number of qualitative considerations. "B" level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. "C" level evidence reflects well-done observational or cohort studies with controls. "D" level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

- The 2012 Surviving Sepsis Campaign Guidelines recommend the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission. During the first 6 hours of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol (Grade 1C):
  - Central venous pressure (CVP) 8-12 mm Hg
  - Mean arterial pressure (MAP) ≥65 mm Hg
  - Urine output ≥0.5 $mL \bullet kg^{-1} \bullet hr^{-1}$
  - Central venous (superior vena cava) or mixed venous oxygen saturation ≥70 percent or ≥65 percent, respectively

  Early goal-directed resuscitation has been shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single-center study. [1] Resuscitation directed toward the previously mentioned goals for the initial 6-hour period of the resuscitation was able to reduce 28-day mortality rate. The consensus panel judged use of central venous and mixed venous oxygen saturation targets to be equivalent. Either intermittent or continuous measurements of oxygen saturation was judged to be acceptable. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation. In mechanically ventilated patients or patients with known pre-existing decreased ventricular compliance, a higher target CVP of 12-15 mm Hg is recommended to account for the impediment to filling.[4] Similar consideration may be warranted in circumstances of increased abdominal pressure or diastolic dysfunction.[5]

  Elevated central venous pressures may also be seen with pre-existing clinically significant pulmonary artery hypertension. Although the cause of tachycardia in septic patients may be multifactorial, a decrease in elevated pulse rate with fluid resuscitation is often a useful marker of improving intravascular filling. Observational studies have demonstrated an association between good clinical outcome in septic shock and MAP ≥65 mm Hg as well as central venous oxygen saturation ($ScvO_2$, measured in superior vena cava, either intermittently or continuously) of ≥70 percent.[6] Many studies support the value of early protocolized resuscitation in severe sepsis and sepsis-induced tissue hypoperfusion.[7-12]

Studies of patients with shock indicate that SvO_2 runs 5 percent to 7 percent lower than central venous oxygen saturation ($ScvO_2$),[13] and that an early goal-directed resuscitation protocol can be established in a non-research general practice venue.[14]

There are recognized limitations to ventricular filling pressure estimates as surrogates for fluid resuscitation.[15,16] However, measurement of CVP is currently the most readily obtainable target for fluid resuscitation. There may be advantages to targeting fluid resuscitation to flow and perhaps to volumetric indices (and even to microcirculation changes).[17-20] Technologies currently exist that allow measurement of flow at the bedside.[21, 22]

The Surviving Sepsis Campaign suggests targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (Grade 2C). If $ScvO_2$ is not available, lactate normalization may be a feasible option in the patient with severe sepsis-induced tissue hypoperfusion. $ScvO_2$ and lactate normalization may also be used as a combined end point when both are available. Two multicenter randomized trials evaluated a resuscitation strategy that included lactate reduction as a single target or a target combined with $ScvO_2$ normalization.[23, 24] The first trial reported that early quantitative resuscitation based on lactate clearance (decrease by at least 10 percent) was noninferior to early quantitative resuscitation based on achieving $ScvO_2$ of 70 percent or more.[23]

The Grade 2 suggestion below is a weaker recommendation for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

- The 2012 Surviving Sepsis Campaign Guidelines suggest that during the first 6 hours of resuscitation of severe sepsis or septic shock, if $ScvO_2$ or SvO_2 of ≥70 percent or ≥65 percent respectively is not achieved with fluid resuscitation to the CVP target, then transfusion of packed red blood cells to achieve a hematocrit of ≥30 percent and/or administration of a dobutamine infusion (up to a maximum of 20 $\mu g.kg^{-1}.min^{-1}$) be utilized to achieve this goal (Grade 2C).

  The protocol used in the study cited previously targeted an increase in $ScvO_2$ to ≥70 percent.[1] This was achieved by sequential institution of initial fluid resuscitation, then packed red blood cells, and then dobutamine. This protocol was associated with an improvement in survival. Based on bedside clinical assessment and personal preference, a clinician may deem either blood transfusion (if Hct is less than 30 percent) or dobutamine to be the best initial choice to increase oxygen delivery and thereby elevate $ScvO_2$ when fluid resuscitation is believed to be already adequate. The design of the aforementioned trial did not allow assessment of the relative contribution of these two components (i.e., increasing O_2 content or increasing cardiac output) of the protocol on achievement of improved outcome.

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Content adapted extensively from:

- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*. 2013;41(2):580-637.
- Rhodes A, Bennett ED. Early goal-directed therapy: An evidence-based review. *Critical Care Medicine*. 2004;32(Suppl):S448-S450.

TIPS

1. Create a standardized protocol that includes a goal CVP ≥8 mm Hg for patients with lactate ≥4 mmol/L (36 mg/dL) or hypotension not responding to initial fluid resuscitation (septic shock).
2. Stress the importance of prioritization: initial fluid challenge as defined, followed by central line placement, followed by assessment of CVP; if CVP is low, the addition of PRBCs is appropriate if hematocrit is less than 30 percent and MAP remains <65 mm Hg, followed by further fluid challenges to keep CVP ≥8 mm Hg.
3. If your emergency department does not commonly perform these techniques, provide in-service training to emergency department personnel regarding CVP monitoring and the importance of leveling equipment relative to the patient's heart.
4. Do not wait for transfer to the ICU to initiate CVP monitoring.

6-Hour Bundle

3. Remeasure Lactate If Initial Lactate Was Elevated

Background

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 a lactate level is essential to identifying tissue hypoperfusion in patients who are not yet hypotensive but who are at risk for septic shock.

Limitations

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. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation.

Implications

Mortality rate is high in septic patients with both hypotension and lactate ≥4 mmol/L, and is also increased in severely septic patients with hypotension alone and lactate ≥4 mmol/L.[5] If $ScvO_2$ is not available, lactate normalization may be a feasible option in the patient with severe sepsis-induced tissue hypoperfusion. $ScvO_2$ and lactate normalization may also be used as a combined end point when both are available.[6, 7]

Turnaround Time

Serum lactate must be available in your institution with rapid turnaround time (within minutes) to treat severely septic patients effectively. 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.

Arterial vs. Venous Lactate

In the course of the Surviving Sepsis Campaign the question has been raised many times as to whether an arterial or venous lactate sample is appropriate. While there is no published consensus on this question, an elevated lactate of any variety is typically abnormal, although this may be influenced by other conditions such as a variety of medications, hepatic insufficiency, or hyperlactatemia due to primarily cardiac causes of hypoperfusion.

Grading the Evidence

The Grade 2 suggestion below is a weaker recommendation for care based on a number of qualitative considerations. "C" level evidence reflects well-done observational or cohort studies with controls.

- The use of lactate as a method to detect severe sepsis and septic shock and as a rationale for further therapies was evaluated as part of the larger recommendation on initial resuscitation in the 2008 Surviving Sepsis Campaign Guidelines. There, the guidelines committee recommended the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L) (Grade 2C).

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