

CONGRESS REVIEW



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EVIDENCE-BASED NUTRITIONAL GUIDELINES IN 2010

Artificial nutrition support has come a long way since its introduction more than 50 years ago. Mounting evidence demonstrates that nutrition therapy impacts morbidity and mortality in the intensive care unit (ICU), underscoring the need for intensivists to institute changes in their practice and to implement guidelines.

The SCCM/A.S.P.E.N. Nutritional Guidelines: Examining the Evidence Stephen A. McClave, MD

Representing a collaborative effort between the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), guidelines for nutrition support in critically ill adults were published in May 2009 (Martindale RG, et al. *Crit Care Med.* 2009;37:1757). Development of this document was a five-year process involving about 50 expert reviewers and five rounds of review. The guidelines were targeted to adult critically ill medical and surgical patients with an expected ICU stay of at least two or three days.

"The guidelines are a basic list of recommendations and nothing more," stated Stephen A. McClave, MD, from the University of Louisville in Louisville, Kentucky, USA. "They are not absolute requirements. If your judgment at the bedside tells you one thing and the guidelines say something else, you are obligated to go with your clinical judgment. Nonetheless, some of these guidelines reflect the most rigorously defended and researched documents in the literature."

Although the guidelines committee focused on data from prospective randomized controlled trials (RCTs), they also considered national and international guidelines from other societies, expert opinion, and clinical practicality. In the absence of prospective RCTs, recommendations were based on expert opinion. When polarity existed among experts, the committee focused on providing total parenteral nutrition (TPN) recommendations that were most likely to result in outcome benefit.

One controversial area of the guidelines is the recommendation of permissive enteral nutrition (EN) underfeeding in obese ICU patients. "We recommended that these patients receive 60% to 70% of the caloric requirements of a target weight-based equation, along with significantly increased protein," said McClave. "However, around the time the guidelines were being published, review data emerged suggesting that obesity may be beneficial in ICU patients and that permissive underfeeding should not be practiced in this population." The data revealed that – although obesity in trauma/surgical and medical ICU patients was associated with increased infection, length of stay, organ failure, and mechanical ventilation duration – mortality results were mixed (Cave MC, et al. *Nutr Clin Pract.* 2008;23:16). Obese trauma/surgical ICU patients had a seven-fold increase in mortality, whereas obese medical ICU patients had reduced mortality. Another study found that mortality was reduced among ICU patients with a body mass index (BMI) of 35 or higher who had received an additional 1,000 calories (Alberda C, et al. *Intensive Care Med.* 2009;35:1728).

In addressing this matter, the committee considered the ways in which morbid obesity interferes with patient care, such as the need for special

equipment, increased risks of pressure sores, atelectasis, pneumonia, and deep vein thrombosis as well as mechanical ventilation difficulties and challenges with diagnostic studies due to transport difficulty and inability to fit in imaging scanners. The committee also sought the opinion of an expert highly experienced in permissive underfeeding and obesity, who cited two physiologic studies supportive of permissive underfeeding (Elwyn DH. *Crit Care Med.* 1980;8:9; Hill GL, et al. *Br J Surg.* 1984;71:1). This research demonstrates that, if protein is increased to levels sufficient to stimulate protein synthesis to match degradation, the obese ICU patient can be fed 60% of required calories and maintain lean body mass while decreasing the fat mass (see Figure 1).

Another debated recommendation pertains to tolerance of EN. The guidelines recommend that patients be monitored for tolerance and that clinicians: 1) avoid inappropriate cessation of EN; 2) avoid holding EN for gastric residual volumes (GRVs) of less than 500 mL in the absence of other signs of intolerance; and 3) minimize oral restrictive periods to promote EN delivery and avoid prolonged ileus. "Raising the GRV to the high level of 500 mL naturally prompted such questions as: Is 500 mL appropriate? What is the literature to support that? And do you agree with it as an individual practitioner?" noted McClave.

Clinicians may be concerned that raising the GRV to 500 mL in the critically ill patient increases the risk of aspiration pneumonia. "However, four prospective RCTs indicate that raising the GRV was associated with better, not worse, outcomes," stated McClave. In a British study, the incidence of complications significantly decreased when GRV was increased (Taylor SJ, et al. *Crit Care Med.* 1999;27:2525). Two other studies revealed that the incidence of vomiting and overall intolerance remained the same when GRV was raised from 150 mL to 250 mL (Pinilla JC, et al. *JPEN J Parenter Enteral Nutr.* 2001;25:81) and from 200 mL to 400 mL (McClave SA, et al. *Crit Care Med.* 2005;33:320); no difference occurred in aspiration or regurgitation (McClave SA, et al. *Crit Care Med.* 2005;33:324). Supportive evidence also comes from a multicenter RCT in Spain, which reported a significant reduction in gastrointestinal complications with 500 mL GRV versus 200 mL GRV (Montejo, JC. Monitoring of gastric emptying. Presented at: The European Society of Intensive Care Medicine's 20th Annual Congress; October 2007; Berlin Germany).

"What would happen if we stopped measuring GRVs altogether? Would it be harmful? The answer is no," McClave said. A small nursing study showed no significant differences in incidence of aspirate pneumonia with routine GRVs compared with no GRVs, although tube clogging dramatically decreased (67% versus 8%) with no GRVs (Powell KS, et al. *JPEN J Parenter Enteral Nutr.* 1993;17:243). A more recent study found that intolerance improved, increased EN was delivered, and vomiting and pneumonia incidence rates remained the same when GRVs were stopped. (Poulard F, et al. *JPEN J Parenter Enteral Nutr.* 2010;34[2]:125). "It's ironic," McClave added. "Lowering the GRV to protect the patient may impede the delivery of enteral nutrition, and the risk of pneumonia might actually increase."

A third area of controversy in the guidelines relates to fish oil, specifically the recommendation that patients with acute respiratory distress syndrome (ARDS) or severe acute lung injury (ALI) receive EN characterized by an anti-inflammatory lipid profile formula (i.e., omega-3 fish oils, borage oil and antioxidants). "This was based on three prospective randomized trials," McClave explained. "Then, within two months of publishing the guidelines, we received news that the EDEN-Omega study from the ARDSNet group had been stopped for reasons of futility." The study, which compared trophic with full feeds and a fish oil/borage oil supplement versus placebo, was terminated early because, at the interim analysis, a difference in mortality emerged between the two groups. At question was whether this suggested potential harmful effects of fish oils.

In probing further, the committee learned there was no indication that fish oil was deleterious. Rather, of concern was an error of randomization, in which the control group was less sick than the study patients (specifically, an unexpected low mortality in controls). "Therefore, the therapy just couldn't be good enough for the study group to catch up," McClave said. "The message here is that we don't have a danger signal regarding fish oil."

In summary, McClave noted that "it's important to understand that with any controversy, there may not be a right answer, but controversy provides great opportunity to grow. The most important element in integrating guidelines is transparency: tracking the recommendation back to the evidence." He added that ICUs are obligated to review the supporting literature, decide how they stand on controversial issues, and determine whether that interpretation should alter their clinical practice.

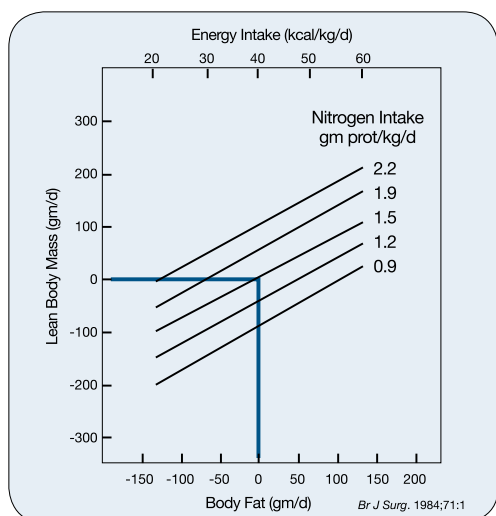


Figure 1. Effect of Low-Energy, High-Protein Intake on Fat and Lean Body Mass

Implementation of Nutrition Guidelines: Who Succeeds and Why? Naomi Cahill, MSc, RD

“To be worthwhile, guideline recommendations need to represent best practice and should have a beneficial impact on clinical outcomes,” stated Naomi Cahill, MSc, RD, from Queen’s University in Kingston, Ontario, Canada. Cahill presented data from an international survey indicating that clinicians have mixed opinions about whether Canadian nutritional guidelines reflect best practice and would improve outcomes if implemented. “Some of this diversity of opinion or uncertainty might be because, to date, we have had little success in implementing guidelines. We haven’t been able to demonstrate an impact of nutrition guidelines on clinical outcomes.”

