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## Advances in Surgical Critical Care

With an aging population and an increased demand from the public to care for extreme medical conditions, admissions to the intensive care unit (ICU) have increased. A total of 87,400 ICU beds in the United States accept 4.4 million ICU admissions annually.<sup>1</sup> Despite these numbers representing a 26.2% increase in beds over the previous 15 years, access to the ICU has been more difficult due to a combination of medical, legal, financial, and administrative factors. ICU beds account for approximately 10% of all hospital inpatient beds, yet result in 20% to 35% of all hospital operating costs. It has been estimated that ICU expenses in the United States represent 1% of the gross domestic product, approximating \$90 billion annually.<sup>2</sup>

The overall ICU mortality of approximately 15% accounts for nearly 60% of all in-hospital deaths and translates into 500,000 ICU deaths per year.<sup>3</sup> As of 2000, there were 10,244 intensivists in the United States. Even if the demand is expected to rise by 30% over the next 3 decades, the supply is expected to remain constant. Critical care certification is typically achieved after a 1-year fellowship. Although more than two thirds of intensivists originate from the medical track, surgeons have sought critical care board certification in increasing numbers over the last decade. Most surgeons with critical care credentials follow a trauma surgery career.

Organized efforts have been put in place by multiple societies, governmental agencies, and large corporations to improve the delivery of ICU care. These efforts target the reduction of the risk of death while reducing cost at the same time.<sup>2</sup> Significant technological advances have been introduced to satisfy these goals. The ICU remains a hotbed for contradictory principles, such as innovation and standardization, cost curtailment, and increased resource allocation. Intricately bound with technology, the care we deliver to our ICU patients is destined to change continuously and rapidly. In the following chapters we describe some of the interesting trends and new methods that have been tried and succeeded or failed in the ever-challenging ICU environment.

## Advances in Bedside Procedures

Surgical patients in the ICU frequently require transport to and from the operating room (OR). Although the OR is traditionally thought to be the safest place to perform these procedures, the transport itself harbors major risks. Since the 1970s, when 1 cardiorespiratory arrest or death per month was directly related to transport,<sup>4</sup> monitoring equipment and transport protocols have greatly improved. However, safety of transport still remains a formidable issue.

The morbidity of transport of critically ill patients ranged from 13%<sup>5</sup> to 33%<sup>6</sup> and required significant changes in management in up to 25% of the patients.<sup>7</sup> With an average of 6 access lines, monitoring devices, and life-support modalities connected to ICU patients,<sup>6</sup> it is not hard to imagine how mishaps can occur. The American College of Critical Care Medicine developed guidelines for the transport of critically ill patients.<sup>8</sup> According to the guidelines each hospital should have a formalized plan for transport addressing: a) pretransport coordination and communication, b) transport personnel, c) transport equipment, d) monitoring during transport, and e) documentation. The transport plan should be developed by a multidisciplinary team and evaluated regularly. The commitment to resources is obvious and the strain to personnel not hard to imagine. Despite our intensive efforts to prevent errors, transport of ICU patients remains an inherently risky endeavor. Events that range from relatively innocuous (dislodgement of electrocardiographic [ECG] leads) to potentially life-threatening (inadvertent extubation) events will always be associated with out-of-ICU transports despite the best designed plans.

### *Rationale for Bedside Procedures in the ICU*

Beyond the obvious elimination of transport-related complications, performing procedures at the ICU bedside may have important financial and resource benefits. According to Van Natta and colleagues,<sup>9</sup> the difference in cost between performing percutaneous tracheostomies, gastrostomies, and vena caval filter placements at the bedside and the OR was \$611,944 over a period of 69 months in 379 patients, averaging \$1624 per patient. The margin (a ratio of hospital charges divided by hospital cost and a measure of profitability) was 54% higher at the bedside than the OR and 9.6% higher than the radiology suite. Savings of \$1844 to \$2245 have been reported if vena caval filter insertion takes place at the bedside rather than the radiology suite or OR.<sup>10,11</sup> Performing an open tracheostomy at the bedside rather than in the OR decreases cost by \$1740.<sup>12</sup> In another study, the

hospital charges for the 12 patients who had percutaneous dilatational tracheostomy (PDT) in the ICU were \$3400 less per patient when compared with the 36 patients who had open or percutaneous tracheostomy in the OR.<sup>13</sup>

Operating room congestion is routine. Tracheostomies, gastrostomies, and vena caval filter placements are rarely an emergency, and for this reason placed on the waiting list. It is not unusual to either have the procedure canceled or performed at the most inconvenient time. Cancellations and delays are stressful for the surgeon, the patient, and the relatives. Bedside procedures can be performed without delays on the day of request and independent of OR availability.

### *The ICU as an OR*

It is important that no shortcuts are used in the ICU when preparing for and performing a surgical procedure. All rules of sterility are followed, exactly as they would have been implemented in the OR. The surgeons are fully gowned and the patient properly prepped and draped. Monitoring should be adequate. The ICU room should be prepared by moving the bed and surrounding devices in a way that ensure comfortable operating conditions and ease of circulation of personnel. There should be enough space at the head of the bed to accommodate 2 persons. It is not unusual to have ventilators, poles, tubes, and monitors entangled in tight spaces, making easy access to the patient—and particularly the patient's head—quite challenging. All this equipment should be rearranged to make access and intervention easy. Adequate lighting is very important and often missing. There is no need to have anesthesiologists and OR nurses on site, as the intent is to decrease human resources and cost. However, help should be prompt if required.

In general, the ICU room can become a very safe operative environment with small temporary modifications. The operating surgeon should supervise these details personally at the beginning. The setup of the room quickly becomes routine, as long as everybody understands the importance of an optimally arranged room. Nobody wants to jump over cables or be blocked by a device in case of an emergency.

### *Percutaneous Dilatational Tracheostomy*

The ability to insert a tracheostomy tube with minimal surgical dissection has revolutionized this procedure. The percutaneous dilatational technique, as described by Ciaglia and colleagues in 1985,<sup>14</sup> became the most popular technique in the United States. There are several commercial kits available on the market; the Ciaglia Blue Rhino kit

(Cook Critical Care, Bloomington, IN) and the Per-fit kit (SIMS Portex Inc., Keene, NH) are more widely used in the United States. The 2 kits are very similar and include all the tools required for the technique, making the cumbersome search for instruments, drapes, prepping devices, and sutures unnecessary.

**Procedure.** The procedure starts by inserting a bronchoscope through the endotracheal tube and withdrawing the tube under bronchoscopic guidance above the intended level of tracheostomy. In this way all instruments entering the trachea during the procedure are inspected bronchoscopically. A vertical 2.5-cm incision is placed in the middle of the distance between the cricoid cartilage and the sternal notch. The pretracheal tissues are dissected bluntly and any small bleeding is controlled only by pressure. A fluid-filled syringe is connected to a needle covered by a sheath. The needle is inserted in the trachea and air from the trachea is aspirated, showing as bubbles in the fluid of the syringe. This confirms correct placement into the trachea, also confirmed bronchoscopically. The syringe and needle are removed, and the sheath is left in place. A guidewire is inserted through the sheath, which is then removed also. A track is established by inserting a small and stiff dilator over the guidewire. The dilation of the trachea is then achieved by inserting the Blue Rhino dilator over the guidewire. The final step consists of the insertion of a tracheostomy tube fed over a guiding dilator into the trachea. The tracheostomy tube is secured in place by sutures and tape, appropriate positioning is confirmed bronchoscopically, and ventilation is resumed through the newly constructed tracheostomy.

**Pitfalls and Complications.** The most feared complication is loss of airway. Patients with unfavorable anatomy (eg, obese, in spinal precautions, tracheomalacia) are at higher risk. False passage has been reported in approximately 9% of cases, but in most instances bronchoscopy was not used.<sup>15,16</sup> Although “blind” techniques have been performed safely by experienced teams,<sup>17</sup> we recommend routine bronchoscopy for most cases. The endotracheal tube should not be removed before the correct placement of the tracheostomy tube is confirmed by bronchoscopy and unobstructed mechanical ventilation. A thick neck may require an extra long tracheostomy tube. Postoperative loss of the airway can lead to death.<sup>18</sup> Tracheostomy tube displacement can occur during transport, mobilization, nursing care, or episodes of agitation.

Tracheostomy tube exchange is safe only after the track is mature around the fifth to seventh day after insertion for percutaneously inserted tubes. The exchange can occur over a catheter or a guiding dilator. An intubation set should be in the room.

Bleeding is rarely a problem as the track is tight around the tube and any bleeding vessel is blocked. We never use electrocoagulation and did not have any episodes of significant bleeding. On a few occasions a single suture or pressure controlled superficial bleeding. Similarly, infection is not a common complication. Superficial erythema is responsive to antibiotics, and we never had to remove a tracheostomy tube or open a wound for major infection.

***Comparison Between Open and Percutaneous Tracheostomy.*** There are 7 prospective randomized studies comparing open and percutaneous tracheostomy, but the technique, complications, and site of operation (bedside vs OR) vary. In Table 1, we describe these studies and list the total number of complications, resulting in a 40% incidence for the percutaneous group and 39% for the open.<sup>19-24</sup> Table 2 shows the same studies with only the major complications, which were clinically significant and directly related to the method of tracheostomy (7% percutaneous and 8% open).

### *Percutaneous Endoscopic Gastrostomy*

Percutaneous endoscopic gastrostomy (PEG) was originally developed by Ponsky and Gauderer at the Rainbow Babies and Children's Hospital in Cleveland.<sup>25</sup> It has now essentially replaced open gastrostomy, which is reserved only for cases in which the percutaneous approach is not possible. The 2 most frequently used techniques are the "pull" and the "push," the former used by surgeons and the latter mostly by interventional radiologists. Outcomes related to the 2 techniques are similar.<sup>26</sup> We describe below the pull technique, which is common among surgeons.

***Technique.*** The procedure starts with esophagogastrosopy, which examines the stomach and insufflates it to achieve apposition of the anterior gastric wall to the anterior abdominal wall. The exact point of insertion is identified by pushing the anterior abdominal wall with 1 finger and visualizing the indentation gastroscopically. Transillumination indicates that no organs (eg, colon, liver) are interposed between the stomach and abdominal wall. A sheathed needle is introduced in the anterior abdomen and observed gastroscopically to enter into the stomach. The needle is removed and the sheath remains in place. A wire is inserted through the sheath and snared. The snare and gastroscope are removed, pulling the snared wire through the mouth. At this point 1 end of the wire comes out of the abdominal wall (through the sheath) and the other through the mouth. The end of the wire that comes through the mouth is knotted with the edge of the gastrostomy tube. The other end of the wire is pulled, and in this way, the gastrostomy tube travels through the mouth, esophagus, and out through the stomach. The tube is pulled to the point

**TABLE 1.** Seven prospective randomized studies comparing percutaneous dilatational tracheostomy (PDT) and open tracheostomy

Study	N	Specifics	Overall complications	
			PDT	Open
Hazard <sup>19</sup>	48	PDT kit used: not mentioned Bronchoscopy: not mentioned Site: open in OR or bedside; PDT at bedside	25% (6/24)	58% (14/24)
Crofts <sup>20</sup>	53	PDT kit used: "old" Cook kit Bronchoscopy: no Site: open in OR; PDT at bedside	20% (5/25)	36% (10/28)
Friedman <sup>21</sup>	53	PDT kit used: "old" Cook kit Bronchoscopy: no Site: open in OR; PDT at bedside	46% (12/26)	85% (23/27)
Porter <sup>18</sup>	24	PDT kit used: "old" Cook kit Bronchoscopy: yes Site: open and PDT at bedside	42% (5/12)	17% (2/12)
Gysin <sup>22</sup>	70	PDT kit used: "old" Cook kit Bronchoscopy: yes Site: open and PDT in OR or bedside	89% (31/35)	66% (23/35)
Heikkinen <sup>23</sup>	57	PDT kit used: Portex kit Bronchoscopy: no Site: open and PDT at bedside	32% (10/31)	19% (5/26)
Massick <sup>24</sup>	100	PDT kit used: "old" Cook kit Bronchoscopy: yes Site: open and PDT at bedside	26% (13/50)	4% (2/50)
Total	405		40% (82/203)	39% (79/202)

OR, operating room; PDT, percutaneous dilational tracheostomy.

As "old" Cook kit, we refer to the previous kit containing the multiple sequential dilators, which has now been replaced by the single progressive dilator kit (Blue Rhino; Cook Critical Care, Bloomington, IN).

that it allows apposition of the stomach with the abdominal wall, usually corresponding to a marking of 2 to 4 cm at the skin level. A bumper is placed over the tube and secures it in place. The gastroscope is reintroduced and confirms the correct placement of the gastrostomy tube.

**Pitfalls and Complications.** The most common—and on occasions devastating—complication is infection. Local infection occurs in 5% to 30% of cases, not exactly a low-rate complication after a relatively straightforward procedure. It has been suggested that creating a large skin incision prevents entrapment of bacteria and decreases the closed space

**TABLE 2.** Major complications directly related to the method of tracheostomy in the 7 prospective randomized studies

Study	N	Major complications		Type of major complication	
		PDT	Open	PDT	Open
Hazard <sup>19</sup>	48	4% (1/24)	25% (6/24)	1 pneumothorax	1 pneumothorax leading to death 1 major stenosis 4 significant infections
Crofts <sup>20</sup>	53	0% (0/25)	7% (2/28)		1 pneumothorax 1 significant infection
Friedman <sup>21</sup>	53	11.5% (3/26)	18.5% (5/27)	1 paratracheal insertion 1 decannulation 1 significant bleeding	4 decannulations leading to death in 2 1 significant bleeding leading to death
Porter <sup>18</sup>	24	8% (1/12)	0% (0/12)	1 paratracheal insertion leading to death	
Gysin <sup>22</sup>	70	3% (1/35)	3% (1/35)	1 cannula obstruction	1 tracheal granuloma
Heikkinen <sup>23</sup>	57	0% (0/30)	8% (2/26)		1 difficulty in swallowing 1 tracheocutaneous fistula
Massick <sup>24</sup>	100	16% (8/50)	2% (1/50)	4 significant bleeds 2 decannulations leading to death in 1 1 significant infection 1 cannula obstruction	1 significant bleed
Total	405	7% (14/203)	8% (17/202)		

PDT, percutaneous dilatational tracheostomy.

infection. We have tried all possible sizes of incision with no apparent change in our wound complication rates. Meta-analysis of trials suggests that a single preoperative dose of antibiotics administered 30 minutes before the procedure reduces the relative and absolute risk of surgical site infection by 73% and 17.5%, respectively.<sup>27</sup> Our personal opinion is that since the gastrostomy tube travels through the mouth, which may host

pathogenic bacteria in patients with prolonged ICU stays, sterility is impossible and a certain degree of wound infection unavoidable. For this reason, close postoperative scrutiny, often not reserved for such “minor” procedures, is mandatory to uncover wound infections early and avoid devastating progression to necrotizing soft tissue infections.