One theoretical model that can be used to demonstrate how clinical practice guidelines can be implemented successfully is the knowledge-to-action model by Graham and colleagues which links the creation of knowledge with implementation of that knowledge (Graham ID, et al. *J Contin Educ Health Prof.* 2006;26:13). In nutrition, the creation of knowledge has grown substantially over the past 30 years. “Since 1980, more than 200 randomized trials of nutrition intervention have been published, involving more than 2,000 critically ill patients,” Cahill said. “However, many of these studies were small, of poor methodological quality, and included a heterogeneous patient population. That makes it difficult to make inferences from these studies and apply them to practice.”

The next step in the Graham model after creating knowledge is synthesizing the evidence. Thus far, this has been achieved through systematic reviews and meta-analyses on 34 nutrition topics. Knowledge synthesis is followed by the creation of knowledge tools. “This involves packaging the synthesized evidence into a form (such as clinical practice guidelines) that makes it more useful to be applied in practice,” explained Cahill. “The information becomes more succinct and easier to apply at the bedside.”

Cahill discussed problem areas that reflect differences between nutrition guidelines and what is actually happening in the ICU. “In the three international nutrition practice audits we conducted to identify problem areas, we consistently observed large variations in practice in terms of percentage of calories received versus prescribed during the first 12 days of ICU stay,” Cahill said. “If we think of this variation in nutritional adequacy as a surrogate marker for overall adherence to guidelines, we see there are gaps between guidelines and what’s actually happening in practice. We need to bridge that knowledge-practice gap.”

Three cluster RCTs addressing the implementation of critical care nutrition guidelines have produced mixed results. One Canadian study of 14 ICUs found that incorporation of guideline recommendations into a feeding algorithm resulted in shorter hospital stay and a trend toward reduced mortality (Martin CM, et al. *CMAJ.* 2004;170:197). Another Canadian study, which randomized 50 ICUs into either the passive arm (paper copy of guidelines) or the active arm (multifaceted interventions in which the dietitian, serving as the opinion leader, received Web-based tools and training toolkits), revealed overall improvement in enteral nutrition adequacy but no differences in clinical outcomes except glucose control (Jain MK, et al. *Crit Care Med.* 2006;34:2362). The most recent cluster study involved 27 ICUs in Australia and New Zealand (Doig GS, et al. *JAMA.* 2008;300:2731). In the intervention arm, ICU opinion leaders attended a two-day guideline development conference, where they helped develop the evidence-based guidelines and received in-service training on implementing 18 different change strategies, including an educational outreach session by the research team. The results showed small differences in nutrition practices, including the mean number of days that nutrition support was received, and no differences in clinical outcomes.

“What are the lessons learned from these studies?” asked Cahill. “First, we can acknowledge that delivery of nutrition therapy is complex and involves a multiprofessional team, which can be problematic when implementing change,” she said. “Second, guideline implementation is time-consuming and underappreciated, so these trials show that more work needs to be done. Third, the ‘one-size-fits-all’ approach, where each ICU in the intervention arm received the same change strategies, may be flawed.”

Guideline recommendations must be adapted to the local context and must be aligned with the values and practices at that site. To tailor

guideline implementation strategies to local needs, barriers and enablers should be identified and addressed. “A barrier is any factor that may limit, hinder or restrict implementation of a guideline recommendation at the bedside,” Cahill noted, “while an enabler is any factor that might promote or help implementation.” To identify predictors of adherence to nutritional guidelines, Cahill and coworkers asked clinicians from four ICUs about the factors that helped or hindered guideline implementation. The results of these interviews were amalgamated into a framework for adherence to clinical practice guidelines in the ICU (see Figure 2).

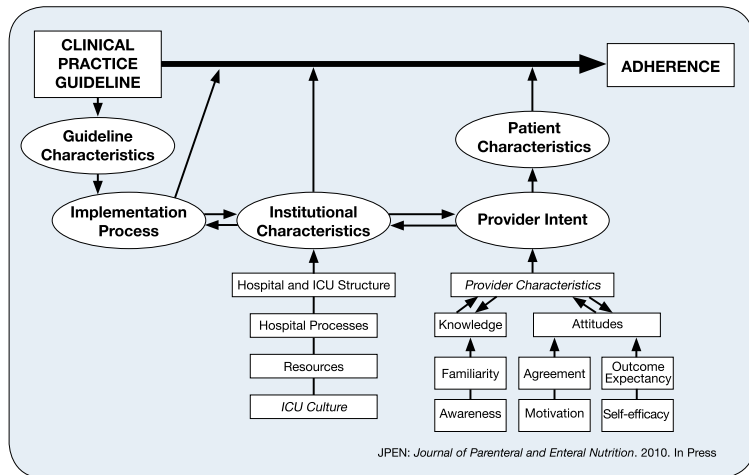


Figure 2. Framework for Adherence to Clinical Practice Guidelines in the ICU

The framework identifies five domains associated with guideline adherence: guideline characteristics, implementation process, institutional characteristics, intent of the intensivist to implement the recommendations, and patient characteristics.

Guideline characteristics. To enable implementation, guidelines must be up-to-date, evidence-based, user-friendly and developed by a respected team. **Implementation process.** Multifaceted implementation strategies are needed to increase awareness in the ICU (e.g., posters), to increase knowledge of ICU clinicians through education (e.g., workshops, rounds, academic detailing), and to provide reminders/assistance for incorporating the recommendations into daily practice (e.g., preprinted orders, feeding algorithms, checklists).

Institutional characteristics. Large teaching hospitals with closed ICUs in urban locations were better able to adhere to guidelines than their smaller counterparts in rural locations. Long, slow hospital processes that dictate approval of multiple committees can hinder guideline implementation. Lack of resources (staff, equipment, nutritional products, specialist services) can also be barriers. A positive ICU culture (shared beliefs, attitudes, values, and behaviors) enables guideline implementation; this calls for multiprofessional teamwork, support from the ICU leadership, collaborative decision making, respect for the expertise of each team member, and informal, open communication.

Provider intent. Intent to follow guidelines is based on providers’ knowledge and attitudes towards those guidelines. Knowledge is a function of familiarity with, and awareness of, the recommendations; attitude is a function of outcome expectancy, self-efficacy, motivation and agreement with the recommendations. Providers’ intent also is influenced by their roles and experiences in the ICU, educational background and personality.

Patient characteristics. Guideline recommendations are made for the average critically ill patient. Therefore, when applying them in practice, patient characteristics must be considered. For example, surgical patients are more difficult to feed than medical patients.

“Clearly, we need to tailor interventions so that any change strategy is specifically chosen to address the barriers identified at a specific ICU

setting, at a specific time," urged Cahill. Current and future research projects are focusing on identifying the most effective methods of measuring barriers and tailoring guideline implementation strategies to overcome these barriers. In the meantime, Cahill suggested that clinicians wishing to optimize their nutrition practices can adopt an 'ABC' strategy:

- Automate – make feeding easy through checklists, verbal reminders, preprinted orders, and protocols
- Benchmark – participate in the 2011 international nutrition audit
- Communicate – make sure all ICU staff are educated and motivated about feeding their patients

The Future of Nutrition Therapy: Looking into the Crystal Ball Paul Wischmeyer, MD

Before moving forward with nutrition in the ICU, clinicians need to look to the past. "We must identify what we need to unlearn and what we need to learn," said Paul Wischmeyer, MD, from the University of Colorado School of Medicine in Denver, USA. "The first thing we need to unlearn is that nutrition in the ICU is bad food that comes up from the kitchen that nobody eats. This is not nutrition therapy. The reality is that nutrition therapy saves lives and changes outcomes."

Nutrition science has advanced to the point where the mechanisms of nutrients are now understood. Nutrients can change gene expression at the most basic level and are vital to the functioning of cells under stress. Another clear advantage is that nutrition therapy is inexpensive and reduces hospital costs in comparison to most other drugs. "If we can achieve outcome changes from nutrients at a fraction of drug costs, that's a huge advance in the care of our patients," said Wischmeyer, "but the data are useless unless they are translated into practice. For instance, even though all medical society guidelines advocate use of glutamine in critically ill patients, we know this is not practiced in most ICUs."

One hindrance to guideline implementation has been a body of evidence limited to small clinical trials. Although this is now changing as data from larger trials emerge, mechanistic science to explain how nutrients works was previously lacking. "Therefore, nutrition therapy was always something clinicians didn't want to talk about on rounds," remarked Wischmeyer. "This attitude has to change, because we now have laboratory and clinical research supporting the value of nutrition therapy in critically ill patients."

Wischmeyer called for intensivists to actively change this attitude by keeping in mind and disseminating three positive insights gained through research: 1) nutrition can modulate the immune system; 2) nutrition can prevent infection; and 3) calories and protein may reduce mortality among critically ill patients.

Nutrients have been identified that can up-regulate and down-regulate the immune system, but they should be viewed as drugs that provide risks as well as benefits. Another crucial consideration: different patients have different nutrient needs. As an example, patients experiencing an inflammatory response to sepsis and infection require glutamine and omega-3 to intervene and attenuate the sepsis-associated hyperinflammation and immunosuppression. In contrast, patients undergoing an immunosuppressed response to surgery or trauma should receive arginine to reverse the immunosuppression caused by a deficiency of this nutrient.

Diets high in animal fat (omega-6 fatty acids) are linked to hyperinflammation and immune insufficiency, and such intake before hospitalization will affect the ICU patient's health status. "Many patients arrive at the ICU in this condition, and we may be able to reverse that and improve ICU outcomes with omega-3," stated Wischmeyer, noting that the omega-6 to omega-3 ratio of the American diet is 18:1 – a huge departure from the ideal "caveman" ratio of 1:1. Wischmeyer discussed the evolution of dietary intake as a means to understanding how omega-3 therapy can affect disease outcomes. Dietary fatty acids, inflammation and coronary artery disease (CAD) risk are known to exist in a linear relationship. Simply changing the ratio of dietary omega-6 to omega-3 fatty acids within the same population has been shown to reduce the mortality associated with CAD. (Simopoulos AP. *Exp Biol Med* [Maywood]. 2008;233:674).

Pharmacologic and clinical data provide evidence supporting the correction of the omega-6: omega-3 ratio in ICU patients. In 16 healthy volunteers, two doses of fish oil infused twice before an endotoxin bolus reduced the tumor necrosis factor (TNF)- α response, febrile response, and overall catechol response to endotoxin shock (Pluess TT, et al. *Intensive Care Med*. 2007;33:789). Favorable effects also were revealed in a meta-analysis of three clinical trials, each involving at least 100 patients with ARDS who predominantly also had sepsis (Pontes-Arruda A, et al. *JPENJ Parenter Enteral Nutr*. 2008;32:596). The results linked omega-3-based feeding with an 83% reduction in organ failure and a 60% reduction in mortality.

"All clinical practice guidelines agree that fish oil should be given to patients with ARDS, so in the future we need to look toward applying this to the right patients," Wischmeyer stated. "We need trials that focus on sepsis patients, because almost all of the data thus far involved sepsis-induced ARDS. We also need to begin looking at biomarkers and treating patients based on inflammatory markers."

Nutrition therapy has another crucial role in the ICU: prevention of infection. Up to 30% of major surgery patients develop infection, costing as much as \$10,000 per patient. "This is an enormous burden that we can prevent because we know there is a nutritional mechanism for this problem," remarked Wischmeyer.

Surgery and trauma induce a deficiency of arginine, an amino acid required for T cells to divide and monitor the immune system. Arginine deficiency syndrome is a well-known condition correlated with increased infection among cancer and surgery/trauma patients. Surgery/trauma patients require different nutrition therapy than sepsis patients, as sepsis is a pro-inflammatory state mediated by different cytokines than those involved in the immunodepressed state that occurs following surgery or trauma. In fact, arginine deficiency is not present in sepsis.

A meta-analysis of 30 randomized controlled trials with more than 3,000 patients evaluated the effects of arginine therapy following surgery (Drover et al. *Annals of Surgery*. 2010. [In Press.]). The results showed that five to seven days of arginine-based nutrition reduced infectious complications by 40% and reduced length of stay by as much as one-third. None of the trials revealed harm in the arginine feedings. "Thus, we see enormous potential cost savings associated with arginine use in patients following surgery," said Wischmeyer. "I am not sure we need more research on this amino acid in surgery, but a definitive large-scale clinical trial would establish it as the standard of care."

As for caloric and protein intake among the critically ill, the needs vary from patient to patient. Surveys show that most ICU patients are underfed. "This may be safe for some, but harmful for others," Wischmeyer said. "If nutrition therapy is to save lives and improve outcomes, we have to actually feed the patients so they can receive the nutrients. Also, we must realize that our patients have different nutrition goals."

Determining caloric and protein amounts is challenging. According to one hypothesis, BMI defines chronic nutritional risk. ICU data show that patients with a low (<25) or very high (>35) BMI and low caloric intake have increased mortality rates; however, caloric intake does not have as great an impact in the patients with BMIs of 25 to 35. Protein intake also affects outcomes. For every additional 30 g/day of protein given to critically ill patients, the odds ratio of mortality significantly decreases. As with caloric intake, this effect of protein is BMI-dependent.

"Because we're unsuccessful in getting calories into our high-risk patients, should we start total parental nutrition sooner in malnourished and very obese patients?" asked Wischmeyer. "That is probably something the Europeans have right and that constitutes a topic in need of future study." It is worth noting that nutrition products have varied availability in different parts of the world.

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Continuing Education Self-Assessment

EVIDENCE-BASED NUTRITIONAL GUIDELINES IN 2010

1. Which of the following was observed in a prospective randomized controlled trial regarding gastric residual volumes (GRVs)?
 - a. Higher GRVs were associated with a decreased incidence of gastrointestinal complications.
 - b. Higher GRVs were associated with an increased incidence of aspiration.
 - c. Stopping GRVs was associated with an increased incidence of pneumonia.
 - d. Stopping GRVs was associated with an increased incidence of vomiting.
2. Arginine therapy is recommended in patients with sepsis-induced ARDS.
 - a. True
 - b. False

DELIRIUM: SHOULD “NEVER” OCCUR, BUT IF IT DOES ...

With increasing evidence linking delirium to serious sequelae, many intensive care units (ICUs) are adopting delirium screening in daily practice. In addition, government officials are wondering whether delirium should be deemed a “never” event in the hospital, prompting a close look at the identification, treatment and prevention of delirium among critically ill patients.

Delirium as the Next “Never” Event: Is That Realistic? Pratik P. Pandharipande, MD, MSCl

In 2009, the Centers for Medicare & Medicaid Services (CMS) considered proposing delirium in the hospital as the next “never” event (i.e., a medical care error that has serious consequences but is identifiable and preventable). “Can delirium realistically be a ‘never’ event in the ICU?” asked Pratik P. Pandharipande, MS, MSCl, from Vanderbilt University School of Medicine in Nashville, Tennessee, USA. “Perhaps not yet, but there are measures we can take to reduce the burden of this brain dysfunction.”

Regardless of whether delirium becomes a “never” event, one thing is clear: the problem of delirium in the hospital has been gaining attention. “Delirium is no longer the organ dysfunction that nobody cares about,” said Pandharipande, noting that the past 10 years has witnessed a significant rise in delirium research.

Delirium is a brain organ dysfunction characterized by a disturbance of consciousness. It has a rapid onset and fluctuating course and is marked by inattention and disorganized thinking (impaired ability to receive, process, store and recall information). Perceptual disturbances such as illusions and hallucinations can be present. The hypoactive or mixed forms of delirium are most common, while the hyperactive form (e.g., patients pulling out tubes or trying to get out of bed) is rare.

“There’s a wide range of prevalence rates for delirium in the ICU, depending on the diagnostic instrument used and the patient type,” reported Pandharipande. Delirium has been reported to occur in 60% to 80% of mechanically ventilated patients and 20% to 50% of ICU patients with lower severity of illness. “Research suggests that unless the ICU performs routine monitoring for mental status, the majority of delirium cases will go undiagnosed,” Pandharipande said.

The medical community should be concerned about delirium because it has serious consequences. It is associated with adverse outcomes: higher hospital costs, longer hospital stays, a threefold higher risk of mortality within six months, and prolonged neuropsychological dysfunction (Milbrandt EB, et al. *Crit Care Med.* 2004;32:955; Ely EW, et al. *JAMA.* 2004;291:1753; Ouimet S, et al. *Intensive Care Med.* 2007;33:66; Lin SM, et al. *Crit Care Med.* 2004;32:2254). In addition to trying to prevent delirium, it is also important to reduce its duration, because longer duration has been linked to worse neuropsychological outcomes and higher mortality risk (Pisani MA, et al. *Am J Respir Crit Care Med.* 2009;180:1092).

“Delirium represents a spectrum of brain organ dysfunction, with delirium on one end, normal on the other, and subsyndromal delirium in the middle,” explained Pandharipande. “Patients with subsyndromal delirium present with some symptoms of delirium but do not fulfill all diagnostic criteria. Higher mortality and longer length of stay occur more with clinical delirium than subsyndromal delirium, which in turn is associated with worse outcomes than in patients with normal mental status. So we need to realize that delirium is similar to other organ dysfunctions, in which severity of the disease impacts the outcomes.”