Injury to intra-abdominal organs can occur during placement if they are interposed between the stomach and abdominal wall. Colonic perforations, intrahepatic abscesses, and multiple other complications have been reported. Gastrostomy tube dislodgement (out of the stomach) or migration (toward the pylorus) may occur with symptoms of peritonitis or outlet obstruction respectively. The “buried bumper” syndrome occurs when the external bumper used to stabilize the tube is placed under high tension and eventually erodes into the skin. Extraction and replacement of the bumper is necessary, as well as treatment for the frequently associated wound infection.

In general, percutaneous gastrostomy is far from an innocuous procedure. Despite its seeming ease and lack of complexity, it may result in serious complications, if taken lightly and rigorous attention to technique and postoperative care is not paid.

### *Percutaneous Inferior Vena Cava Filter Placement*

The use of inferior vena cava (IVC) filters in critically ill patients to prevent pulmonary embolism (PE) has been increasing over the last 20 years. It is unclear whether the rate of PE has been decreasing correspondingly. Recently, the development of removable filters has allowed more liberal use, as the physicians believe that the intravascular device can be only temporary. Unfortunately, reality is different, and studies show that the rate of removal remains below 20%.<sup>28</sup> A variety of reasons exist, with loss to follow-up, persistence of risk factors, unwillingness of the patient to be subjected to additional procedures, and technical inability being among them. Filters are placed percutaneously by using 3 methods: fluoroscopy, external ultrasonographic guidance, or endovascular ultrasonography. A duplex ultrasound to examine for femoral clots and decide the place of insertion is the common beginning of all the techniques.

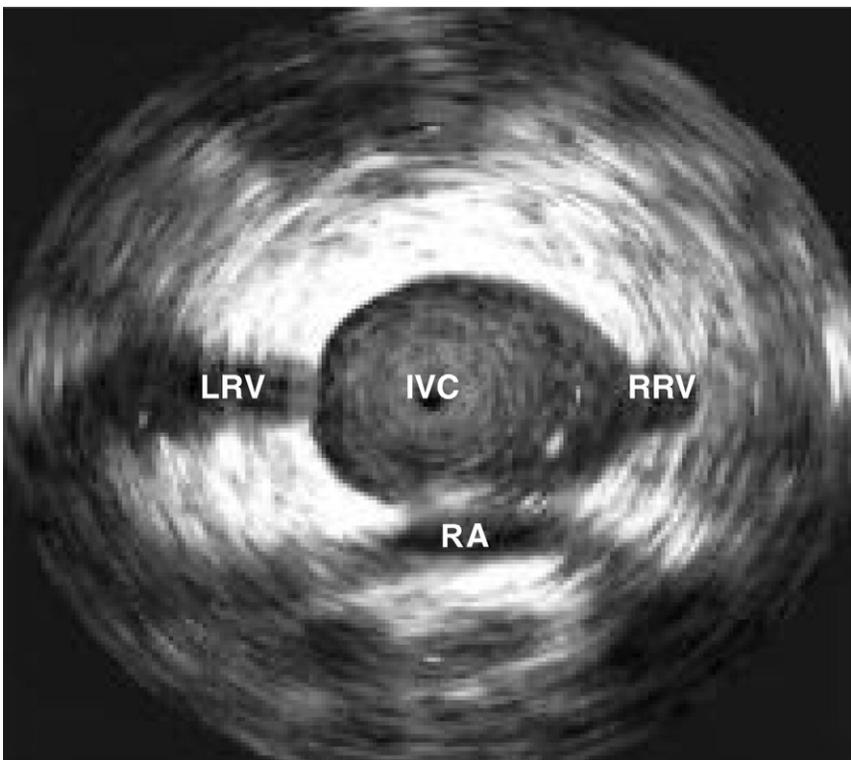
#### ***Techniques***

*Fluoroscopic.*<sup>29</sup> This is now the most common technique. Venous cannulation is performed typically at the left or right femoral vein, using a Seldinger technique. A 4 or 5 Fr angiographic catheter is advanced over a guidewire into the IVC and up to the second lumbar vertebra. The L4-L5 region is marked and the anatomy and width of the IVC is visualized by contrast. The renal veins are defined. After venography is completed, the

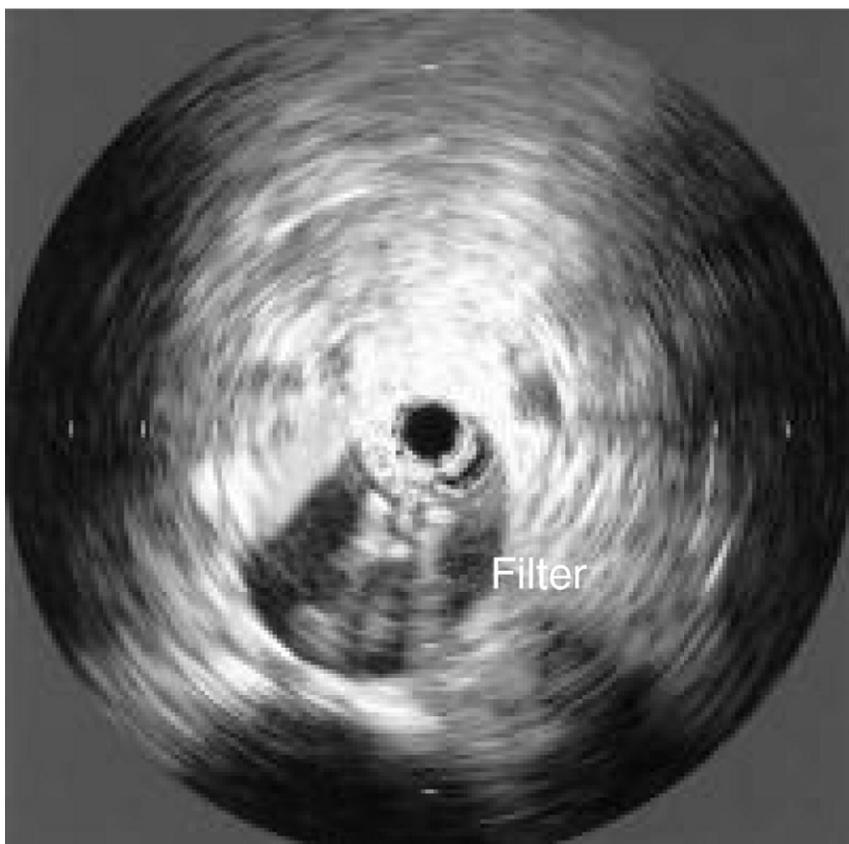
pigtail catheter is exchanged for the sheath, which is inserted over a dilator. The sheath is positioned under the renal veins and the filter carrier system is advanced into the sheath. The filter is then deployed, completion venography is performed, and the sheath is withdrawn. In correct position, the filter should not be tilted more than 15° relative to the IVC axis and its tip should be immediately below the renal veins.

*Ultrasonographic.*<sup>30</sup> The exact same maneuvers are performed, but guidance is achieved by ultrasound. Because most ICU surgical patients have abdominal operations with distorted anatomy or distended bowel, which compromises ultrasonographic imaging, we believe that this technique is not ideal in the ICU.

*Intravascular ultrasonographic.*<sup>31</sup> Through a puncture in the femoral vein a wire and 8 Fr sheath is inserted into the IVC, and the intravascular ultrasound is advanced over the wire. It visualizes the IVC and renal veins, and measures the maximal diameter of the IVC (Fig 1). A second



**FIG 1.** Location of renal veins by intravascular ultrasound as an anatomical landmark below which the filter is deployed. LRV, left renal vein; IVC, inferior vena cava; RRV, right renal vein; RA, renal artery.



**FIG 2.** Filter deployed in the IVC.

puncture in the contralateral femoral vein is required to insert another wire and introduce the delivery sheath for the filter. The sheath and filter are positioned immediately below the renal veins and the filter is deployed while visualized directly by the intravascular ultrasound (Fig 2).

A postinsertion plain radiograph is performed routinely to verify correct placement at the L2-L4 level (Fig 3).

***Pitfalls and Complications.*** Access site complications include bleeding, arterial puncture (and arterial damage), and deep venous thrombosis (DVT). Misplacement of the filter has been reported to occur in 4% of the cases in locations that include the suprarenal IVC or vessels other than the IVC. Migration of the filter to the atrium and perforation of the IVC or heart are rare complications that can be associated with serious morbidity. The true incidence of caval thrombosis is unknown



**FIG 3.** Postinsertion abdominal film showing filter in the IVC.

and ranges from 0% to 25% according to the type of population and intensity of follow-up.

**Retrieval of Filters.** The retrieval is usually performed through the jugular vein. After cannulation of the vein, a sheath is introduced to the site of the

filter. A snare captures the filter, which collapses within the sheath. The sheath and filter are removed as a unit. As mentioned above, the retrieval rates are disappointing and the causes have not been fully explored. It is likely that thorough follow-up by the service introducing the filter (eg, interventional radiology, cardiac or vascular surgery, trauma surgery, other) will increase the rate of removal.

Filters are currently improving in design, effectiveness, and safety, and new devices are constantly brought into the market. Similarly, the time to retrieval is continuously increasing and currently exceeds 6 months.

## **Advances in Noninvasive Hemodynamic Monitoring**

Despite the paramount importance of clinical examination in any surgical setting, one would appreciate its unreliability for a sedated, intubated, and paralyzed ICU patient. The quality and accuracy of monitoring of the critically ill surgical patient becomes a cornerstone for correct diagnosis and decision making. Ever since a shadow was cast over the use of pulmonary artery catheters by the seminal study of Connors and colleagues,<sup>32</sup> arguing for a higher mortality rate among patients with such catheters, new methods of monitoring are constantly being proposed. In a complex ICU or emergency department environment, it is important that monitoring is continuous, reliable, safe, and easy to use and interpret. Noninvasive methods are preferable for obvious reasons.

Traditional blood pressure and heart rate monitoring is subject to significant variation and associated with low specificity in detecting compromised tissue perfusion and impending or present shock. It is not unusual for a septic or bleeding patient to maintain a “normal” blood pressure and/or heart rate. Young patients with robust compensatory mechanisms can vasoconstrict intensively and demonstrate normotension in the face of profound tissue hypoxemia. On the other extreme, old patients who are hypertensive in their daily life, may manifest a blood pressure in the low 100s, which could be perceived as normal, even if it is profoundly low for their own standards. Heart rate is even more unreliable, as patients can become tachycardic for a variety of reasons unrelated to shock or remain normocardic despite significant vasodilatation or volume loss. For all these reasons, monitoring besides a blood pressure and heart rate is highly desirable. Arterial blood gases and lactate levels provide excellent information that, however, is episodic and usually arrives late. Methods that provide the information the moment a clinical event occurs and allow continuous online monitoring should theoretically allow prompt interventions with improved outcomes. Unfortunately, even if many methods claim early

and accurate detection of hypoperfusion, the improvement in outcomes is yet to be documented. All of the methods described below are noninvasive and provide continuous, concurrent measurements.

### *Thoracic Bioimpedance*

Several noninvasive methods have attempted to describe cardiac output. The discovery of bioelectric principles regarding the flow of blood within the thoracic aorta allowed estimation of stroke volume and cardiac output.<sup>33</sup> Impedance changes are measured across the thoracic cavity, assuming that changes in aortic volume is the primary cause of change in thoracic impedance. However, it is possible that changes in hematocrit, interstitial fluid (particularly in patients with leaking capillaries), hemothorax, or the shape of the chest, among other parameters, may influence impedance. Taking account these limitations, multiple corrections in the equation that estimates the cardiac output have been performed to improve accuracy. The patient is connected to the transducer through a series of disposable surface electrodes. Stroke volume, cardiac output, and the contractility/ejection fraction are being displayed continuously on a monitor. The technique has been validated by direct comparison with cardiac output values derived by a pulmonary artery catheter and shown to have excellent correlation.<sup>34</sup> Monitoring of trauma patients with a bioimpedance monitor has demonstrated that hemodynamic changes due to bleeding or shock can be identified early.<sup>35,36</sup>

### *Heart Rate Variability*

Despite heart rate in itself being a relatively unreliable measure of tissue hypoperfusion, the study of heart rate variability has shown promising results in detecting the fine balance of the autonomic system as it relates to shock. Spectral analysis of the ECG waveform has been used to prove that high-frequency variations are associated with the parasympathetic nervous system and low-frequency variation with the sympathetic nervous system. Such waveform measurements have shown an association with outcome in multiple disease states, including infection, multiple organ failure, and myocardial infarction. A reduced heart rate variability, mentioned as “cardiac uncoupling,” independently predicts morbidity and mortality.<sup>37</sup> Interestingly and as opposed to other parameters that may lose their predictive power as the interval from injury increases, heart rate variability remains a robust predictor of outcome throughout the ICU stay. Cardiac uncoupling increases in response to inflammation, infection, and multiple organ failure. Loss of variability and increase in periodicity in heart rate of critically ill

patients are linked with parallel deterioration of organ dysfunction and high mortality rates.<sup>38</sup>

### *Pulse Pressure Variability*

Changes in pulse pressure should be associated linearly with changes in blood volume, provided that the arterial distensibility remains constant. Based on this principle the measurement of pulse pressure variability provides information about loss of volume.<sup>39</sup> However, it has been found that arterial distensibility is not constant and depends on the sympathetic activation and the inherent elastic properties of the vessel walls. Algorithms that can combine measurements of pulse pressure with sympathetic nerve activity have been used and found successful to prove that a reduction in pulse pressure tracks the reduction of stroke volume during graded hypovolemia.