In determining whether delirium is identifiable (an essential feature of a “never” event), Pandharipande said progress has been made but more is needed. To ascertain whether delirium is preventable (another feature of a “never” event), it is important to understand the pathogenesis and risk factors. “We need to elucidate the mechanisms and identify risk factors,” said Pandharipande. “Delirium pathogenesis research is in its infancy, but some data suggest that inflammation may play a role, as well as disturbances of neurotransmitters, especially serotonin, dopamine, acetylcholine and norepinephrine.”

Prevention of delirium can be facilitated by avoiding risk factors. Although most of the known risk factors are not modifiable (aging, baseline dementia, psychiatric disorders, underlying inflammation or coagulation, metabolic disturbances, hypoxemia, and perhaps genetic predisposition), two potentially modifiable risk factors have been identified: psychoactive medications and sleep deprivation. Research reveals a temporal relationship between the administration of lorazepam and the occurrence of delirium, with the risk of transitioning to delirium being nearly 100% after a 24-hour period of receiving 20 mg lorazepam (1 mg/h), as shown in Figure 1 (Pandharipande P, et al. *Anesthesiology.* 2006;104:21).

Similar findings suggest that another benzodiazepine – midazolam – is also a risk factor for delirium, but the data on opiates are mixed (Pandharipande P, et al. *J Trauma.* 2008;65:34). Some findings suggest that reducing pain adequately with morphine is associated with lower rates

of delirium although this may not be true when fentanyl is used for the added benefit of sedation (Pandharipande P, et al. *J Trauma.* 2008;65:34). “In the trauma ICU, morphine looked protective versus fentanyl,” reported Pandharipande. “Additionally, among burn ICU patients, benzodiazepines were associated with delirium, whereas adequate control of pain with opiate administration seemed to reduce the risk of developing delirium on the following day (Pandharipande P, et al. American Society of Anesthesiologists Annual Meeting; 2009).”

In light of this and other data, clinicians can take the following measures to try to reduce delirium in the ICU: monitor patients for delirium, consider evidence-based nonpharmacologic interventions, and reduce or modify exposure to sedatives.

Monitoring for delirium begins with discussions of the patient’s status during daily rounds. “We want to know where our patient’s brain is going, where the brain is now and how it got there,” explained Pandharipande. “We need to have a grasp of the patient’s state of arousal and the content of this arousal.” Arousal status can be detected using validated sedation scale and the content of the arousal with delirium-measuring instruments. Two such tools have been implemented on a large scale: the Confusion Assessment Method-Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC).

Risk can be reduced through the use of delirium prevention protocols involving nonpharmacologic interventions. One non-ICU study evaluating a multicomponent intervention for geriatric patients found that delirium incidence decreased when protocols were implemented that addressed reorientation and continuity of caregivers, sleep architecture improvement, reduction of deliriogenic medication exposure, cognition stimulation, and geriatrician/trained neuropsychologic personnel visits (Inouye SK, et al. *N Engl J Med.* 1999;340:669). In addition, a study of mechanically ventilated patients demonstrated that early physical and occupational therapy resulted in reduced duration of both delirium and ICU stay (Schweickert WD, et al. *Lancet.* 2009;373:1874).

Implementation of sedation protocols that reduce sedative exposure may be effective in reducing delirium in the ICU, but more evidence is needed. “There is some suggestion that if you reduce benzodiazepine exposure, at least in the sickest of your patients – those with sepsis – you will reduce the duration of delirium,” Pandharipande said.

To decrease or avoid use of benzodiazepines, agents with different mechanisms should be considered. Results from the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial revealed that administration of dexmedetomidine (an α_2 -agonist) resulted in more days alive without delirium or coma and more time at the targeted level of sedation compared with lorazepam (Pandharipande PP, et al. *JAMA.* 2007;298:2644). Similar results have been demonstrated with dexmedetomidine versus midazolam. The recent Safety and Efficacy of Dexmedetomidine Compared to Midazolam (SEDCOM) trial showed lower prevalence of delirium in the dexmedetomidine group when

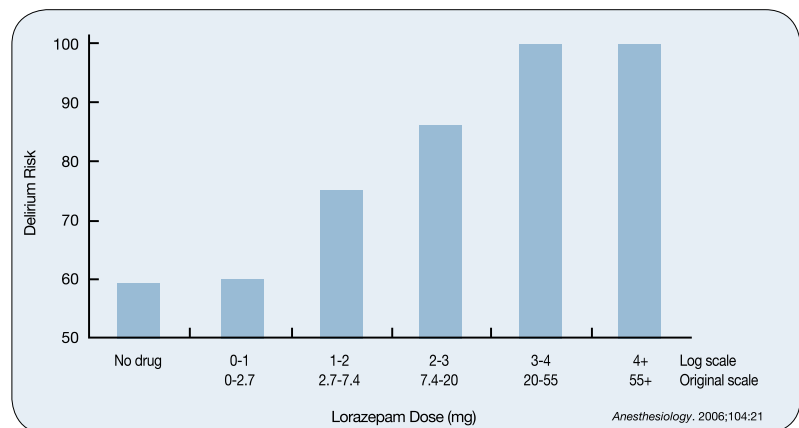


Figure 1. Lorazepam and Delirium

compared to midazolam (Riker RR, et al. *JAMA*. 2009;301:489).

Investigators also have evaluated the effects of antipsychotic agents on delirium risk among ICU patients. One double-blind randomized controlled trial found that following cardiac surgery, a single dose of 1 mg risperidone administered upon arrival to the ICU reduced the delirium incidence rate from 31.7% to 11.1% (Prakanrattana U, et al. *Anaesth Intensive Care*. 2007;35:714). In one of the first placebo-controlled studies of antipsychotics in critically ill patients, there was no difference in resolution of delirium and coma with the use of a typical (haloperidol) versus atypical (ziprasidone) antipsychotic agent (Girard TD, et al. *Crit Care Med*.

2010;38:428). Another recent study showed that in patients with delirium, there was faster time to resolution of the first episode of delirium with quetiapine versus placebo (Devlin JW, et al. *Crit Care Med*. 2010;38:419). This will be discussed later in this article.

Pandharipande summarized his remarks by noting that progress has been made in making delirium identifiable and emphasizing some of the risk factors that can drive the targeting of therapies and improve outcomes. "We're focusing more on trying to reduce the duration of delirium, as has been seen in many studies, while still trying to clarify the best way to reduce delirium incidence and make it a 'never' event in the future."

Typical Versus Atypical Antipsychotics: Which Is the Better Option? John W. Devlin, PharmD, FCCM

Haloperidol currently may be the drug of choice for delirium in many ICUs, but are atypical antipsychotic agents a better option? "The mechanisms for delirium in the critically ill patient are numerous and complex, and one of the common pathways by which delirium occurs is neurotransmitter imbalance, including a decrease in acetylcholine and an increase in dopamine," stated John W. Devlin, PharmD, FCCM, from Northeastern University School of Pharmacy in Boston, Massachusetts, USA. "This creates a compelling area for focusing treatment interventions, particularly considering the availability of many different antipsychotic agents that modulate these neurotransmitters."

Devlin noted that pharmacologic therapy should be considered only after the underlying causes of delirium have been treated, and it should usually be reserved for severe agitation that puts at risk the safety of the patient or caregiver. In general, the positive signs of delirium (e.g., agitation, hallucinations) are more likely to respond to antipsychotic therapy than the negative signs (e.g., hypoactivity, inattention, disordered cognition, depressed level of consciousness). The number of causes of delirium is substantially greater among ICU versus non-ICU patients. "Therefore, we have to be careful about extrapolating the results of non-ICU studies," Devlin said.

The receptor adherence properties differ widely among antipsychotic agents. For example, haloperidol is predominantly D₂ dopaminergic; ziprasidone is almost entirely serotonergic; olanzapine and risperidone are predominantly serotonergic; and quetiapine is predominantly adrenergic and histaminic. All antipsychotics appear to be equally efficacious in psychosis, but are they also similar in delirium, considering their differing pharmacologic properties? "A 2 to 20 mg/day dose of haloperidol is adequate to achieve the 60% binding to D₂ receptors necessary for an antipsychotic effect, but we're not sure of the exact dose needed in delirium treatment," said Devlin.

Clinical practice guidelines released by the American Psychiatric Association suggested that 1 mg to 2 mg of haloperidol be administered every two to four hours and be titrated to higher doses if agitation continues; some physicians also reported using atypical antipsychotics at that time. In 2002, the Society of Critical Care Medicine sedation guidelines (*Crit Care Med*. 2002;30:119) included a grade C recommendation stating that haloperidol is the preferred agent for delirium treatment in critically ill patients. Most recently, the United Kingdom Delirium Guidelines have offered more conservative recommendations, recognizing the paucity of studies regarding anti-delirium therapy.

Although haloperidol has been shown to reduce mortality rates in critically ill patients, it is unclear whether its use in delirium improves outcome (Milbrandt EB, et al. *Crit Care Med*. 2005;33:226). In fact, haloperidol use has been identified as an independent predictor for prolonged delirium (Pisani MA et al. *Crit Care Med*. 2009;37:177). Additionally, intravenous (IV) haloperidol and higher-than-recommended doses of haloperidol have been linked to QT prolongation and torsades de pointes.

Atypical antipsychotic agents offer several potential advantages compared with haloperidol and other conventional antipsychotics. These include decreased incidence of extrapyramidal symptoms (EPS), little effect on the QTc interval (with the exception of ziprasidone), decreased hypotension and fewer orthostatic effects (compared with IV haloperidol), lower risk of neuroleptic malignant syndrome, low chance of causing laryngeal dystonia, and lower mortality rates (when administered to elderly patients with dementia to control behavioral symptoms). "Thus, there are compelling reasons suggesting safety advantages with atypical antipsychotics compared with haloperidol," remarked Devlin. "Certainly, the use of atypical antipsychotics is increasing." In 2001 only 4% of clinicians used antipsychotics to treat delirium in the ICU compared with 40% in 2007 (Ely EW, et al. *Crit Care Med*. 2004;32:106; Patel RP, et al. *Crit Care Med*. 2009;37:825).

Few prospective randomized placebo-controlled trials on antipsychotic therapy for delirium in the ICU have been reported. The Modifying the Incidence of Delirium (MIND) trial compared the use of haloperidol

5 mg, ziprasidone 40 mg, and placebo for up to 14 days in mechanically ventilated adults with an abnormal level of consciousness or who were receiving sedative or analgesic therapy (Girard TD, et al. *Crit Care Med*. 2010;38:428). Drug titration was allowed. Primary outcome of the study was the number of days alive without delirium or coma during the 21-day study period. Exclusion criteria were extensive; of the 3,297 patients screened, 103 met eligibility requirements. Not all of the patients had delirium at baseline.

The results showed that, while the number of patients alive without delirium or coma increased over 21 days, no differences occurred among the three groups (i.e., haloperidol, ziprasidone or placebo) with respect to the number of delirium-free and coma-free days, number of days on the study drug, or number of doses of additional haloperidol. "Based on this randomized double-blind, placebo-controlled evidence, we can conclude that there isn't necessarily a role for haloperidol in treatment of delirium in ICU patients," said Devlin.

Another double-blind, placebo-controlled, randomized study investigated the efficacy and safety of quetiapine in critically ill patients with delirium (Devlin, JW, et al. *Crit Care Med*. 2010;38:419). The use of quetiapine 50 mg twice daily, which could be titrated up to 200 mg twice daily, was compared with placebo. The protocol included haloperidol as needed, usual sedation, and analgesia at the discretion of the physician. Oversedation was managed by withholding the study drug when the sedation-agitation scale score was less than 2. Primary outcome for the study was time to first resolution of delirium, defined as an Intensive Care Delirium Screening Checklist Score (ICDSC) score of 3 or less. Exclusion criteria were extensive, permitting enrollment of only 36 of 258 patients with delirium who tolerated enteral nutrition. At study entry, most patients were intubated and both groups had an average ICDSC of 5.

The findings revealed that over the 10-day study period, the quetiapine group experienced greater delirium resolution than the placebo group (see Figure 2). The time spent in delirium was nearly four times longer in the placebo group. The number of patients receiving quetiapine who had delirium recurrence after initial resolution was half that of patients receiving placebo. Hours spent agitated were substantially lower with quetiapine, but there was no difference between groups in the hours spent deeply sedated. Quetiapine also did not differ from placebo in mechanical ventilation duration, ICU and hospital duration, or hospital mortality. No safety concerns led to discontinuation of quetiapine.

Devlin emphasized that there are a number of important methodological differences between MIND study and the quetiapine study that should

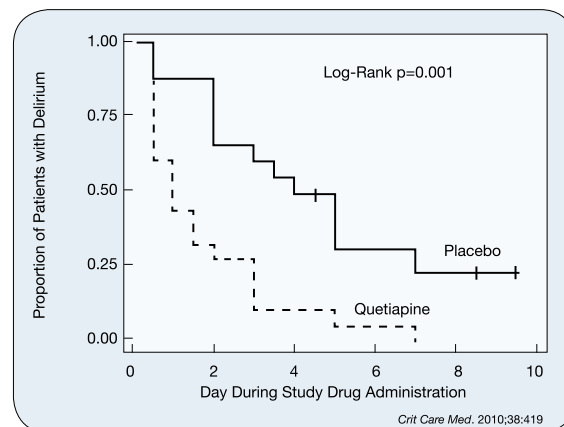


Figure 2. Proportion of Patients With Delirium

be considered before making conclusions about the role of antipsychotic therapy in the ICU for patients with delirium:

- Compared to the MIND study, where approximately half the patients had delirium and one-third had coma at study entry, all of the patients in the quetiapine study had delirium and none had coma at baseline.
- The MIND study included patients undergoing active withdrawal, while the quetiapine study did not.
- The MIND study randomized all patients within 72 hours of ICU admission, whereas the quetiapine enrolled patients far later.
- The primary efficacy outcome was days without delirium or coma, whereas the quetiapine study outcome was time to first resolution of delirium.
- The receptor activity of the antipsychotics studies in each study differ substantially.

"As another limitation, there is also the question of whether the placebo was truly used in either study, given that a substantial number of patients allocated to placebo in each study received haloperidol on many days as needed," Devlin said.

A third randomized trial, which was not placebo-controlled, compared the use of olanzapine 5 mg daily (decreased by 50% in elderly patients) and halo-

peridol 2.5 mg to 5 mg three times daily to treat delirium in critically ill patients (Skrobik YK, et al. *Intensive Care Med.* 2004;30:444). The olanzapine dose was not titrated. As-needed intravenous (IV) haloperidol and benzodiazepines were allowed for agitation. The primary outcome was severity of delirium. Eligibility criteria included delirium at study entry; exclusion criteria were extensive and similar to the aforementioned trials. The results showed no difference between olanzapine and haloperidol in reducing delirium severity. However, no patients in the olanzapine group, compared with six patients in the haloperidol group, developed possible extrapyramidal systems (EPS). "It is important to note that only oral haloperidol was used in the study, and this is associated with a much lower incidence of EPS than IV haloperidol," said Devlin.

"We can conclude from the literature that there are no high-quality data to support the use of haloperidol alone to treat delirium in the ICU, despite guideline recommendations," Devlin stated. "While there are pilot data suggesting that quetiapine added to as-needed haloperidol may improve delirium resolution and patient outcomes, many methodological issues need to be addressed in future studies surrounding this area before firm conclusions surrounding the efficacy and safety of antipsychotic therapy for delirium in the ICU can be made."

Haloperidol as the "Go-To" Drug: Is Dexmedetomidine a Better Option? Richard R. Riker, MD

"I think dexmedetomidine should be the 'go-to' drug to both prevent the development of delirium and clear delirium once it occurs," stated Richard R. Riker, from the University of Vermont College of Medicine and Maine Medical Center in Portland, Maine, USA. Before discussing evidence supporting the use of dexmedetomidine to treat and prevent delirium in critically ill patients, Riker summarized the serious implications of delirium, while emphasizing the need to pay attention to coma (especially the drug-induced form), which is associated with an even lower survival rate than delirium (Oiumet S, et al. *Intensive Care Med.* 2007;33:66). "We really need to consider both coma and delirium when trying to optimize our practice of sedation in the ICU," Riker stressed.

Dexmedetomidine is an α_2 agonist that provides both sedation and analgesia without causing significant respiratory depression. It reduces shivering and also exerts anxiolytic and sympatholytic (i.e., antihypertensive, antitachycardiac) activity. Potential adverse effects associated with dexmedetomidine include bradycardia, hypotension and vasoconstriction with rapid infusion or at high doses.

Riker presented six reasons why dexmedetomidine should be the drug of choice for delirium in the ICU:

- Increased delirium has been observed with γ -aminobutyric acid (GABA) agonists, the most commonly used sedatives for ICU patients.
- Improved outcomes for ICU patients have been associated with dexmedetomidine compared with GABA agonists.
- Delirium incidence has been reduced with dexmedetomidine.
- Delirium clearing is facilitated by use of dexmedetomidine.
- Cost savings have been achieved with dexmedetomidine compared with GABA antagonists.
- Evidence suggests that dexmedetomidine may be better than haloperidol.