### *Transcutaneous Oxygen and Carbon Dioxide*

For more than 40 years transcutaneous oxygen and carbon dioxide have been used as a noninvasive and easily applicable method to monitor tissue perfusion in infants and premature neonates, as a surrogate of arterial blood gases. Transcutaneous oxygen correlates well with partial arterial oxygen tension and cardiac output during normal and abnormal flow conditions.<sup>40</sup> Similarly, transcutaneous carbon dioxide correlated well with partial arterial carbon dioxide tension during normovolemia but became flow-dependent during low-flow states. In a study of critically injured patients marked changes were observed in the transcutaneous oxygen and carbon dioxide measurements, which correlated well with temporal patterns of resuscitation.<sup>41</sup> As indicators of tissue perfusion/oxygenation, these values identified early the presence of shock.

### *Gastric Tonometry*

The measurement of gut mucosal carbon dioxide has been used to detect decreased blood flow. Accumulation of carbon dioxide is predominantly a result of hypoperfusion and not hypoxia. Because the introduction of a nasogastric tube is almost routine in critically ill patients, the measurement of gastric carbon dioxide can be an easy method to monitor tissue perfusion. The gastric mucosal pH is measured according to an equation that assumes that arterial bicarbonate is equal to intramucosal bicarbonate, an argument that is not always valid.<sup>42</sup> Given that the gastric mucosal carbon dioxide is the directly measured value, whereas the gastric mucosal pH is the derived

and possibly inaccurate value, studies that used gastric pH to monitor perfusion may be inherently flawed. Most studies have failed to effectively affect gastric pH and for this reason failed to produce improvements in outcome. One study, by Gutierrez and colleagues, has shown that therapeutic interventions guided by gastric tonometry improved survival in critically ill patients.<sup>43</sup> In a direct comparison of splanchnic-oriented therapy as guided by gastric tonometry with conventional shock management of trauma patients, there was no difference in mortality rates, organ dysfunction rates, or length of stay.<sup>44</sup> After a surge in popularity, the use of gastric tonometry waned and it is currently found with less frequency in surgical ICUs.

### *Sublingual Capnometry*

A natural extension of the above principle is the measurement of mucosal carbon dioxide in sites other than the stomach and, in this way, limits the effect of gastric acid production or medication administration in the reliability of the measurements. Microvascular blood flow abnormalities are frequent in critically ill patients. A decrease in capillary density and in the percentage of perfused capillaries is observed in septic shock. Weil and colleagues have produced multiple studies in critically ill patients using sublingual capnography and confirmed that values correlate with severity and progression of disease, reflect accurately lactate levels, and predict survival.<sup>45</sup> As with gastric tonometry, sublingual capnography has failed to gain the confidence of clinicians for widespread use.

### *Near-Infrared Spectroscopy*

Based on the principles of light transmission through fluids, near-infrared spectroscopy (NIRS) has been developed to assess the redox state of hemoglobin.<sup>46</sup> In the near-infrared region, light transmits through skin, bone, and muscle without attenuation. As light passes through blood the absorption spectra of oxyhemoglobin and deoxyhemoglobin differ. The relative concentration of oxygenated hemoglobin can be estimated. Because the majority of blood volume is intravenous, NIRS estimates primarily the venous concentration of oxyhemoglobin. In animal models of hemorrhagic shock, NIRS was used to measure oxygen saturation in central and peripheral tissues and found to detect tissue hypoxia in specific cellular beds even if the global parameters of resuscitation were restored to normal.<sup>47</sup> NIRS showed a higher level of accuracy compared with gastric tonometry to detect abnormalities of splanchnic perfusion.

The basis of the current use of NIRS is the understanding that peripheral muscle oxygenation correlates with tissue oxygen delivery and consumption during resuscitation. In fact, because the muscle may be deprived of adequate oxygen delivery before central organs are, it is possible that NIRS will provide an early indicator of impending shock. In a multicenter study with 383 patients, 50 of whom developed multiple organ failure, muscle tissue oxygenation as measured by NIRS at the thenar eminence tracked parallel with base deficit.<sup>48</sup> NIRS and base deficit has similar negative and positive predictive values for multiple organ failure and death. Although the negative predictive value was good (88% to 91%), the positive predictive value ranged only from 18% to 20%. However, the benefit of having a continuous and noninvasive monitoring method was considered a significant advantage over drawing blood and waiting for laboratory results on an episodic fashion. This study established a cutoff value of 75% as an equally good or better predictor than a base deficit of 6 mEq/L or systolic blood pressure of 90 mm Hg for hypoperfusion and the need for resuscitation.

### *Pulse Contour Analysis*

This method uses the aortic pressure waveform to estimate the stroke volume and cardiac output.<sup>49</sup> It does require an invasive method—peripheral arterial catheterization—but this is almost routine for critically ill surgical patients. Because it does not require additional interventions exclusively for the purpose of this methodology, we describe it here under noninvasive techniques. The aortic waveform is affected by the intravascular volume and resistance of the arterial tree. Because the aortic waveform is not obtained from the aorta itself but is derived via an arterial line from a peripheral artery, assumptions need to be made in the equation about changes in pulse shape. The accuracy of flow prediction depends on diligent calibration, which allows precise computing of the different parameters and accurate representation of the cardiac output. Frequent recalibration every 4 hours may be required in unstable patients who may be subject to ongoing variation of the arterial tree mechanical properties. Two systems are commercially available (PiCCO by Pulsion Medical Systems, Munich, Germany, and PULSECO by LiDCO Ltd., Cambridge, UK).

Several studies have compared pulse contour cardiac output with thermodilution results, as obtained by a standard pulmonary artery catheter, and found good agreement even when tested in critical illness. It is notable that in most studies patients with arrhythmias had poorly defined arterial waveforms and were excluded from analy-

sis.<sup>49,50</sup> The continuous nature of PiCCO monitoring is attractive, but its limitations and dependence on frequent calibration establish the need for further development of the technology.

### *Transesophageal Doppler*

The esophageal Doppler technique has shown an ability to measure cardiac output and guide fluid resuscitation in critically ill patients. It measures blood flow velocity in the descending aorta by a Doppler transducer that is placed at the tip of a flexible probe introduced into the esophagus through the mouth.<sup>49</sup> Although most comparisons of this method with the thermodilution technique have found good agreement, there are skeptics who are unsure about the validity of the technique. In a meta-analysis, most reports were related to the Deltex monitor (Cardio Q, Deltrex Medical, Chichester, UK) and only 2 referred to the Arrow device (Hemasonic, Arrow International, Reading, PA). The authors concluded that the pooled outcomes showed sufficient validity of the method.

Transesophageal Doppler measurement has been proposed as a technique to guide resuscitation and optimize fluid administration in a goal-oriented algorithm for trauma and emergency surgical patients. Besides continuous measurement of the cardiac output, transesophageal echocardiography can assess preload by measuring the left ventricular end-diastolic volume.<sup>51</sup> In many ICU settings transesophageal echocardiography is being frequently used by trained critical care physicians to evaluate the hemodynamic status of the patient by the appearance of the cardiac cavities.

## **Advances in Resuscitation**

Shock, regardless of etiology, is characterized by decreased delivery of oxygen and nutrients to the tissues, and our interventions are directed toward reversing the cellular ischemia and preventing its consequences. The treatment strategies that are most effective in achieving this goal obviously depend on the different types of shock (eg, hemorrhagic, septic, neurogenic, and cardiogenic). This section focuses on the 2 leading etiologies of shock in the surgical ICU patients: bleeding and sepsis.

### *Hemorrhagic Shock*

Exsanguination is 1 of the leading causes of death following trauma<sup>52</sup> and prompt hemorrhage control along with adequate fluid resuscitation are the key components of early trauma care. Similarly, hemorrhage is often encountered in nontrauma patients as a complication following

major operations. Despite hemorrhage being a common problem, the optimal resuscitative strategy remains controversial, with vigorous debate about issues such as the type of fluid, volume, rate, route of administration, and endpoints of resuscitation.<sup>53</sup>

***Futility of Current Methods/Adverse Effects of Aggressive Resuscitation.*** Although it is widely believed that early aggressive fluid resuscitation is beneficial, clinical and basic science literature fails to provide conclusive supporting evidence. As a matter of fact, the basic rationale for administering intravenous fluids in patients with ongoing bleeding has been challenged repeatedly for almost a century. Theoretically, fluid resuscitation in the absence of (or before) hemorrhage control can exacerbate bleeding due to the disruption of early soft thrombus, coagulopathy, and hemodilution.<sup>54</sup> A systematic review of 52 animal trials concluded that fluid resuscitation appeared to decrease the risk of death in models of severe hemorrhage (relative risk [RR] = 0.48), but increased the risk of death in those with less severe hemorrhage (RR = 1.86).<sup>55</sup> Furthermore, hypotensive resuscitation, whenever tested, reduced the risk of death (RR = 0.37).<sup>55</sup> Similarly, a critical review of the literature failed to find any evidence that prehospital advanced life support improved outcomes in trauma patients.<sup>56</sup> In a study that has generated vigorous debate since its publication in 1994, hypotensive patients with penetrating torso injury were randomized to routine fluid resuscitation, or resuscitation was delayed until bleeding had been surgically controlled.<sup>57</sup> The results of this study demonstrated a survival advantage in the delayed resuscitation group (70% vs 62%,  $P = 0.04$ ). Despite all the controversy, the most impressive finding remains that withholding fluid resuscitation until hemorrhage control did not increase the mortality. The issue of timing and volume of fluid resuscitation in bleeding patients has also been addressed by the Cochrane Database of Systematic Reviews.<sup>58</sup> Only 6 randomized clinical trials met the inclusion criteria, and a careful review failed to provide any evidence in support of (or against) early or large volume intravenous fluid administration in uncontrolled hemorrhage. Based on all this information, it is reasonable to conclude that fluid resuscitation is not a substitute for early hemorrhage control. Low volume, careful resuscitation is reasonable, especially when trying to get a dying patient to definitive care. However, early aggressive fluid resuscitation, in the absence of hemorrhage control, cannot be justified.

In addition to the impact of resuscitation on bleeding, resuscitation fluids have very profound cellular effects. It is now widely recognized that resuscitation fluids are not completely innocuous, and they may

actually potentiate the cellular injury caused by hemorrhagic shock. This concept of “resuscitation injury” has steadily gained attention since a report by the Institute of Medicine (1999) described in detail the wide spectrum of adverse consequences that can follow resuscitative efforts.<sup>59</sup> Historically, the concept of large volume crystalloid resuscitation was a product of seminal work by Shires, Moyer, Moss, and others during the 1960s, and it became common practice during the Vietnam conflict. Their work suggested that infusion of large-volume isotonic crystalloids improved survival, and resuscitation fluids were needed not only to replace the intravascular volume loss, but also to replenish interstitial deficits. Therefore, these investigators recommended fluid replacement equal to 3 times the volume of blood loss (and as high as 8:1 for severe shock). At that time the emphasis was on restoration of intravascular and interstitial fluid deficits, without much importance attached to the cytotoxic effects of crystalloid fluids. Isotonic fluids were used widely in Vietnam and it was during this period that the appearance of “shock lung/Da Nang lung” (later termed acute respiratory distress syndrome or ARDS) was first described in soldiers that received massive crystalloid resuscitation. Today, ARDS and multiple organ dysfunction syndrome are major causes of delayed mortality in trauma patients. An ever-increasing basic science literature supports the new paradigm that cellular injury is influenced not only by shock, but also by our resuscitation strategies. Today, with the easy availability of advanced cellular research techniques, we can study the effect of resuscitation fluids on the biological systems in much greater detail. Review of the literature suggests that commonly used resuscitation fluids can exaggerate the post-trauma immune activation.<sup>60</sup> Therefore, in addition to the immediate side effects (worsening of hemorrhage), delayed complications of fluid resuscitation such as systemic inflammatory response, fluid overload (leading to compartment syndromes, pulmonary edema, etc), anemia, thrombocytopenia, electrolyte/acid-base abnormalities, and cardiac and pulmonary complications must also be kept in mind. Excessive fluid resuscitation increases the chances of developing abdominal compartment syndrome in critically ill surgical/trauma, burn, and medical patients. Similarly, in a multicenter study of burn patients, administration of excessive fluids (in excess of 25% of predicted) increased the odds of ARDS (odds ratio = 1.7), pneumonia (odds ratio = 5.7), multiple organ failure (odds ratio = 1.6), bloodstream infections (odds ratio = 2.9), and death (odds ratio = 5.3).<sup>61</sup>

***New Developments.*** It is now being appreciated that resuscitation fluids, like other drugs, have indications for appropriate use, safe therapeutic doses, potential side effects, and complications. Despite a paucity of good

randomized controlled trials (RCTs) in this arena, clinical practices are rapidly changing. In general, large volume aggressive fluid resuscitation is becoming increasingly rare, and low volume, carefully guided resuscitation is more common. Permissive mild hypotension in appropriate patients (ie, in young victims of penetrating trauma) before hemorrhage control is becoming routine. Prompted by the recommendations of some consensus conferences, and due to the unique logistical challenges of the battlefield, the resuscitation strategies being used by the US military have changed dramatically; resuscitation is selective, emphasizing low volume and practical endpoints, and the use of fluids with logistical advantages (eg, hetastarch) is preferred. Also, early hemorrhage control is prioritized over aggressive fluid resuscitation. It is difficult to determine the direct impact of these new strategies on combat casualty outcomes, but it is very encouraging to note that for the first time since the Crimean War, the killed-in-action rate has dropped markedly below the historic 20% to approximately 10% to 14%.<sup>62</sup>