The risks of transitioning to delirium with the use of sedative-analgesics have been reported, indicating a strong association between relatively low doses of lorazepam and development of delirium (Pandharipande P, et al. *Anesthesiology.* 2006;104:21). "In contrast, we now have a number of studies indicating that dexmedetomidine appears to reduce the incidence of delirium," Riker said. When patients receiving mechanical ventilation received sedation with infusions of either lorazepam or dexmedetomidine (the MENDS study), the incidence of delirium was significantly lower with dexmedetomidine than lorazepam. Moreover, the dexmedetomidine group had a significant increase in delirium-free and coma-free days compared with those treated with lorazepam (Pandharipande PP, et al. *JAMA.* 2007;298:2644).

Midazolam, another benzodiazepine agent, also has been implicated in the development of delirium and has been associated with poorer outcomes than dexmedetomidine. The Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) study (Riker RR, et al. *JAMA.* 2009;301:489) showed a higher prevalence of delirium among intubated ICU patients treated with midazolam compared with dexmedetomidine. Other findings revealed that time to extubation was reduced with dexmedetomidine versus midazolam, and that patients receiving dexmedetomidine were more communicative, more cooperative, and had a trend towards better ventilator tolerance, as rated by nurses caring for them.

"We can't talk about GABA agents without talking about propofol," said Riker. "As we consider the desirable rapid onset and offset of this

drug, we must also keep in mind that propofol infusion syndrome – a life-threatening complication – occurs not just with high doses given for a long duration. We're also seeing increased case reports of this syndrome occurring with reasonable doses over hours, rather than days. This is definitely something we want to monitor."

Dexmedetomidine was compared with propofol and midazolam in a randomized, open-label study involving cardiac surgical ICU patients, with dexmedetomidine demonstrating favorable results (Maldonado JR, et al. *Psychosomatics.* 2009;50:206). A significant reduction in delirium incidence was observed with dexmedetomidine compared with either propofol or midazolam.

Discussing the beneficial effects of dexmedetomidine in facilitating the clearance of delirium, Riker returned to data from the SEDOM trial (Riker RR, et al. *JAMA.* 2009;301:489). The investigators found that among patients who had delirium at baseline, delirium persisted during study drug therapy in only 68.7% of dexmedetomidine-treated patients, compared to 95.5% of midazolam-treated patients.

Pharmacoeconomic data suggest financial benefits for using dexmedetomidine in the ICU. A 12-month retrospective database analysis examined billing claims from 2003 for more than 10,000 patients who received midazolam plus propofol with or without dexmedetomidine (Dasta JF, et al. *Pharmacotherapy.* 2006;26:798). Results showed a significant reduction in mean total treatment charges with the addition of dexmedetomidine compared to the two-drug combination of midazolam and propofol. The SEDCOM trial yielded similar cost-saving data for dexmedetomidine compared with midazolam (Dasta JF, et al. *Crit Care Med.* 2010;38:497).

Riker's final reason for advocating the use of dexmedetomidine in the ICU relates to evidence that the agent may be better than haloperidol. "In addition to the data we have comparing the atypical antipsychotics to haloperidol, a recent small pilot study from Australia reported favorable results for dexmedetomidine in comparison to haloperidol. Dexmedetomidine was associated with significantly shorter hours to extubation and significantly decreased ICU length of stay (Reade MC, et al. *Crit Care.* 2009;13:R75)."

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Continuing Education Self-Assessment

DELIRIUM: SHOULD IT BE A "NEVER" EVENT IN THE ICU?

3. Which one of the following statements is true regarding evidence on the use of pharmacologic agents in critically ill patients with delirium?
 - a. Dexmedetomidine reduced time to extubation compared with midazolam.
 - b. Quetiapine reduced days on mechanical ventilation compared with placebo.
 - c. Robust evidence supports the use of haloperidol alone in the treatment of delirium.
 - d. Ziprasidone was associated with more delirium-free days than haloperidol.
4. Early physical and occupational therapy appears to have no effect on reducing delirium duration in critically ill patients.
 - a. True
 - b. False

THE SCIENCE AND MEDICINE OF SEPSIS MANAGEMENT

Current understanding of sepsis is marked by a variety of theories on the pathophysiology of sepsis and an expanded number of implicated mediators. Of particular interest are Toll-like receptors (TLR), which play a critical role in inflammation and represent promising potential targets for antisepsis therapy.

The Immunopathophysiological State of Sepsis H. Shaw Warren, MD

First described by Hippocrates in 400 B.C., sepsis is a controversial topic eliciting various hypotheses as to its immunopathophysiology. The first crucial steps in understanding the pathophysiology occurred in the late 1800s at the Pasteur Institute in France, where landmark experiments demonstrated that heat-killed bacteria injected into animals induce fever and death. "From those experiments, the concept eventually grew into what we know today: that it isn't the replication of bacteria in animals or humans that kills us, but rather the consequences related to the inflammatory response," said H. Shaw Warren, MD, from Massachusetts General Hospital in Boston, Massachusetts, USA.

Another milestone in understanding the pathophysiology of sepsis took place in the 1980s, when recombinant technology made it possible to purify secondary mediators such as cytokines and inject them into animals to induce inflammation. Widespread clinical trials on sepsis treatments, most of which failed, followed in the 1990s. The most recent significant advance in understanding emerged in the late 1990s and early 2000s with the discovery of TLRs and signaling mechanisms used by immune cells to identify microbial threats.

Sepsis is defined according to a disease continuum based on the experiments of Bone and colleagues (*Chest*. 1992;101:1644). The continuum proceeds from infection/trauma to systematic inflammatory response syndrome (SIRS) to sepsis to severe sepsis. In this model, sepsis is characterized as SIRS with a presumed or confirmed infectious process. Severe sepsis, the focus of most research thus far, consists of SIRS and sepsis with one or more signs of organ failure.

"It seems to me that the controversy surrounding sepsis comes from the way it is defined. As defined, sepsis syndrome is a challenge to study," remarked Warren. Sepsis, according to the current definition, is associated with a high, variable mortality rate, encompasses a heterogeneous patient population, and has an unpredictable disease progression. Sepsis also is challenging to investigate because its etiology and pathogenesis remain unclear, and because it is defined by inflammation, regardless of the source.

"Also, very importantly, our knowledge base has expanded tremendously since 1992, when the definition was agreed upon," said Warren. "We now know that sepsis involves more mediators than previously thought, and that Toll-like receptors play an important role. Thus, I think it is time to begin to think about a narrower definition of sepsis." Warren discussed a few theories of sepsis that have surfaced in the past two decades. According to the coagulopathic theory, sepsis represents microbe-induced disseminated intravascular coagulation, as occurs in *Neisseria meningitidis* infection. Similar clotting problems have been linked to ancient organisms (e.g., *Limulus polyphemus* or horseshoe crabs), and knowledge derived from this link has evolved into use of the *Limulus* Amebocyte Lysate test to detect endotoxin. The coagulopathic theory has led to the clinical use of heparin and activated protein as anticoagulation therapies.

The cytokine theory of sepsis rests on the concept that soluble proinflammatory mediators are released in response to a microbial challenge, amplify the host response (inflammation), and can cause death. In animal models, neutralization of some cytokine mediators protects against high-dose bacterial infusion. "This theory emerged in the mid-1980s, with studies demonstrating that tumor necrosis factor (TNF) was a necessary mediator of acute septic shock, and that bacterial-induced death could be blocked by anti-TNF antibodies," explained Warren.

Research over the past 15 or 20 years has also revealed that sepsis can be treated by blocking mediators other than TNF, including various interleukins, leukotrienes, prostaglandins and others. "Our understanding now includes evidence that macrophages get their signal through Toll-like receptors that all converge in a complex signaling system," Warren said. Eventually, the signaling cascade is amplified and modified, inducing inflammation. Clinical response is determined by combi-

nations of receptors and the temporal history of each receptor's activation, making it possible for a limited number of receptors to generate a multitude of clinical syndromes.

Scientists also have discovered that many immune cell agonists have synergistic properties, which can exist between different microbial TLR agonists and between microbial and endogenous agonists. Such synergy creates the potential for interrupting proinflammatory response by blocking either the TLR mechanism or endogenous agonists themselves.

Another theory of sepsis is the anti-inflammatory hypothesis, which purports that sepsis is a biphasic syndrome. The initial phase (i.e., the systemic inflammatory response syndrome) is pro-inflammatory. This is followed by the compensatory anti-inflammatory response syndrome, characterized by an influx of anti-inflammatory molecules such as TNF, interleukin-4 and interleukin-10. "It has also been proposed that these different responses may occur simultaneously, with proinflammatory signals in the tissue and anti-inflammatory signals in the blood trying to control systemic spread," said Warren. "In addition, some have proposed that the anti-inflammatory response is due to apoptosis of cells."

The apoptotic theory of sepsis, based on experiments by Hotchkiss and colleagues, reflects the observation that massive apoptosis of lymphocytes is seen in lymphoid tissues of animals and humans with sepsis. "Hotchkiss proposed that the later phase of immunosuppression may be due, in part, to apoptosis," explained Warren. "He reasoned that, therefore, the secondary nosocomial infections we see, and perhaps viral reactivation, is one of the root causes of sepsis in our intensive care units."

Warren completed his discussion of sepsis hypotheses by explaining the neuroendocrine theory of sepsis. Although much is known about the adrenergic pathways, epinephrine and the role of the adrenal gland, less is understood about the cholinergic pathways and cholinergic anti-inflammatory reflex. "In a remarkable series of experiments, Tracey revealed a reflex arch that shows immune modulation occurs not through humeral mechanisms, but through nerve endings," noted Warren. An afferent arc of the reflex, consisting of nerves that sense injury and infection, activates efferent neural circuits such as the cholinergic anti-inflammatory pathway that modulates immune responses and progression of inflammatory diseases (Tracey KJ. *Nat Rev Immunol*. 2009;9:418). "We can think about this as the vagus nerve providing a constant brake on the inflammatory system, and there are at least two potential implications of this system," said Warren. "One is that a root cause of sepsis could be due to decreased braking, resulting in too much inflammation. The other is the possibility that this pathway could be manipulated either neurologically or pharmacologically to provide treatment."

After discussing these various sepsis theories, Warren asked: "Is inflammation really essential for host defense? Is microbial-induced inflammation always in proportion to what is required?" According to the current paradigm, inflammation has evolved to the right proportion for host defense. "Using the metaphor of walking a tightrope, the person who doesn't have enough inflammation would be immunocompromised or have acute and chronic infection," Warren said. "On the flip side, the person who has too much inflammation would have sepsis or chronic inflammatory disease. Thus, our current paradigm holds that health consists of just the right balance of inflammation to maintain host defense but not cause disease."

Summing up what is known about the immunopathophysiology of sepsis, Warren noted that an all-encompassing single mechanism remains elusive. Host inflammation is believed to be the cause of the syndrome, yet no single component of the immune system is solidly implicated. He added that the natural resistance of mice to inflammation relative to humans might suggest a potential role for blockage of TLRs without compromising host defense.

The Role of Toll-Like Receptors in Sepsis Judith Hellman, MD

Sepsis is induced by interactions between components of microorganisms and host cells that lead to the upregulation of inflammation pathways, complex coagulation disturbances, problems with oxygen delivery and utilization, and vascular leak; TLRs play a central role in these interactions and the downstream inflammatory effects. "TLRs are critical in the early inflammatory responses to infection and are involved in the development of 'adaptive immunity,'" stated Judith Hellman, MD, from the University of California in San Francisco, California, USA.

"We know that TLR agonists circulate in the bloodstream in sepsis, and that TLR polymorphisms have been identified," Hellman continued, pointing to the higher incidence of TLR4 polymorphism noted in patients with meningococemia (Smirnova I, et al. *Proc Natl Acad Sci USA*. 2003;100:6075) and the increased susceptibility to *Legionella* observed in patients with common TLR5 mutation (Hawn TR, et al. *J Exp Med*. 2003;198:1563). TLRs also are postulated to participate in SIRS from endogenous processes and have been implicated in a broad range of human disease, including ischemia-reperfusion injury, neurologic processes such as neurodegenerative disease, autoimmune diseases and allergies, allograft rejection and atherosclerosis.

The basic structure of TLRs consists of two domains. The extracellular domain contains amino-terminal leucine-rich repeats that interact with the TLR agonists. The cytoplasmic carboxy-terminal Toll interleukin-1 receptor (TIR) domain is responsible for interacting with adapter molecules, inducing the downstream effects of TLR activation and ultimately the production of cytokines and other mediators. There are many different TLRs. Unlike the receptors of the adaptive immune system, which recognize very specific ligands, the TLRs more broadly recognize conserved molecular motifs rather than specific antigens.

The complex TLR signaling system can be simplified conceptually by using two broad categories to describe the different pathways: those that mediate through myeloid differentiation primary response gene (MyD88) and those that mediate through TIR domain-containing adapter-inducing interferon- β (TRIF), as shown in Figure 1. "Most of the TLRs mediate inflammation through the adapter protein MyD88," said Hellman. "TLR2 recognizes bacterial lipoproteins, while TLR4 is unique in that it activates both TRIF and MyD88, so it has two different pathways to induce inflammation. That may explain, in part, why TLR4 is such a potent activator of inflammation."

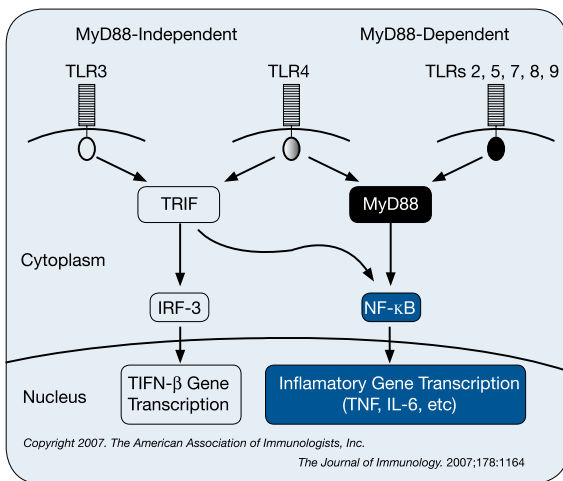


Figure 1. Toll-Like Receptors Signaling System

Research indicates that TLR agonists circulate in the bloodstream both attached to microorganisms, and also separately from microorganisms. Multiple studies have detected lipopolysaccharide (LPS), an agonist for TLR4, in the blood of septic humans and rodents and found TLR2 agonists in septic rodents. "A vast number of studies over the

decades indicate that LPS induces inflammation and other classic septic responses," reported Hellman, "and growing evidence suggests the involvement of bacterial lipoproteins (TLR2) in Gram-positive, fungal, and most recently Gram-negative infection."

There are many reasons why TLR2 should be the focus of interest in sepsis, Hellman stressed. "First, TLR2 agonists are present in all of the major classes of microorganisms that cause sepsis. Second, TLR2 agonists are shed by Gram-negative bacteria into human serum, and they circulate in sepsis models. Third, TLR2 agonists induce inflammation, and fourth, TLR2 activation profoundly modulates inflammatory responses to other Toll-like receptors." The latter point is likely to be important in the clinical context, because patients usually have more than one type of TLR agonist circulating in the bloodstream.

Researchers have observed that TLR2 induces a septic-like process in the lung. TLR2 agonists have been shown to induce lung inflammation, and TLR activation impairs hypoxic pulmonary vasoconstriction and decreases blood oxygenation (Petersen B, et al. *Am J Physiol Lung Cell Mol Physiol*. 2008;294:L300; Hellman J, et al. *J Biol Chem*. 2002; 277:14274).

The endothelium is also important in sepsis and other inflammation-driven processes seen in intensive care unit patients. Endothelial cells actively participate in inflammation through cytokine production, expression of adhesion molecules, activation and trafficking of white blood cells, and expression of other inflammatory mediators. The endothelium contributes to the balance between coagulation and anticoagulation. Endothelial leak occurs in sepsis and other similar inflammation-driven disorders. Interestingly, endothelial cells are activated by TLR agonists. Both TLR2 and TLR4 agonists have been shown to lead to activation of endothelial cells.

"Derangements of coagulation and thrombosis are common during sepsis," noted Hellman. "Coagulation disturbances are believed to be important in the complications of sepsis and SIRS states, with some data linking a coagulation cascade to poor outcomes in sepsis." Such research observed that elevated levels of plasminogen activator inhibitor-1 (PAI-1), an agent involved in inhibiting fibrinolysis, were associated with increased incidences of organ failure and death in sepsis (Mesters RM, et al. *Thromb Haemost*. 1996;75:902; Madoiwa S, et al. *Int J Hematol*. 2006;84:398). "This suggests a role for a hypercoagulable state in the pathogenesis of sepsis-induced organ failure." Activation of TLRs and pathways also has been shown to induce coagulation abnormalities, although the mechanism is not well understood.