Another new development is the renewed interest in hypertonic saline (HTS), not just as a volume expander but also as an immune modulator. The use of HTS for resuscitation from hemorrhage was first described in 1980, when separate studies reported that hypersomotic sodium chloride rapidly expands plasma volume after major blood loss. Because of its ability to mobilize interstitial fluids into the vascular space, 250 mL of 7.5% saline can achieve results comparable to resuscitation with 2 to 3 L of 0.9% saline. Since the original reports, HTS or HTS combined with dextran (HSD) have been tested in several RCTs, without showing a clear survival advantage.<sup>63</sup> A meta-analysis evaluated HSD as the initial treatment for hypovolemic shock by reviewing the original records from 6 trials (and 604 subjects).<sup>64</sup> Overall discharge survival rates were better with HSD resuscitation compared with conventional resuscitation. Hypertonic saline combined with dextran resuscitation was particularly effective for the subgroup of patients who had sustained head injury, with a discharge survival rate of 38%, compared with a rate of 27% for the control group receiving saline. All of these trials had used HTS as a volume expander, but a more advantageous effect of HTS administration may be the attenuation of immune-mediated cellular injury. Several preclinical studies have demonstrated that HTS has the potential to modulate the immune response, with an overall attenuation of immune-mediated cellular injury. A small RCT has also shown that initial treatment of trauma patients with HSD inhibits neutrophil adhesion molecule expression and favorably modulates the inflammatory response.<sup>65</sup> The recently established Resuscitation Outcome Consortium (ROC), funded by the Na-

tional Institutes of Health and the US Department of Defense has initiated 2 multicenter trials of hypertonic resuscitation in 2 populations of trauma patients to be conducted simultaneously.<sup>66</sup> Study 1 would determine the impact of hypertonic resuscitation on survival for blunt or penetrating trauma patients in hypovolemic shock, whereas study 2 would evaluate its impact on long-term (6 month) neurologic outcome after severe traumatic brain injury. Both studies will be 3-arm, randomized, blinded intervention trials comparing HTS/dextran (7.5% saline/6% dextran 70, HSD), HTS alone (7.5% saline, HTS), and normal saline (NS) as the initial resuscitation fluid administered to these patients in the prehospital setting. In addition to the primary endpoints, comprehensive data about the immunologic consequences of hypertonic resuscitation would also be collected. Hopefully, these studies would provide the conclusive evidence that is needed to get regulatory approval for the routine use of HTS in the treatment of trauma patients. Another fluid that remains controversial is albumin. A recent report (post hoc analysis of patients from the Saline versus Albumin Fluid Evaluation [SAFE] study) suggests that albumin should be avoided in patients with traumatic brain injury, since it was associated with a significant increase in mortality.<sup>67</sup>

An idea that is gaining momentum due to the ongoing war is the concept of hemostatic/damage control resuscitation. Trauma patients are often coagulopathic due to shock and tissue injury, and this coagulopathy can be worsened by resuscitation with crystalloids and packed red blood cells (PRBC), since both are deficient in clotting factors. Observational data from civilian trauma centers and the battlefield seem to suggest that early administration of component therapy (fresh frozen plasma and platelets) may be beneficial.<sup>68</sup> The US Army has recently instituted a policy of using a 1:1 ratio of PRBC/FFP in the battlefield for those patients who meet the criteria for massive resuscitation (expected to receive >10 units of PRBC). However, no well-designed RCT has scientifically validated this approach so far. Our own institutional policy is to start FFP infusion as early as possible in massively bleeding patients, using a PRBC/FFP ratio of 2:1, and to administer 6 units of platelets after each estimated total blood volume loss.

## *Septic Shock*

***Initial Resuscitation.*** As opposed to hemorrhagic shock, early goal-directed resuscitation has been shown to improve 28-day mortality rates in a single center, prospective, RCT.<sup>69</sup> Although the exact parameters used to guide resuscitation in that study have been challenged, the basic concept is clearly sound, and has been validated by several subsequent

studies. For optimal results, the resuscitation protocol should be initiated as soon as shock is diagnosed and should not be delayed until admission to the ICU. Due to venous dilation, and increased capillary leak, most of these patients require aggressive fluid resuscitation over the first 24 hours. The SAFE study<sup>67</sup> has shown that albumin and crystalloids are equally safe and effective (except for patients with traumatic head injury). More specific recommendations to guide the initial resuscitation are presented at the end of this section.

***Vasopressors and Inotropes.*** Within reasonable limits flow through the tissue beds is more important than blood pressure. However, during septic shock autoregulation is not normal and perfusion can become linearly dependent on pressure. Therefore, after the initial fluid resuscitation (or concomitantly) hypotensive patients may require administration of vasopressors to keep the mean arterial pressure greater than 65 mm Hg (which has been shown to preserve tissue perfusion). Whenever possible, vasopressors should be started after providing adequate initial fluid resuscitation. There is no compelling, high quality evidence that shows one catecholamine to be superior to another.<sup>70</sup> However, norepinephrine has some attractive features because it increases mean arterial pressure (MAP) due to vasoconstriction, with little change in heart rate and some increase in stroke volume. Dopamine is another good choice, which increases MAP and stroke volume. However, it also increases heart rate, which may not be desirable. Other choices have some unattractive features. For example, epinephrine can cause tachycardia, decreased splanchnic circulation, and hyperlactemia. Phenylephrine is a pure vasopressor and is least likely to cause tachycardia, but it decreases stroke volume. Vasopressin has recently gained popularity for treating refractory hypotension in patients with septic shock, since there is a relative deficiency of this hormone in septic shock. However, the recent Vasopressin and Septic Shock Trial (VASST), which enrolled 779 patients, failed to show a survival advantage of vasopressin (0.03 units/min) over norepinephrine (abstract presented at the Society of Critical Care Medicine meeting, February 2007, Orlando, FL). An a priori subgroup analysis showed that survival of patients receiving less than 15  $\mu\text{g}/\text{min}$  norepinephrine at the time of randomization was better with vasopressin. In addition to agents that restore the vascular tone, patients with documented or suspected decrease in cardiac output should be given dobutamine as an inotropic agent. Administration of these agents should be guided by serial measurements of markers of tissue oxygenation, filling pressures, and cardiac output (when decreased cardiac output is suspected).

**Blood Products.** The optimal hemoglobin level has not been determined for severely septic patients. Rivers and associates in the early goal-directed therapy trial<sup>69</sup> used a target hematocrit of 30% in patients who continued to show oxygen saturation in superior vena cava. In a more recent multi-institutional trial of mixed ICU patients (not necessarily septic shock patients) hemoglobin levels of 7 to 9 g/dL and 10 to 12 g/dL were associated with identical outcomes.<sup>71</sup> Thus, it is reasonable to aim for a target hemoglobin between 7 and 9 g/dL if parameters of tissue oxygenation are good. But in case of depressed tissue oxygenation, or in patients with other comorbid issues (eg, coronary artery disease, stroke, etc), hemoglobin levels can be pushed up to 10 to 12 g/dL to optimize oxygen delivery.

**Recommendations.** The Updated Surviving Sepsis Campaign has recently reviewed the literature and published comprehensive guidelines.<sup>72</sup> The highlights of their recommendations related to resuscitation are shown in Table 3.

## Advances in Mechanical Ventilation

Over the last few years our understanding of lung injury, its pathophysiology, and relationship to mechanical ventilation has advanced dramatically. Several landmark studies have recently provided important data about the efficacy (or lack thereof) for various treatment modalities, as summarized below.

**Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS).** First described 40 years ago, these devastating syndromes are characterized by the sudden onset of severe hypoxemia and diffuse pulmonary infiltrates, in the absence of congestive heart failure. The severity of hypoxemia differentiates the 2 entities, with a  $\text{PaO}_2/\text{FiO}_2$  ratio of less than 200 mm Hg for ARDS and less than 300 mm Hg for ALI. Both can occur from a wide variety of etiologies that cause either direct or indirect injury to the alveolar capillary membrane. ALI has an age-adjusted incidence of 86 per 100,000 person-years, and an in-hospital mortality rate of 38.5%, with 190,600 estimated cases in the United States every year associated with 74,500 deaths and 3.6 million hospital days.<sup>73</sup> According to the same study, the ratio of ARDS cases to ALI cases is 74%, with ARDS carrying a mortality rate of 41%.

**Ventilator-Induced Lung Injury (VILI).** There is now increasing recognition of the fact that although mechanical ventilation (MV) may be a life-saving strategy, it is clearly nonphysiological. No form of MV has ever been shown to help repair an injured lung. On the contrary, it is now well recognized that MV can actually worsen the lung injury. This

**TABLE 3.** Resuscitation guidelines with levels of evidence from the Surviving Sepsis Campaign<sup>72</sup>

Initial Fluid Resuscitation (first 6 hours)

Resuscitation goals (1C)

- CVP 8 to 12 mm Hg (12 to 15 mm Hg if on mechanical ventilation or decreased ventricular compliance)
- Mean arterial pressure = 65 mm Hg
- Urine output = 0.5 mL/kg/hr
- Central venous (superior vena cava) oxygen saturation = 70% or mixed venous saturation = 65%

If venous O<sub>2</sub> saturation target not achieved (2C)

- Consider further fluid
- Transfuse packed red blood cells if required to hematocrit of 30% and/or dobutamine infusion (max 20 µg/kg/min)

Hemodynamic Support and Adjunctive Therapy

Fluid therapy

- Fluid-resuscitate using crystalloids or colloids (1B)
- Target a CVP of 8 mm Hg (12 mm Hg if mechanically ventilated) (1C)
- Use a fluid challenge technique while associated with a hemodynamic improvement (1D)
- Give fluid challenges of 1000 mL of crystalloids or 300 to 500 mL of colloids over 30 min. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion (1D)
- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement (1D)

Vasopressors

- Maintain MAP 65 mm Hg (1C)
- Norepinephrine or dopamine centrally administered are the initial vasopressors of choice (1C)
- Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C)
- Vasopressin 0.03 units/min may be added subsequently to norepinephrine with anticipation of an effect equivalent to norepinephrine alone
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B)
- Do not use low-dose dopamine for renal protection (1A)
- In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)

Inotropic therapy

- Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output (1C)
- Do not increase cardiac index to predetermined supranormal levels (1B)

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CVP, central venous pressure; MAP, mean arterial pressure.

phenomenon of ventilator-induced lung injury (VILI) is best understood by considering: 1) end-inspiratory alveolar overdistention (volutrauma), 2) end-expiratory alveolar derecruitment (atelectrauma), and 3) biomechanical injury and inflammation (biotrauma).<sup>74</sup> Because injured, nonaerated lung has low compliance, ventilation with large tidal volumes results in overdistention of the less injured, aerated alveoli. Other critical

variables contributing to VILI are high transpulmonary pressures (difference between the airway and pleural space pressures), and repeated collapse and distention of alveoli (due to lack of adequate positive end-expiratory pressure [PEEP]). There is also evidence to suggest that the inflammatory response induced during VILI has systemic consequences, and may contribute to multiorgan failure. The cumulative animal and clinical data now very convincingly show that although some strategies are less injurious, no form of MV is actually “good” for the lung. This prompted the American College of Chest Physicians almost 15 years ago to recommend that the tidal volumes should be limited in patients with ARDS who had a plateau pressure of greater than 35 mm H<sub>2</sub>O.<sup>75</sup>

### *Lung-Protective Strategies and Other Treatment Options for ALI/ARDS*

Although the first major randomized trial to provide direct evidence of a potential benefit of low tidal volume ventilation in patients with ARDS was published in 1998,<sup>76</sup> most of the contemporary recommendations rely heavily on the series of large studies performed by the Acute Respiratory Distress Syndrome Network (ARDSNet) over the last few years.

***Tidal Volumes (TV) and Plateau Pressures (PP).*** In the initial ARDSNet trial, application of a combined volume and pressure-limited strategy in patients with ALI/ARDS resulted in a 9% decrease in all causes of mortality (40% to 31%).<sup>77</sup> In the lung protection group patients were ventilated with tidal volume (TV) of 6 mL/kg of predicted body weight (compared with 12 mL/kg), and the plateau pressure (PP) was kept at less than 30 cm H<sub>2</sub>O. It is highly likely that the reported benefits of low tidal volume ventilation are a function of the PP. It is not entirely clear whether there is any threshold below which PP are not injurious, prompting some to recommend that TV should be lowered even when PP are less than 30 cm H<sub>2</sub>O. However, there is convincing evidence that TV greater than 6 mL/kg are safe as long as the PP remains below 30 cm H<sub>2</sub>O. A meta-analysis of 6 trials (1297 patients) revealed that lung-protective ventilation significantly reduced 28-day mortality rate (RR = 0.74) and the hospital mortality rate (RR = 0.80).<sup>78</sup> But lung-protective ventilation had no impact on the overall mortality rate (RR = 1.13) if the PP were kept at less than 31 cm H<sub>2</sub>O in the control group.

Based on these studies, we suggest that end-expiratory PP should be measured routinely in patients with ALI/ARDS. Clinicians should aim for a “low” TV (~6 mL/kg of predicted body weight) in conjunction with a PP of less than 30 cm H<sub>2</sub>O. If PP remains high, TV may be further

reduced to as low as 4 mL/kg. This may cause hypercapnea, which is safe in the majority of the patients and an acceptable tradeoff for preventing VILI. An important caveat is that in patients with high pleural pressures without an associated increase in transpulmonary pressures (eg, stiff chest wall, distended abdomen, etc), it is reasonable to allow the PP to rise above 30 cm H<sub>2</sub>O. In addition to hypercapnea, other consequences of low TV ventilation include hypoxemia, which may necessitate an increase in the PEEP, and sensation of dyspnea that often requires heavier sedation. It should be pointed out that no mode of mechanical ventilation (eg, pressure control, volume control) has an inherent advantage as long as the basic concepts of lung-protective strategy are applied.

**Positive End-Expiratory Pressure (PEEP).** An increase in PEEP keeps the alveoli open to participate in gas exchange, resulting in higher PaO<sub>2</sub>. In animal models, a combination of high PP and lack of PEEP results in VILI due to repeated opening and collapse of the alveoli. In the ARDSNet trial, protocol driven use of higher PEEP (13.2 ± 3.5) in conjunction with low TV did not show any benefit (or harm) compared with low PEEP (8.3 ± 3.2).<sup>79</sup> However, neither group was subjected to excessive PP. Mortality rates were better than in the initial ARDSNet trial (25% and 28% in the low and high PEEP groups, respectively) reflecting the overall improvement in the management of ARDS over time. A recent study has reported a survival advantage when high PEEP, low-moderate TV was compared with conventional TV and the least PEEP to achieve adequate oxygenation.<sup>80</sup> Taken together, the evidence suggests that high PEEP is safe as long as the PP is not excessive. Therefore, adequate PEEP should be provided to keep the alveoli from collapsing at the end of expiration. Adjustment of PEEP at the bedside can be guided by measurement of thoracopulmonary compliance or simply by titrating it against F<sub>1</sub>O<sub>2</sub> needed to maintain adequate oxygen (ARDSNet protocols).

**Fluid Management.** Because of damage to the alveolar capillary membrane and an increase in capillary permeability, ALI/ARDS patients are prone to develop pulmonary edema. Thus, it is logical to avoid unnecessary fluid overload in these patients. In a prospective randomized study (n = 1000) of patients with ALI, no difference in 60-day mortality was noted after a protocol-driven 7-day period of conservative or liberal fluid management strategy.<sup>81</sup> However, conservative strategy (directed by central venous pressure or pulmonary artery catheter along with clinical parameters) significantly improved oxygenation, decreased days of mechanical ventilation, and reduced ICU stay without any adverse consequences (eg, renal failure, shock). Therefore, a conservative fluid manage-

ment strategy should be used to minimize pulmonary edema in patients with ALI/ARDS who do not have evidence of tissue hypoperfusion.

**Positioning.** Change in position can influence pulmonary toilet and alveolar gas exchange. There is general consensus that mechanically ventilated patients should be maintained with the head of the bed elevated 45°, to decrease the incidence of ventilator-associated pneumonia (VAP).<sup>82</sup> Also, feeding patients who are supine is associated with a 50% incidence of developing VAP, and this practice should be avoided. Prone positioning has been shown to improve oxygenation in patients with ALI/ARDS.<sup>83</sup> In this large, multi-intuitional trial, prone positioning for approximately 7 hours per day improved oxygenation but did not decrease the overall mortality rate. Another large trial (prone positioning for 8 hr/day for 4 days) showed very similar findings, with improvement in oxygenation but no difference in survival.<sup>84</sup> However, the most recent study reported a survival advantage when the duration of prone positioning was increased to 17 hours for a mean period of 10 days.<sup>85</sup> In this study, randomization to supine positioning was an independent risk factor for mortality by multivariate analysis. Overall, the literature clearly shows that prone positioning improves oxygenation, but whether this translates into an improvement in survival remains controversial. Thus, prone positioning may be considered in selected patients with severe ARDS to improve oxygenation, in those centers that have experience with this practice.

**Steroids.** Although a small study (24 patients) reported improved outcomes with moderate doses of corticosteroids in patients with ARDS (for longer than 7 days),<sup>86</sup> the much larger randomized ARDSNet study (n = 180) failed to confirm these beneficial findings.<sup>87</sup> In this trial, the overall 60-day mortality rate in the steroid and placebo groups was the same (29%), but on post hoc analysis, 60- to 180-day mortality rates were significantly higher in patients when steroids were started more than 2 weeks after the onset of ARDS. Additionally, although steroids improved oxygenation, ventilator-free, and shock-free days during the first 28 days without increasing the incidence of infectious complications, neuromyopathy was significantly more common in steroid-treated patients compared with placebo (30% vs 22%). Thus, routine use of steroids cannot be justified in patients with ARDS.

**Other Pharmacological Therapies.** Numerous pharmacological therapies have been evaluated in recent years for the treatment of ALI/ARDS, with disappointing results. A Cochrane meta-analysis of 33 trials (3272 patients) found insufficient evidence to support the use of prostaglandin E1, N-acetylcysteine, early high-dose steroids, and surfactant.<sup>88</sup> Simi-

larly, another review found no compelling evidence in favor of inhaled nitric oxide.<sup>89</sup> In the 1990s, inhaled nitric oxide generated a lot of excitement as a potential therapy for ARDS because of its ability to selectively decrease pulmonary vascular resistance (without affecting systemic blood pressure) and improve oxygenation (enhanced ventilation-perfusion matching). However, subsequent evidence suggests that although nitric oxide may be useful as an adjunct in patients with acute hypoxemia or life-threatening pulmonary hypertension, these benefits are short-lived and do not translate into improved survival.<sup>90</sup> Currently, licensed indications for inhaled nitric oxide are restricted to pediatric patients, and its routine use in adult patients with ARDS cannot be recommended.

### *Alternative Modes of Ventilation*

Recently, there has been a growing interest in the use of alternative modes of mechanical ventilation that fulfill the requirements of lung-protective ventilation and are theoretically less likely to induce lung injury. High frequency oscillatory ventilation (HFOV) and airway pressure release ventilation (APRV) are 2 such alternative modes. They represent open lung strategies designed to recruit and maintain adequate end-expiratory lung volume, attenuate atelectasis, and improve oxygenation by using higher mean airway pressures. In addition, HFOV uses very low tidal volumes and APRV maintains spontaneous breathing, which may have some additional benefits.

High frequency oscillatory ventilation superimposes rapid pressure oscillations (3 to 10 Hz in adults) on a constant distending mean airway pressure to generate tidal volumes ( $\sim 1$  to 4 mL/kg) that are often less than the dead space volumes. Gas exchange takes place through novel mechanisms as a result of increased gas mixing due to the high energy of gas molecules. Active expiration in the HFOV mode prevents gas trapping and allows ventilation. Typically, HFOV requires heavy sedation and neuromuscular blockade. Airway pressure release ventilation, on the other hand, uses continuous positive airway pressure at a relatively high level ( $P_{\text{high}}$ ) with superimposed time-cycled release phases to a lower pressure level ( $P_{\text{low}}$ ). It is a partial ventilatory support mode with allowance for spontaneous breathing. Theoretically, alveolar recruitment (and oxygenation) can be improved by maximizing the time spent at  $P_{\text{high}}$ . Several preclinical and small clinical studies have evaluated these modalities. Fan and Stewart have published an excellent review that explains in detail the mechanics of these modalities and summarizes the findings of the various clinical trials.<sup>91</sup> Unfortunately, due to the limited

sample size and suboptimal design, these studies fail to provide convincing evidence that these modes of mechanical ventilation offer any real advantage over the conventional methods. Currently, their use remains limited to selected centers that have a special interest/expertise in these strategies.

## **Advances in Surgical Infections**

Surgical infections are a primary concern for the critically ill patient and an issue of endless discussions (and contention) among health care providers. The involvement of infectious disease specialists offers a welcome added expertise. However, it is not unusual for disagreements to occur between the medical specialist and the surgeon. A questionnaire, polling opinions regarding the management of common surgical infections, was sent to 396 medical infectious disease specialists practicing in New York State and 515 surgeon members of the Surgical Infection Society.<sup>92</sup> The questions covered areas involving choice of antibiotics, and timing and duration of treatment in given clinical scenarios, including elective and emergent colorectal surgery, perforated peptic ulcer, and appendicitis. Medical specialists used therapeutic antibiotics twice as long as surgeons, because of their failure—according to the authors—to understand the conceptual difference between contamination and infection.

Pressure from pharmaceutical companies is relentless, as new antibiotics are continuously developed and released. Overuse or wrong choice of antibiotic regimen is frequent in the ICUs, and patients receive different types and doses for unclear reasons.<sup>93</sup> Inappropriate use of antibiotics may not be just a matter of cost but may also increase mortality. Creating protocols based on institutional data provides a pathway for rational use and improved outcomes.

### *Antibiotic Prophylaxis*

Surgical patients receive prophylaxis by multiple drug combinations, including third-generation cephalosporins or carbapenems, for prolonged period, of times, and against clinical guidelines.<sup>93</sup> Surgical site and respiratory tract infections are the primary targets of antibiotic prophylaxis, and there is abundant evidence that appropriate administration of antibiotics decreases the rate of both. Similarly, there is abundant evidence that more antibiotics or longer durations of administration do not add any benefit and may increase resistance, which may eventually increase morbidity and mortality. Multiple RCTs and 7 meta-analyses have been published since 1991 without firm resolution of the main

questions: how much, how long, and what type? The pooled estimates from 16 randomized trials with 3361 patients on the effect of topical and systemic prophylactic antibiotics showed a significant reduction in respiratory tract infections (odds ratio = 0.35, 95% confidence interval [CI] = 0.29, 0.41) and mortality rates (odds ratio = 0.80, 95% CI = 0.69, 0.93).<sup>94</sup> Five and 23 patients needed to be treated to prevent 1 infection and 1 death, respectively. In a multicenter study from 12 Dutch hospitals, surgical site infections from clean and contaminated operations were effectively reduced despite the implementation of a restrictive prophylactic antibiotic protocol.<sup>95</sup> Such effectiveness depends on many factors, with timeliness of administration being 1 of the most important. However, evidence and practice fail to align in this field and, despite having knowledge of guidelines, clinicians fail to order prophylactic antibiotics timely. Thematic analysis revealed several obstacles to the observance of guidelines including: 1) low priority, 2) inconvenience, 3) workflow, 4) organizational communication, and 5) role perception.<sup>96</sup> Hospital-wide initiatives, by which timely prophylactic antibiotics administration before the operation becomes a priority and is monitored closely, have succeeded in increasing compliance.

The duration of antibiotic prophylaxis is debated, but short periods are shown to be as effective as longer ones. Even in the presence of heavy contamination at the time of surgery, as occurs with penetrating injuries to hollow viscera and particularly the colon, a single-day single-antibiotic prophylaxis is as effective as prophylaxis with multiple drugs for prolonged periods of time. In a prospective randomized study of high-risk patients with penetrating abdominal trauma 2 g of cefoxitin every 6 hours for 24 hours after the operation was compared with the same regimen administered for 5 days.<sup>97</sup> There was no difference in intra- or extra-abdominal infectious complications, length of hospital stay, or mortality rate. Of interest, 100% of the patients from both groups that developed intra-abdominal infections cultured organisms resistant to cefoxitin. In a prospective study of critically injured patients, all managed in a surgical ICU, patients who receive a single antibiotic for 1 day were compared with patients who received 1 or more antibiotics for multiple days.<sup>98</sup> There was no difference in sepsis, organ failures, hospital stay, or mortality rate in the 2 groups. The only 2 differences that came closer to statistical significance ( $P = 0.18$ ) were organ failures and multidrug-resistant infections. Both favored the single-antibiotic, single-day group.

It is unknown if a restricted prophylactic antibiotic regimen is as good or as bad as more complex combinations. It is possible that critically ill patients are inadequately managed by standard doses of antibiotics due to

increased volume of distribution and erratic tissue perfusion. Therefore, the argument can be made that relatively small doses of antibiotics are not expected to change outcome regardless of the duration or type of antibiotics. So, it is likely that longer and multiple antibiotics, not given in appropriate doses, fail to produce any better outcome than single and shorter antibiotics, not given in appropriate doses. No matter what the truth is, violations of antibiotic prophylaxis guidelines are costly. Despite an academic hospital's ICU guidelines for antibiotic prophylaxis of 1 day, 61% of the orders were continued for more than 1 day.<sup>99</sup> The cost of antibiotic prophylaxis beyond 1 day totaled \$44,893. Bacteremia and line infection were more frequent in the patients receiving more than 4 days of prophylaxis, increasing the cost further.

Selective decontamination has also been used to prevent infection in ICU settings. In a variety of combinations, selective decontamination regimens have been used by nasal or oropharyngeal application, intestinal administration, or intravenous injection. There have been 51 RCTs between 1987 and 2005, including 8065 critically ill patients; of those 4079 were randomized to some decontaminating antibiotic regimen and 3986 were controls.<sup>100</sup> Selective decontamination reduced significantly blood sepsis and mortality. In particular, it reduced Gram-negative blood sepsis without affecting Gram-positive ones. When enteral or parenteral antibiotics were used the effect on reducing infections and improvement in mortality was more pronounced. Twenty patients need to be treated with selective decontamination to prevent 1 Gram-negative bloodstream infection and 22 patients to prevent 1 death. Targeting exclusively trauma patients, a recent study randomized 201 patients with an Injury Severity Score (ISS) greater than 16 to receive polymyxin E, tobramycin, and amphotericin B in the throat and gut throughout ICU care combined with cefotaxime for 4 days, whereas 200 similar patients were randomized as controls.<sup>101</sup> The mortality rate was not different between the 2 groups, but the overall infection rate was reduced in the decontamination group (48.8% vs 61%). Fewer airway infections and Gram-negative bloodstream infections accounted for the bulk of the reduction. For unknown reasons and despite the encouraging outcomes research, selective decontamination is not practiced widely in the United States.

### *Antibiotic Treatment*

The treatment of infection with antibiotics is either empiric or targeted. In empiric treatment the clinical signs of infection are present, but there is still no documentation of an infectious source on cultures. Physicians start broad-spectrum antibiotics with the intent to de-escalate after the

cultures allow targeted treatment. Inadequate initial empiric therapy increases the mortality rate in patients with VAP. The mortality related to VAP was 16.2% in patients who had adequate coverage compared with 24.7% in those who received antibiotics not covering the subsequently cultured micro-organism.<sup>102</sup> Inadequate initial antimicrobial therapy was an independent risk factor for ICU mortality rate among patients with Gram-negative infections.<sup>103</sup> Therapy that started after 24 hours from the establishment of diagnostic criteria for VAP was related to a 7-fold increase in the odds of mortality.<sup>104</sup> Even if appropriate antibiotics are started after the initial delay, the mortality rate trends are not reversed.<sup>11</sup> It is important, therefore, for each ICU of every hospital to study carefully its own antibiogram and offer the correct empiric therapy early.

Many hospitals have instituted antibiotic rotation protocols. By these protocols certain antibiotics are selected and used for a defined period of time, after which they are substituted by a different combination. It is assumed that by cycling antibiotics the ability of bacteria to develop resistant strains is diminished. One major theoretical advantage of antibiotic cycling is the ability to reintroduce a previously withdrawn antibiotic into clinical use, its efficacy being maximized by limiting its widespread use as a chronic “workhorse” antibiotic by using it only once every cycle. Multiple studies have shown decreases in VAP and mortality rates by antibiotic cycling.<sup>105,106</sup> Other studies have failed to document a similar improvement in outcome.<sup>107,108</sup> The variability of the studies, including cycles as short as 1 month or as long as 2 years, could be 1 of the main reasons for the inconsistent results. Lack of compliance and poor choice of antibiotics are additional reasons.

De-escalation of antibiotics when a culture declares the pathogenic organism is as important as the aggressive initial therapy. However, this is often neglected and the “shotgun” approach is maintained throughout therapy.