In light of the critical role of TLRs in sepsis, can TLR signaling pathways be considered good potential targets for antiseptic therapies? "There's substantial logic supporting targeting Toll-like receptors," stated Hellman. Much of the data involve TLR4, whose agonist is LPS. TLR4-deficient mice have been shown to be LPS-hyporesponsive and yet they do worse with infection, suggesting they require the inflammatory response to help combat infection. "Preclinical studies support targeting TLR4 or MyD88, which are both somewhat required in conjunction for LPS signaling," Hellman said.

TLR2 is also a potential target in sepsis. Among its agonists are lipoproteins, lipoteichoic acid (LTA), lipoarabinomannan and possibly peptidoglycan. Because TLR2 recognizes many different microorganisms, it may be particularly useful in treating early sepsis before pathogen identification. Studies have demonstrated that TLR2 knockout mice are more susceptible to infection (Takeuchi O, et al. *J Immunol*. 2000;165:5392; Puliti M, et al. *Infect Immun*. 2009;77:1524; Echchannaoui H, et al. *J Infect Dis*. 2002;186:798), and some data suggest that TLR2 deficiency is protective against bacterial infection (Wiersinga WJ, et al. *PLoS Med*. 2007;4:e248). Strategies targeting TLR2 have shown promise in preclinical studies (Meng G, et al. *J Clin Invest*. 2004;113:1473; O'Brien GC, et al. *J Immunol*. 2005;174:1020).

Hellman concluded her remarks by emphasizing that TLR4 is the most extensively studied therapeutic target and has shown promise in preclinical studies. "Modulation of TLR4 ligands may represent a therapeutic strategy for sepsis treatment," she said. "Agents directed at TLR4 ligands currently are being investigated for their efficacy and safety in severe sepsis."

Clinical Trials of Anti-TLR4 Agents for Sepsis Mitchell P. Fink, MD, FCCM

“Translating favorable preclinical sepsis findings obtained in animal models into results that are positive in human beings is a daunting task,” said Mitchell P. Fink, MD, from the University of California Los Angeles, California, USA. Further complicating this situation is the fact that one of the preclinical models involves challenging animals or humans with LPS, and this is a model of systemic inflammation but not a model of human sepsis.

Fink noted that the elucidation of TLR4 signaling pathway over the past 15 years represents an important advance in immunology and inflammation research. TLR4 is a receptor for both pathogen-associated pattern molecules (e.g., LPS and lipoarabinomannan) and danger-associated pattern molecules (e.g., HMGB1, heat shock proteins, hyaluronan, biglycans, and fibronectin). Of these substances, LPS (endotoxin) is the most important exogenous ligand for TLR4.

Several clinical trials have been conducted to evaluate the use of anti-TLR4 agents that target LPS (antibodies against LPS, polymyxin B, and bactericidal/permeability-increasing protein) or TLR4 and the TLR signalosome (TAK-242 and eritoran). Although disappointing mortality outcomes have emerged from the trials investigating antibody-based therapies aimed at the core region of LPS, another therapeutic approach – that of detoxifying endotoxin with a small or mid-sized molecule that binds to endotoxin and neutralizes it – may have promise. The classic compound for accomplishing this in the laboratory is the antibiotic polymyxin B.

“The question is: Can you take advantage of the ability of polymyxin B to neutralize endotoxin and use it therapeutically in the clinic? The answer is: Maybe by using a special cartridge designed for hemofiltration,” said Fink. Favorable results have been reported with the use of the polymyxin B hemoperfusion cartridge, which is approved in Japan for the adjuvant treatment of severe sepsis and septic shock. In a multicenter, unblinded controlled trial, 64 patients with severe sepsis or septic shock who underwent surgery for intra-abdominal infection were randomized to receive either standard therapy or two treatments (24 and 48 hours postsurgery) of hemoperfusion using the endotoxin-binding cartridge (Cruz DN, et al. *JAMA*. 2009;301:2445). “The results were encouraging, and indicated a statistically significant difference in survival,” noted Fink. Furthermore, a meta-analysis of the many trials investigating the cartridge yielded positive data regarding the use of this device (Cruz DN, et al. *Crit Care*. 2007;11:R47).

Another molecule that binds to and neutralizes endotoxin is bactericidal/permeability-increasing (BPI) protein, an endogenous protein found in the granules of neutrophils. In both *in vitro* and preclinical models, BPI is capable of neutralizing the pro-inflammatory effects of LPS. A recombinant form, rBPI-21, was evaluated in a randomized controlled trial involving 393 patients with severe meningococcal sepsis (Giroir B et al. *Lancet*. 356:961). Although no significant difference was observed in overall mortality, the therapy was associated with reduced incidences of amputation or long-term residual neurologic dysfunction. “Unfortunately, because the study failed to meet its primary endpoint, development of BPI-21 stopped,” stated Fink. “As far as I’m aware, this protein is no longer being developed.”

A third molecule of interest in the treatment of sepsis is TAK-242, a small molecule that is highly specific for TLR4 and does not block any other TLRs. In a concentration-dependent fashion, TAK-242 blocks the secretion of cytokines from macrophages stimulated with LPS and γ -interferon. Survival is improved markedly with administration of TAK-242, either given as a pretreatment or as a post-treatment, in mice challenged with a lethal dose of endotoxin. “The results of preclinical studies were dramatic,” said Fink. “TAK-242 appeared to be nontoxic, it’s not expensive to manufacture, and I thought it had great promise. However, despite these favorable preclinical data, the results in a phase 2 trial of patients with severe sepsis were very disappointing.” Thus, development of TAK-242 also has ceased.

“That leaves us with eritoran, which is a modified form of lipid A,” Fink stated. “Eritoran binds to the Toll-like receptor and prevents the binding of lipid A or LPS. However, eritoran is not an agonist and does not activate downstream signaling via the TLR4 pathways. Rather, eritoran is a classic competitive antagonist of the TLR4 signaling system.” In human volunteers challenged with LPS, 100 and 250 μ g doses of eritoran blocked all clinical signs and symptoms of LPS-induced toxicity (chills, fever, headache, myalgia, and tachycardia) as well as all biochemical effects of an LPS challenge.

Data from a phase 2 study of eritoran in patients with severe sepsis recently were published (Tidswell M, et al. *Crit Care Med*. 2010;38:72). Patients received either 45 mg or 105 mg of eritoran over six days. Results showed a trend toward a lower mortality rate among patients treated with eritoran versus placebo, particularly with the dose of 105 mg. An analysis of prospectively defined subgroups indicated that eritoran tended to have a greater effect among sicker patients, but the results were not statistically significant (see Figure 2). Trends toward improved survival occurred in patients with shock versus without shock and in patients with gram-positive infection versus gram-negative infection. No demonstrable effect on circulating levels of interleukin-6, a classic marker of systemic inflammation, was observed.

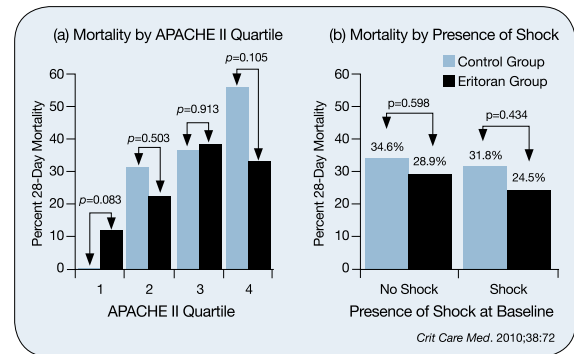


Figure 2. Mortality by APACHE II Quartile Versus Mortality by Presence of Shock

“We will soon hear the results of the phase 3 trial of eritoran, which has enrolled 2,000 patients in almost 160 centers worldwide,” reported Fink. “At this time, we don’t know whether the results will be favorable or not.”

In closing, Fink emphasized that TLR4 is an attractive target for the treatment of severe sepsis, in part because it is specific not only for LPS but also for a number of endogenous ligands involved in orchestrating the inflammatory response. Two strategies that target TLR4 signaling – polymyxin B cartridges and eritoran – appear to be promising and are under investigation.

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Continuing Education Self-Assessment

THE SCIENCE AND MEDICINE OF SEPSIS MANAGEMENT

- Which one of the following theories is explained by a reflex arch involved in modulating the immune responses and progression of inflammatory disease?
 - Anti-inflammatory theory of sepsis
 - Apoptotic theory of sepsis
 - Cytokine theory of sepsis
 - Neuroendocrine theory of sepsis
- Endothelial cells are important in sepsis and are activated by both TLR2 and TLR4 agonists.
 - True
 - False