### *Activated Protein C*

Several therapies have been developed recently to improve outcome after sepsis. Activated protein C (APC) has been in the center of controversy for the last decade. Sepsis involves a constellation of pathophysiologic disturbances, including endothelial alterations with coagulation disorder and microthrombus formation. This, in turn, leads to microvascular occlusion and inadequate perfusion of crucial tissue beds. Activated protein C has been shown to improve survival after severe sepsis, but recent evidence suggests that the risks of bleeding may outweigh the benefits. The Recombinant Human Activated Protein C Worldwide Evaluation in

Severe Sepsis trial was a randomized, double-blind, placebo-controlled multicenter study in which patients with organ failure from acute infection were randomized to receive activated drotrecogin alpha (ie, APC) for 96 hours or placebo.<sup>109</sup> In 1690 randomized patients the mortality rate was 30.8% in the placebo group and 24.7% in the APC group. The relative risk reduction of death was 19.4% (95% CI = 6.6 to 30.5) and the absolute reduction was 6.1% ( $P = 0.005$ ). The incidence of serious bleeding was higher in the APC group than in the placebo group (3.5% vs 2.0%,  $P = 0.06$ ). Specifically, APC was not effective for surgical sepsis, but after review of the data it was suggested that surgical patients at high risk of death (Acute Physiology and Chronic Health Evaluation [APACHE] II score  $\geq 25$  points) may benefit from APC. Several comparable studies have now been aggregated in the International Integrated Database for the Evaluation of Severe Sepsis and Drotrecogin alfa (activated) Therapy database, which shows a significant reduction in mortality rate (odds ratio = 0.66; 95% CI = 0.45 to 0.97) for therapy with APC of surgical patients with severe sepsis and a high risk of death.<sup>110</sup> However, the risk of bleeding is higher in those treated with APC. In contrast, surgical patients at a lower risk of death do not benefit from therapy with APC but are still placed at risk for bleeding.

## Advances in Thromboprophylaxis

In providing a high quality of surgical care, the issue of appropriate venous thromboprophylaxis (VT) continues to be discussed vividly. In various quality measures reflecting individual physician and collective hospital performance, the percentage of surgical and trauma patients who received prophylaxis for thromboembolism remains a closely scrutinized indicator. However, the appropriate method, timing, and duration of VT invite disagreement, and a universally agreed on standard of care on these issues does not exist despite multiple consensus conferences, expert group reports, and evidence-based guidelines. The Surgical Care Improvement Project (SCIP), a partnership of the Centers for Medicare & Medicaid Services, the Centers for Disease Control and Prevention, the American College of Surgeons, and the Department of Veteran Affairs, explored measures of surgical quality and the feasibility of their implementation in surgical practice.<sup>111</sup> The participants in an SCIP-related study agreed with a recent National Institutes of Health consensus on total knee replacement, which stated that “there is no persuasive evidence supporting or opposing prophylaxis of deep venous thrombosis in these patients.”<sup>112</sup> An evidence-based report from the Agency for Healthcare Research and Quality about post-traumatic VT concluded that there was no evidence to

support the use of low-dose heparin or sequential compression devices in trauma patients.<sup>113</sup>

### *Unfractionated Heparin*

Following the seminal studies in the 1970s by Kakar and colleagues<sup>114,115</sup> subcutaneous low-dose unfractionated heparin became the main method of VT in surgical patients. The authors reduced the rate of deep venous thrombosis (DVT) and, more importantly, fatal pulmonary embolism (PE) among large surgical populations who received operations of variable severity and location. The effectiveness of unfractionated heparin in patients with severe illness is in doubt. Heparin works through antithrombin III, which, as an acute phase protein, may be compromised in quality or quantity following a major insult and the resultant inflammatory response.<sup>116</sup> Multiple studies have shown that in the presence of severe trauma or critical surgical illness, unfractionated heparin is not effective.<sup>117,118</sup> Among 261 patients with a mean APACHE II score of 25.5 and protocol-directed universal VT, the incidence of DVT was 9.6% over the ICU stay.<sup>119</sup> Similarly, the incidence of DVT was 12% among 200 critically injured patients who received VT. In most ICUs low-molecular-weight heparin has replaced unfractionated heparin.

### *Sequential Compression Devices*

Venous thromboprophylaxis by sequential compression devices (SCD) relies on proper application and patient compliance. In a prospective study a total of 1343 observations were made on 227 patients who had physician's orders for SCD prophylaxis.<sup>120</sup> Only 19% were fully compliant with the orders. In a similar observational prospective study the compliance rate was limited to 58.9%.<sup>121</sup> Given the short-lived anti-thrombotic effect of SCD, even limited periods of noncompliance may encourage clot formation. A meta-analysis of 21 relevant studies, including 811 patients from 5 randomized controlled trials and 3421 patients from observational studies, indicated no significant difference between patients receiving SCD and controls.<sup>122</sup> Mechanical prophylaxis can be used as a supplement to pharmacological prophylaxis or reserved for patients with a high risk for bleeding. Its effectiveness in critically ill surgical and trauma patients is unknown.<sup>123</sup>

### *Low-Molecular-Weight Heparin*

There is no level 1 evidence for the safety and effectiveness of low-molecular-weight heparin (LMWH) in critically ill patients. A pilot study that examined the feasibility of performing a randomized

trial about LMWH reported that such a study would be feasible but it has not yet been done.<sup>124</sup> The best available evidence is from a randomized controlled trial among major trauma patients (ISS greater than 9).<sup>125</sup> Of them, 136 received unfractionated heparin and 129 received LMWH. All patients were evaluated by contrast venography. The LMWH group had a significantly lower total DVT (31% vs 44%,  $P = 0.014$ ) and proximal DVT rate (6% vs 15%,  $P = 0.012$ ). Of note, there were 9 patients who bled in the LMWH group versus 1 in the unfractionated heparin group, but this difference did not achieve statistical significance due to the low numbers ( $P = 0.12$ ). The single unfractionated heparin patient had epistaxis, but the LMWH patients bled in the chest, abdomen, head, and retroperitoneum. It is also interesting that 2 other prospective randomized studies on similar major trauma patients, comparing LMWH with SCD, produced vastly different results in terms of rates of DVT and reduction of risk by LMWH.<sup>126,127</sup> The incidence of DVT among LMWH and SCD was 0.8% versus 1.6% ( $P = 0.567$ ) in 1 study of 181 patients<sup>128</sup> and 0.5% versus 2.7% ( $P = 0.122$ ) in the other of 224 patients.<sup>129</sup>

In another prospective randomized trial of patients with spinal cord deficits there was no difference in the rate of thromboembolic events between patients randomized to receive unfractionated heparin/SCD and those randomized to receive LMWH (63.3% vs 65.5%,  $P = 0.81$ ).<sup>130</sup> However, in orthopedic surgery LMWH is considered the most effective modality. In a meta-analysis of randomized controlled trials it was found that the relative risk of DVT for LMWH versus unfractionated heparin was 0.76 and for LMWH versus warfarin was 0.78.<sup>131</sup>

Additional concerns about LMWH include optimal dosing. Although adequate activity is claimed for most patients with a standard dose, critically ill patients are subject to compromised tissue perfusion and increased volume of distribution, both affecting the bioavailability of any medication, particularly if administered subcutaneously. Among 17 critically ill patients receiving 40 mg of enoxaparin daily the trough levels of its anti-Xa activity were substantially lower than the lowest normal limit in all but 2 patients.<sup>131</sup> Similarly, in a comparison between critically ill and regular patients, critically ill patients demonstrated significantly lower anti-Xa activity in response to a single daily dose of subcutaneous enoxaparin.<sup>132</sup>

Despite these alarming results, LMWH is currently considered by many as the preferred choice of VT for critically ill surgical patients. However, as shown above, there is only 1 study<sup>125</sup> on surgical patients who were reasonably sick (major trauma patients), in which LMWH has shown a

clear benefit compared with unfractionated heparin. Extrapolation from this and other studies in noncritical patients, surgical or otherwise, has led to the unfounded belief that LMWH is truly effective in critically ill surgical patients. Although this claim may or may not be true, the evidence is lacking.

### *Selective Inhibitors of Factor Xa and Thrombin*

A new generation of antithrombotic agents targets a single enzyme within the procoagulant cascade. These new agents promise higher efficacy and safety profiles and some prospective randomized studies have shown that to be true. None of these studies focuses on critically ill surgical patients.

Fondaparinux is a synthetic heparin pentasaccharide that inhibits factor Xa through interaction with antithrombin but without antifactor IIa activity. Fondaparinux was compared with enoxaparin in 4 multicenter, randomized, double-blind trials of major orthopedic surgery.<sup>133</sup> Assessment of DVT was performed by contrast venography. The incidence of all episodes of venous thromboembolism was 13.7% (371 of 2703) in the enoxaparin group compared with 6.8% (182 of 2682 patients) in the fondaparinux group. When other and clinically more meaningful endpoints were used (proximal DVT, fatal PE, any death) the rates were much lower but still in favor of fondaparinux (3.3% vs 1.7% and 3.9% vs 2.1%, according to different endpoints used). In a large uncontrolled study of 5704 patients with major orthopedic surgery, fondaparinux was administered daily for 3 to 5 weeks postoperatively.<sup>134</sup> The rate of venous thromboembolism was 1% and major bleeding 0.8%. Because of the size of its molecule, fondaparinux is too small to be recognized by the majority of heparin-reactive antibodies and, therefore, could be an excellent candidate agent for patients with heparin-induced thrombocytopenia (HIT).<sup>135</sup>

Direct thrombin inhibitors like hirudin and argatroban have FDA approval for treatment of HIT but not for standard prophylaxis.<sup>136</sup> New anticoagulant drugs such as parenteral pentasaccharides, oral direct thrombin inhibitors, oral direct factor Xa inhibitors, and tissue factor-factor VIIa complex inhibitors are under investigation and promise a predictable anticoagulant response and a higher efficacy and safety profile.<sup>137</sup>

### *Inferior Vena Cava Filters*

In essence the use of inferior vena cava (IVC) filters is always prophylactic, since the filter never treats a PE but only prevents a new one

from developing. The effectiveness and safety of IVC filters has been an ongoing controversy. Conventional wisdom dictates that a device capturing clots that depart from the lower extremity veins should effectively have decreased the incidence of PE and death from it. This is not so. McMurty and colleagues compared 2 periods of time in their institution.<sup>138</sup> During 1 period the use of IVC filters was scarce. During the second period formal guidelines were introduced and patients frequently had a filter. Against expectations, the incidence of PE in the first period was lower than the second (0.31% vs 0.48%,  $P = 0.045$ ). In the only prospective randomized study on the topic, Decousous and colleagues randomized 400 patients with DVT at risk for PE to receive or not an IVC filter.<sup>139</sup> Although there was initially a reduction of PE in the IVC filter group (1.1% vs 4.8%,  $P = 0.03$ ), this did not translate into long-term effects at 2 years (3.4% vs 6.3%,  $P = 0.16$ ). The initial benefit in PE rate was counterbalanced by a higher recurrent DVT rate in the IVC filter group at 2 years (20.8% vs 11.6%,  $P = 0.02$ ). Most importantly, there was no survival benefit of IVC filter insertion; the PE-related or total number of deaths at 2 years was not different between the 2 groups (at 2 years: 21.6% vs 20.1%,  $P = 0.65$ ).

Particularly, in critically ill surgical and trauma patients the use of IVC filters has never been scrutinized adequately. The reasons for lack of convincing evidence of the effectiveness of filters in this population are multifactorial. It is possible that the general inflammatory response leads to an adrenergic state within the pulmonary circulation and renders the vascular endothelium procoagulatory and vasospastic. This would allow primary clot formation within the lungs, as opposed to the theory that clots almost always originate from lower extremity and pelvic veins.<sup>140</sup> Primary pulmonary clot formation due to an inflamed vascular endothelium and stagnant pulmonary microcirculatory flow may explain why it is more common to find multiple small clots instead of a major pulmonary artery embolus in critically ill surgical and trauma patients with PE.

Currently, the indications for IVC filter placement are not clear or universally accepted. Patients with a documented clot in their pelvic or lower extremity deep venous system and a contraindication to anticoagulation are likely to have a filter in most institutions. Other indications, such as severe injury, obesity, coagulation abnormalities, DVT in a patient with compromised cardiorespiratory status, or prolonged immobility are not standardized. The development of removable filters has propelled the use to higher rates. Physicians insert filters under the false assumption that most will be removed. As

discussed previously this does not happen and the device remains permanent in more than 80% of the patients. Filters are associated with complications, such as access site thrombosis or bleeding, perforation, migration, IVC obstruction (Fig 1), or malposition.<sup>141</sup> The rates of complications range from 0% to 30% and average 7%, including breakthrough PE, which may or may not really be a filter complication. In general, the insertion of an IVC filter should be considered a safe procedure, although the occasional complication could be devastating. It is unknown if and to what extent filters prevent a more devastating event, death from PE, and for this their use and indications should be further explored.

Venous thromboprophylaxis is still a contentious issue. From those who support that the current methods of VT are inadequate<sup>142</sup> to those who are comfortable with the existing treatments<sup>143,144</sup> there exists a wide spectrum of disease pathology and severity that cannot possibly be managed in the same way. Consensus conferences recommend LMWH for the majority of surgical patients, but the evidence<sup>145</sup> about surgical critical illness is not convincing. Research is ongoing and hopefully more effective therapies will be discovered soon.

## **Advances in Nutrition**

Sepsis and critical illnesses elicit a profound metabolic response characterized by hypermetabolism, increased energy expenditure, hyperglycemia, muscle wasting, poor healing, and an increased susceptibility to infections. It is widely acknowledged that appropriate metabolic support in these patients may improve outcome, but there is no clear consensus about the optimal approach.

### *Parenteral Nutrition*

Development of total parenteral nutrition (PN) 40 years ago provided a life-saving option for patients who did not have functional gastrointestinal tracts. However, because of the ease of administration, and an underappreciation of the benefits associated with enteral feeding, use of PN soon became widespread, even in patients with a functional bowel. Driving the popularity of PN was the belief that high amounts of calories/protein (“hyperalimentation”) would correct stress-induced metabolic derangements and result in improved outcomes. However, when appropriate clinical trials were finally conducted, PN was found to be inferior to enteral nutrition (EN) in virtually every patient population, despite delivering 30% to 50% more calories. A meta-analysis of data from 8 centers focusing on trauma/surgical/ICU patients showed that PN in-

creased infections (35% vs 16%) and length of hospital stay (22 vs 17 days), but not mortality (10% vs 7%) compared with enteral feeding.<sup>146</sup> In 2001, a systematic review of 82 clinical trials (wide variety of patients) of PN failed to find any convincing outcome improvements.<sup>147</sup> Once again, PN was noted to increase the incidence of infectious complications, which is clearly a concern in critically ill patients. Several recent reviews have specifically addressed this patient population. For example, a meta-analysis of randomized clinical trials of PN versus standard care and PN versus EN in severely ill patients showed that both standard care and EN were associated with decreased infection rates compared with PN (25% and 35%, respectively).<sup>148</sup> There was a nonsignificant decrease in complication rates and no difference in mortality. Similarly, a systematic review of 13 studies in critically ill patients (excluding surgical patients) also showed that EN was associated with reduced infections (RR = 0.64) but no difference in mortality (RR = 1.08).<sup>149</sup> There was no difference in the length of hospital stay (LOS), but PN was associated with a higher incidence of hyperglycemia and increased cost. Another meta-analysis of 30 randomized clinical trials (10 medical, 11 surgical, 9 trauma) found no difference in mortality rate between early PN and EN.<sup>150</sup> However, EN was associated with shorter LOS (mean = 1.2 days) and more diarrhea (8.7%,  $P = 0.001$ ), whereas PN was associated with more infections (7.9%) and noninfectious complications (4.9%,  $P = 0.04$ ). In contrast, when a meta-analysis of 11 trials applying intent-to-treat principle (trauma, cancer, pancreatitis patients) was performed, an overall mortality benefit was detected in favor of PN.<sup>151</sup> However, this benefit was only in comparison with late EN (an a priori subgroup analysis), and mortality rates in patients who received early EN (within 24 hours) were the same as PN. Taken together, the results of all these studies (and meta-analyses) indicate that in critically ill patients enteral feeding is the preferred route of nutritional support, and that EN should be started early (within 24 hours whenever possible). Parenteral nutrition should be reserved for those that cannot tolerate early enteral nutrition. Precisely how long of a delay in the initiation of EN would justify the risks of administering PN is not clearly known. However, a delay in EN is rarely due to a lack of functional small bowel but due to gastric/colonic ileus, exaggerated “concerns” about gastrointestinal anastomosis, and numerous preconceived biases. In reality, once clinicians develop a commitment to early EN in critically ill surgical patients, the use of PN sharply decreases (26% to 3% over 6 years), with a concurrent decrease in a wide range of complications.<sup>152</sup>

## Enteral Nutrition

There is now little doubt about the superiority of early EN over PN in almost all patient populations.<sup>153</sup> In surgical patients, early EN is not only technically feasible, but has been shown to decrease all complications (RR = 0.85,  $P = 0.04$ ), infectious complications (RR = 0.63,  $P = 0.001$ ), anastomotic leak (RR = 0.67,  $P = 0.03$ ), intra-abdominal abscess (RR = 0.63,  $P = 0.03$ ), and LOS ( $P = 0.02$ ).<sup>154</sup> According to the newer studies, there is really no clear advantage in keeping patients nil by mouth after elective gastrointestinal resection.<sup>155</sup> However, as the precise reasons for the benefit of EN are not entirely clear, there remains a fair amount of controversy about the best way to calculate the nutritional needs in critically ill patients, the optimal type and composition of EN, benefits of controlled starvation, and whether the addition of nutritional supplements offers any advantage.<sup>156,157</sup>

**Hypocaloric Nutrition.** In virtually all of the studies on early EN, benefits were noted despite a failure to meet the “calculated” caloric intake. In general, most patients receiving early EN meet between 50% and 70% of caloric goal.<sup>158</sup> This raises several interesting possibilities. Is permissive underfeeding beneficial? Have we incorrectly calculated the caloric requirements? Or does enteral feeding work through mechanisms that far surpass the mere provision of nutrients?

Although numerous guidelines have been published for the clinicians,<sup>159,160</sup> the optimal caloric needs in critically ill patients have not been scientifically validated.<sup>161</sup> There is good evidence that overfeeding is harmful in critically ill patients,<sup>162</sup> and it must be avoided at all cost. Unfortunately, most of the traditional caloric need calculations rely on population-based assessments such as the Harris-Benedict equation. These old formulas were developed before the establishment of modern ICUs and may lead to overfeeding in up to 30% of the patients. Indirect calorimetry may be more reliable,<sup>163</sup> but it is rarely used on a daily basis. Deliberate underfeeding in the ICU cannot be recommended, because permissive underfeeding has not yet been compared against target feeding in critically ill patients. However, the published literature supports our recommendation that EN should be initiated early (within 24 hours) since meeting the calculated caloric goals is clearly not necessary to obtain the benefits of EN. Furthermore, overfeeding and its metabolic consequences (eg, hyperglycemia) should be avoided.

**Early Versus Delayed Nutrition.** Since the mid-1970s, almost 20 RCTs have addressed the question of early (within 24 to 48 hours) versus delayed EN in critically ill patients. Two meta-analyses of these trials demonstrate

that early feeding is clearly superior. The first meta-analysis included only mechanically ventilated patients,<sup>164</sup> and concluded that early EN was associated with a trend toward lower mortality risk (RR = 0.65,  $P = 0.06$ ) and infectious complications (RR = 0.78,  $P = 0.06$ ). Guidelines developed as a result of this analysis recommended that EN should be started within 48 hours, using a standard polymeric enteral formula. Arginine-containing formulas should be avoided, and fish oils and antioxidants should be considered for patients with ARDS. Glutamine-containing formula should be considered for patients with burns/trauma, and supplemental PN should not be used with EN. The authors later performed a prospective observational study to validate these guidelines.<sup>165</sup> The second meta-analysis included all trials,<sup>166</sup> and found that early EN did not alter mortality but significantly reduced infectious complications (RR = 0.45,  $P < 0.001$ ) and hospital LOS (2.2 days,  $P < 0.004$ ). In practical terms, EN should be started at a low rate as soon as patient's hemodynamic status has been stabilized. Strategies to optimize the delivery of EN (protocol-driven feeding, motility agents, small bowel feeding) and minimize the complications (elevation of the head of the bed, monitoring of residuals) should be considered routinely in these patients.

***EN Alone Versus EN Plus Supplemental PN.*** Five RCTs have compared EN alone to combined EN and PN (started simultaneously). The basic concept behind all of the studies was that patients who received supplemental PN might achieve their nutritional goals more rapidly. However, only 1 of these studies provided the actual caloric debt calculations.<sup>167</sup> The target in this study was to deliver 25 kcal/kg/day, and as expected there was a difference between the groups, with the combined EN/PN group reaching 98% (24.6 kcal/kg/day) and EN alone reaching 57% (14.2 kcal/kg/day) of the target, respectively. However, despite delivering higher calories the combined approach did not translate into improved outcomes. A meta-analysis of these 5 trials found no improvement in mortality, infectious complications, hospital LOS, or days on mechanical ventilation.<sup>168</sup> Thus, despite some observational data to suggest that caloric deficit may be associated with poor outcomes, careful analysis of evidence shows that the addition of PN to minimize this deficit is not beneficial.

***Oral Nutritional Supplements (ONS).*** Various concentrates of high amounts of calories, proteins, and micronutrients (including vitamins and minerals) are available and heavily advertised by the industry. There is little evidence to suggest that they improve outcome compared with

conventional feeding.<sup>169</sup> Thus, their routine use in patients without well-identified nutritional deficiencies cannot be recommended.

### *Immunonutrition/Immune-Enhancing Diets*

Several nutrients, such as glutamine, arginine, nucleotides, and omega-3 fatty acids, have pronounced pharmacological properties, and they have been used to modulate the immune system in critically ill patients. Although it is an attractive theory, the evidence in support of this approach is relatively weak, except maybe for glutamine supplementation. One of the major problems in reviewing the data (and comparing the results) is the fact that instead of pure single agents investigators have typically tested different commercial diets, each with its own proprietary mix of nutrients. Blending of components with incompletely understood mechanisms of action, potential side effects, often opposing properties, and unknown interactions further impedes a fair analysis. There are some logistical challenges as well. For example, a prospective, double-blinded, randomized, multicenter French trial has shown that glutamine-supplemented PN decreases infectious complications in critically ill (ICU) patients.<sup>170</sup> This is in line with a review of 14 studies that used glutamine in surgical and critically ill patients, and showed that benefits were most pronounced in patients who received high-dose parenteral glutamine (as opposed to low dose or enteral).<sup>171</sup> However, intravenous glutamine, which is available (and tested) in Europe is not available in the United States.

Whether feeding the patients immune-enhancing diets (IEDs) leads to a measurable improvement in outcomes has been evaluated by several RCTs. The results of these studies must be interpreted in the context of the specific patient populations that were enrolled. For example, formulas enriched with arginine, omega-3 fatty acids, and nucleotides decrease infections and are beneficial in patients undergoing elective gastrointestinal surgery, when administered during the perioperative period.<sup>172</sup> A meta-analysis of 11 RCTs in patients with cancer undergoing gastrointestinal surgery showed that nutritional support with IEDs decreased the risk of developing infectious complications and reduced the hospital LOS.<sup>173</sup> Similar findings were reported in a prospective randomized study of malnourished surgical patients with cancer.<sup>174</sup> These formulas may also be beneficial in the setting of mild sepsis but are actually harmful in patients with severe sepsis.<sup>175</sup> Arginine in particular may be harmful in septic patients by increasing the formation of nitric oxide, which can worsen hypotension. In a prospective RCT in 5 centers (n = 146), a formula rich in omega-3 fatty acids, gamma-linolenic acid, and antioxi-

dants has been shown to reduce ventilator requirements (11 vs 16 days,  $P = 0.011$ ), length of ICU stay (12.8 vs 17.5 days,  $P = 0.016$ ), and incidence of organ failure (8% vs 28%,  $P = 0.015$ ) in patients with ARDS.<sup>176</sup> Another group from Israel has recently reported similar findings in a single-center RCT ( $n = 100$ ),<sup>177</sup> and researchers from Brazil in a RCT ( $n = 165$ ) have also shown a survival advantage (19.4% reduction in mortality,  $P = 0.037$ ).<sup>178</sup> In a small study ( $n = 45$ ) of severe burn patients, administration of enteral glutamine was associated with decreased infections and improved survival.<sup>179</sup> Thus, it seems reasonable to conclude that appropriate immunonutrition may be beneficial in select patient populations (eg, arginine, omega-3 fatty acids, and nucleotides for cancer surgery; fish oil and antioxidants for ARDS; glutamine for trauma/burns), but harmful in others (eg, arginine in septic patients).

So, should immunonutrition be given to all critically ill patients? This question has been addressed by 2 systematic reviews of the RCTs.<sup>180,181</sup> Although there was no survival advantage, investigators reported a decrease in infectious complication and other markers of morbidity in patients who received immunonutrition. Not surprisingly, the impact of the treatment depended on the composition of the diet, the specific patient population, and the methodological quality of the study. Those looking for a simple yes or no answer are bound to be disappointed, because no single IED could be recommended for the general ICU patient population. In general, the more heterogeneous the patient population, the less clear the advantage. The largest RCT of a heterogeneous ICU population ( $n = 597$ ) showed no beneficial effect of immunonutrition on any of the clinical outcome parameters (eg, mortality, LOS, ventilator days, and infectious complications).<sup>182</sup>

There is no perfect nutritional formula for all critically ill patients, and what (and how much) is in the can is important. In reality, it would be naive for a clinician to randomly prescribe an IED and expect positive outcomes. With the wide range of nutrients that have pharmacological properties, deciding which combination may be of benefit for a given patient requires careful analysis. According to the literature, appropriately selected IEDs are beneficial, but administration of randomly selected formulas to critically ill patients cannot be recommended.

## **Advances in Endocrine System Management**

### *Glycemic Control*

***Adverse Effects of Hyperglycemia.*** Hyperglycemia is common in critically ill patients, regardless of previously diagnosed diabetes. It has

now become increasingly clear that even moderate degrees of hyperglycemia are associated with an increase in adverse outcomes in a wide variety of patients.<sup>183</sup> Two landmark studies from the University of Leuven have recently shown that there may be a causal relationship between hyperglycemia and adverse outcomes, and that strict control of blood sugar levels can improve the outcome. However, there are numerous issues that continue to generate vigorous debate, such as the appropriate selection of the candidates, the degree of glycemic control, the risks of hypoglycemia, appropriate monitoring techniques, and duration of therapy.

***Tight Glycemic Control.*** Insulin has several direct anti-inflammatory effects raising the question whether it is the insulin or the tight glycemic control that is beneficial. A well-designed preclinical study has recently demonstrated that the survival benefits are primarily due to the glycemic control, independent of insulin.<sup>184</sup> The clinical data also seem to support this observation, with the risk of death demonstrating a linear correlation with the degree of hyperglycemia,<sup>185</sup> and the most pronounced benefit seen when blood glucose levels are controlled below 110 mg/dL.<sup>186</sup> Furthermore, a prospective cohort study has shown that failure to achieve glycemic control despite intensive insulin therapy in the ICUs is frequent (31%), and is independently associated with increased mortality (odds ratio = 5.9).<sup>187</sup>

***Intraoperative Control.*** Anesthesia and operative stress clearly have an impact on blood sugar levels, and some retrospective studies had suggested that poor intraoperative glycemic control was associated with an increase in postoperative morbidities.<sup>188,189</sup> However, a follow-up prospective randomized study (cardiac surgery patients, n = 400) showed that in the setting of tight postoperative glucose control, strict glycemic control (80 to 100 mg/dL) during the operation itself failed to decrease mortality, morbidity, and length of ICU/hospital stay, while increasing the incidence of stroke.<sup>190</sup> Thus, intraoperative tight glycemic control cannot be recommended as a standard of care.

***Benefits of Blood Glucose Control in Critically Ill Patients.*** Glycemic control in critically ill patients took center stage in 2001 with the publication of the first Leuven study, where surgical ICU patients (n = 1545) were randomized to receive insulin treatment with target blood glucose levels of either 80 to 110 mg/dL or 180 to 200 mg/dL.<sup>191</sup> The mortality rate in the tight glycemic control group was statistically lower (4.6% vs 8.0%,  $P < 0.04$ ), with the maximum benefit in patients who stayed in the ICU for longer than 5 days (10.6% vs 20.2%,  $P = 0.005$ ). There was also an improvement in morbidity. In the follow-up study, this

treatment was tested in the medical ICU patient population, and although morbidity was decreased there was no overall improvement in mortality.<sup>192</sup> Subgroup analysis showed that mortality was decreased in patients who stayed in the ICU for longer than 3 days, but it tended to increase in patients who stayed for shorter periods of time. Is shorter duration of therapy harmful or were the differences due to a selection bias? One explanation is that insulin may have acted as a metabolic stress test and uncovered patients with a deficiency in hormonal responsiveness, rather than directly causing harm.<sup>193</sup> In a combined analysis of both datasets (1548 surgical and 1200 medical patients) Van den Berghe<sup>186</sup> has shown reduction in morbidity and mortality in the total population (intent-to-treat analysis), which was more pronounced when treatment was provided for more than 3 days. Only the patients with pre-existing diabetes mellitus exhibited no survival benefit. Although these are large randomized clinical trials, the fact that they were conducted only at a single center raises concerns about the reproducibility of these findings at other institutions. Concerns have also been raised about the cost-effectiveness of intensive insulin therapy. However, in a post hoc analysis the Leuven group demonstrated substantial cost savings due to a reduction in morbidity and mortality,<sup>194</sup> which has also been validated by others.<sup>195</sup>

***Other Studies/Risks for Hypoglycemia.*** Two recent studies have shown that variability in blood glucose levels is as important as the absolute glucose concentrations, and that higher mortality is associated with a larger fluctuation in blood glucose values.<sup>196,197</sup> Thus, normalization of blood glucose in critically ill patients should be attempted slowly (12 to 24 hours), to prevent acute fluctuations and to avoid episodes of hypoglycemia.

Until recently, infusion of glucose with insulin and potassium was considered a promising therapy for patients with acute myocardial infarctions. However, 2 recent large randomized trials failed to show any benefits of this treatment.<sup>198,199</sup> It is hardly surprising that aggressive insulin therapy increases the chances of developing hypoglycemia. As a matter of fact, 2 large multicenter randomized trials were recently stopped due to an unacceptably high incidence of hypoglycemia. The VISEP trial (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) was designed as a 4-arm study to evaluate the choice of fluid resuscitation and intensive insulin therapy in septic patients. The insulin arm of the study was stopped prematurely due to a 12.1% incidence of hypoglycemia.<sup>200</sup> However, the absolute risk reduction in mortality (3% to 4%) in this study was remarkably similar to the Leuven studies. The other study that was stopped after enrollment of 1109 patients (for a planned study of

3500 patients) was the GluControl (Glucose Control) trial (results presented at the 2007 International Symposium of Intensive Care and Emergency Medicine, Brussels). This prospective, randomized, multicenter study hoped to compare the effects of 2 regimens of insulin therapy titrated to achieve a blood sugar level between 80 and 110 mg/dL and between 140 and 180 mg/dL, respectively.<sup>201</sup> Unfortunately, the number of patients that experienced hypoglycemia reached 9.8% in the aggressive glucose control group, with an associated increase in mortality (18.8% vs 10.8%,  $P < 0.0001$ ). The incidence of hypoglycemia is also influenced by the nature of the patient population, as evidenced by a 3-fold increase in the second Leuven study (medical ICU, hypoglycemia incidence = 18%) compared with the first study (predominantly cardiac surgery ICU, hypoglycemia incidence = 6.2%).

In a critically ill patient population that is unlikely to display typical signs and symptoms of hypoglycemia, concerns about its adverse consequences are clearly justified. However, the real clinical significance of hypoglycemia remains controversial. A recent retrospective cohort study (2 years, mixed ICU) found no association between the first occurrence of hypoglycemia and in-hospital mortality in 245 hypoglycemic episodes (156 patients),<sup>202</sup> whereas another retrospective study (5365 patients, 102 hypoglycemic patients) concluded that even a single episode of severe hypoglycemia was an independent predictor of mortality (odds ratio = 2.28,  $P = 0.0008$ ).<sup>203</sup> Many clinicians also fear that episodes of hypoglycemia may not be as rapidly diagnosed/treated in patients who are not being closely monitored in a clinical trial, and adverse consequences of hypoglycemia may be more significant in a “real life” situation. Monitoring of blood glucose levels is further complicated by questions about the accuracy and reproducibility of point-of-care testing devices. Because of all these concerns, there is wide variability in how the published data are used in the development of different insulin protocols in clinical practice.<sup>204</sup>

**Recommendations.** A multicenter randomized trial (NICE-SUGAR Study) of the effects of blood glucose management on 90-day all-cause mortality in a heterogenous population of ICU patients is currently enrolling patients (target  $n = 5000$ )<sup>205</sup> and is expected to provide definitive answers. Until then, our recommendation would be to aim for moderately aggressive glycemic control (blood glucose  $< 150$  mg/dL), with special attention paid to the prevention of acute fluctuations in glucose levels. This tempered approach strikes a balance between the benefits of glycemic control and the chances of developing hypoglycemic complications. In the near future, development of reliable, continuous blood sugar monitoring devices, and closed-loop computer-assisted sys-

tems should make it much safer to implement more aggressive glycemic control protocols in the ICU.

### *Critical Illness-Related Corticosteroid Insufficiency (CIRCI)*

***Incidence of CIRCI and Benefits of Steroid Treatment in Septic Patients.*** The stress response is largely mediated by the hypothalamic-pituitary-adrenal (HPA) axis, and the sympathoadrenal system (SAS), which are functionally related. Cortisol is the major glucocorticoid secreted by the adrenal cortex. Approximately 90% of cortisol is bound to the corticosteroid-binding globulin with only 10% in free, biologically active form. The adrenal gland does not store cortisol, and increased secretion is almost entirely due to increased synthesis under the control of adrenocorticotrophic hormone (ACTH). Once considered rare, CIRCI is now being reported with increasing frequency in critically ill patients. In a randomized controlled trial of septic shock patients by Annane and colleagues,<sup>206</sup> 77% (229/299) of the subjects were found to have adrenal insufficiency, described as less than 9  $\mu\text{g/dL}$  increase in cortisol level on short corticotropin test. Treatment with low doses of hydrocortisone (200 mg/day) and fludrocortisone (50  $\mu\text{g/day}$ ) for a short duration (1 week) in this group decreased the mortality from 63% to 53% ( $P = 0.02$ ). In a more recent study, using metyrapone testing for diagnosis, the same author reported that the incidence of adrenal insufficiency in patients with severe sepsis/septic shock was 60%.<sup>207</sup> Because 2 earlier smaller RCTs had also shown significant effect on shock reversal with steroid therapy,<sup>208,209</sup> treatment of septic shock patients with steroids rapidly gained popularity after publication of the study by Annane and colleagues. However, several questions remained unanswered, such as how to select the patients who were most likely to benefit, identification of appropriate dose, optimal duration of treatment, and whether to taper the steroids or stop them abruptly. A recent large, European multicenter trial (Corticosteroid Therapy of Septic Shock [CORTICUS]) has recently been completed, and administration of steroids failed to offer a survival advantage.<sup>210</sup> There was, however, faster resolution of shock in steroid-treated patients. It is important to point out that unlike the Annane study, where only patients with hypotension unresponsive to vasopressor therapy were enrolled, the CORTICUS trial included patients with septic shock, regardless of response to vasopressors. Importantly, in the CORTICUS trial the corticotropin test did not reliably predict who would benefit from steroid treatment, and the measurement of serum cortisol levels did not help the decision making. These limitations of cortisol measurement were not surprising as the typical immunoassays measure total cortisol rather than the biologically active free cortisol.

Most of these assays also suffer from an overall lack of accuracy.<sup>211</sup> In this study investigators also noted that the use of etomidate for sedation was the reason for adrenal suppression (and worse outcomes) in several patients.<sup>212</sup> Since exogenous steroids have well-known side effects, proper selection of patients and implementation of proper treatment algorithms are critically important. So the key question remains: which septic patient should be treated with steroids?

***Patient Selection and Treatment Recommendations.*** Patients who are known to have adrenal insufficiency or are receiving chronic steroids should receive appropriate steroid replacement therapy depending on the stress level (hydrocortisone equivalent: 25 mg/day for minor surgery, 50 to 75 mg/day for major surgery, and 100 to 150 mg/day for major surgery).<sup>213</sup> In septic shock patients (without known adrenal insufficiency) the decision to treat with steroids should be based on clinical criteria and not on the measurement of cortisol levels (or response to corticotropin test). We recommend that low-dose steroids (<300 mg hydrocortisone/day intravenously) should be started only if shock is poorly responsive to standard fluid resuscitation and vasopressor therapy, without relying on a corticotropin stimulation test.<sup>214</sup> Since hydrocortisone (preferred agent) has intrinsic mineralocorticoid activity, there is no compelling reason to add oral fludrocortisone. Also, in the absence of data to recommend otherwise, we suggest that steroids should be stopped when shock has resolved (ie, patient is off vasopressors) rather than be given for a fixed period. The total duration of treatment should be limited to 1 week or less. Finally, low-dose steroids given for a short period (~1 week) can be stopped abruptly without any need to perform a slow taper.

## **Advances in ICU Ethics**

Critical care consumes a disproportionately high percentage of in-hospital health care expenditures, even if it involves a relatively small proportion of the patient population. Decisions made in the ICU include end-of-life matters, resource allocation, and complex patient/physician/relative interaction. Conflict is unavoidable, and the physician is often called to navigate through a narrow pathway between consciousness and necessity. The history of medical ethics as they relate to clinical care and medical research can be divided into 3 time periods.<sup>215</sup> The first period started with Hippocrates who established the commitment of a physician to the well-being of the patient, and ended with the Nuremberg trial in 1946, which established the basic tenets of medical experimentation and human subject protection. The second period included multiple violations

of the Code of Nuremberg (the Tuskegee experiment being probably the best known) and resulted in the Belmont Commission report. The third period, extending to our days, includes complex regulations that frequently result in more confusing than reassuring conclusions. Cost containment alternates with patient decision autonomy on the top of the hierarchy for optimal decision making. Quality improvement programs assess not only the outcome but also the process of care—a process that depends on committing resources to a patient and to a population as a whole, 2 often fundamentally opposing conditions.

### *End-of-Life Issues*

One of the most difficult decisions is the timing of interrupting life-sustaining interventions despite the American College of Chest Physicians and the Society of Critical Care Medicine consensus statements on this issue.<sup>216</sup> Futility of care is defined when quality and duration of survival is close to zero. The determination must be made by experienced physicians in accordance with the best available evidence. Another way to conceptualize futility of care is to ask: “Would this patient express gratitude for being alive?”<sup>217</sup> Under this perception, most would not regard a persistent vegetative state as a meaningful survival or one for which a patient or relatives would feel gratitude. Care for such a condition would be considered futile. Similarly, a patient with multiple organ failure who is maintained in life by intensive respiratory and hemodynamic support would have close to zero chances to survive, and therefore, persisting on these interventions leads to unnecessary cost and loss of dignity.

The Patient Self-Determination Act was enacted in 1991 to allow all patients receiving institutionalized care the opportunity to express their preferences regarding resuscitation and life-sustaining therapies on admission before undergoing medical or surgical treatment. It mandates that patients provide documentation of their desires regarding life support on admission to the hospital. Ideally, these “advance directive” documents provide clear and convincing evidence of patients’ wishes. However, advanced directives are available only for a minority of the ICU population. The primary caretaker, in communication with consultants and the health care proxies, should decide. In a study performed in San Francisco General Hospital the agreement among the different parties was studied.<sup>218</sup> When the primary caretaker (surgeon or ICU physician) decided that care should be withdrawn, 45% of patients and/or families agreed immediately and 90% within 5 days. Disagreements by patients or other physicians occurred infrequently and typically resolved within 2 weeks. The issue at hand is whether a valuable resource, such as an ICU

**TABLE 4.** Brain death criteria<sup>219,220</sup>

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Unresponsiveness

- The patient is completely unresponsive to external visual, auditory, and tactile stimuli and is incapable of communication in any manner.

Absence of cerebral and brainstem function

- Pupillary responses are absent, and eye movements cannot be elicited by the vestibulo-ocular reflex or by irrigating the ears with cold water.
- The corneal and gag reflex are absent, and there is no facial or tongue movement.
- The limbs are flaccid, and there is no movement, although primitive withdrawal movements in response to local painful stimuli, mediated at a spinal cord level, can occur.
- Apnea test: An apnea test should be performed to ascertain that no respirations occur at a Pco<sub>2</sub> level of at least 60 mm Hg. The patient oxygenation should be maintained with giving 100% oxygen by a cannula inserted into endotracheal tube as the Pco<sub>2</sub> rises. The inability to develop respiration is consistent with medullary failure.

Nature of coma must be known

- Known structural disease or irreversible systemic metabolic cause that can explain the clinical picture.

Some causes must be ruled out

- Body temperature must be above 32°C to rule out hypothermia
- No chance of drug intoxication or neuromuscular blockade
- Patient is not in shock

Persistence of brain dysfunction

- Six hours with a confirmatory isoelectric EEG or electrocerebral silence, performed according to the technical standards of the American Electroencephalographic Society
- Twelve hours without a confirmatory EEG
- Twenty-four hours for anoxic brain injury without a confirmatory isoelectric EEG

Confirmatory tests (are not necessary to diagnose brain death)

- EEG with no physiologic brain activity
  - No cerebral circulation present on angiographic examination (is the principal legal sign in many European countries)
  - Brainstem-evoked responses with absent function in vital brainstem structures
- 

EEG, electroencephalogram.

bed, can be held from a new patient who needs it, for as long as 2 weeks. Medical ethics committees are instrumental when such disagreement arises to effect resolution. In extreme situations judicial intervention may be needed.

Physicians managing critically ill surgical patients are extremely familiar with the concept of death. As a near-daily event in their lives, death fails to produce the same kind of response that it triggers in lay persons or even physicians of other specialties. Therefore, it is important that the critical care physician allows the relatives “to go through the process” and let the idea of losing a beloved one mature. Although this process should not linger for weeks, it needs adequate time and can hardly be expected to conclude within a single short meeting in a cold ICU conference room.

## *Brain Death and Organ Donation*

The concept of brain death is foreign to most relatives. It is extremely hard to understand that without an external change in appearance, the same patient who is connected to the same tubes and devices, is no longer alive. If the cardiac monitor continues to beep and the respiratory apparatus to move, relatives are unable to capture why the patient is not alive. Explaining that brain death equals death is a principal responsibility of the physician. Brain death criteria are well developed and universally accepted (Table 4).<sup>219</sup>

As the news of brain death is laid on a family, the request for organ donation adds a different level of complexity in the strained physician-patient relationship.<sup>221,222</sup> This request should never come from the principal caretaker. The relatives should make a clear conscious and subconscious distinction between the team who did everything to keep the patient alive and the team that may harvest his organs. The potential for acceptance increases if dedicated teams with professional training on approaching patient families about organ donation and sensitivity on personal, ethnic, and cultural issues take the lead in these discussions. In our unit, we have instituted a rule by which the physicians taking care of the patient identify the criteria and declare brain death, but are not allowed to be the first to approach the family for organ donation. This task is assigned to a specific team from the regional procurement agency that eventually involves all necessary parties in the discussions with the relatives.

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