Part 6: Advanced Cardiovascular Life Support
Section 7: Algorithm Approach to ACLS
7C: A Guide to the International ACLS Algorithms

Summary/Overview

The ILCOR algorithm presents the actions to take and decisions to face for all people who appear to be in cardiac arrest—unconscious, unresponsive, without signs of life. The victim is not breathing normally, and no rescuer can feel a carotid pulse within 10 to 15 seconds. Since 1992 the resuscitation community has examined and reconfirmed the wisdom of most recommendations formulated by international groups through the 1990s. Sophisticated clinical trials provided high-level evidence on which to base several new drugs and interventions. Finally, we have learned that we should continue to place a strong emphasis after 2000 on building a base of critically appraised, international scientific evidence. Evidence-based review opened many eyes; only a small proportion of resuscitation care rests on a base of solid evidence.

Note: The numbers below, such as ‘1 (Fig. 1),’ match numbers in the algorithms.

Fig. 1: ILCOR Universal/International ACLS Algorithm

Fig. 1, the ILCOR Universal/International ACLS Algorithm, and Fig. 2, the Comprehensive ECC Algorithm, are groundbreaking efforts to unify and simplify the essential information of adult ACLS. They demonstrate the integration of the steps of BLS, early defibrillation, and ACLS.

The ILCOR algorithm (Fig. 1) shows how simply the overall approach can be presented, with minimum elaboration of separate steps. The Comprehensive ECC Algorithm (Fig. 2) provides more details, particularly to support the AHA teaching approach based on the Primary and Secondary ABCD Surveys. Both algorithms depict many of the concepts and interventions that are new since 1992.

Notes to the ILCOR Universal/International ACLS Algorithm

1. Check responsiveness
2. Open the airway
3. Check breathing
4. Give 2 effective breaths
5. Assess circulation
6. Compress chest (no signs of circulation detected)

Note that step 6 does not use the term ‘pulse.’ In their 1998 BLS guidelines, the European Resuscitation Council and several ILCOR councils dropped a specific reference in their algorithms to ‘check the carotid pulse.’ They replaced the pulse check with a direction to ‘check for signs of circulation,’ namely, ‘look for any movement, including swallowing or breathing (more than an occasional gasp).’ Their guidelines instruct rescuers to ‘check for the carotid pulse’ as one of the ‘signs of circulation,’ but the pulse check does not receive the prominent emphasis that comes from inclusion in the algorithm. By 2000 many locations had confirmed the success of this European approach. Additional evidence had accumulated that the pulse check was not a good diagnostic test for the presence or absence of a beating heart. After international panels of experts reviewed the evidence at the Guidelines 2000 Conference, they also endorsed the approach of omitting the pulse check for lay responders from the International Guidelines 2000.

2 (Fig. 1)

Attach defibrillator/monitor; assess rhythm. Once the responders start the BLS algorithm, they are directed to attach the defibrillator/monitor and assess the rhythm.

3 (Fig. 1)

VF/pulseless VT. If they are using a conventional defibrillator and the monitor displays VF, the rescuers attempt defibrillation, up to 3 times as necessary. If using an AED, the rescuers follow the signal and voice prompts of the device, attempting defibrillation with up to 3 shocks. After 3 shocks they should immediately resume CPR for at least 1 minute. At the end of the minute, they should repeat rhythm assessment and shock when appropriate.

4 (Fig. 1)

Non-VF rhythm. If the conventional defibrillator/monitor displays a non-VF tracing or the AED signals ‘no shock
indicated,’ the responders should immediately check the pulse to determine whether the nonshockable rhythm is producing a spontaneous circulation. If not, then start CPR; continue CPR for approximately 3 minutes. With a non-VF rhythm the rescuer needs to return and recheck the rhythm for recurrent VF or for spontaneous return of an organized rhythm in a beating heart. At this point the algorithm enters the central column of comments.

5 (Fig. 1)

During CPR: secure airway; IV access. In this period the rescuers have many tasks to accomplish. The central column includes the major interventions of ACLS: placing and confirming a secure airway, starting an IV, giving appropriate medications for the rhythm, and searching for and correcting reversible causes. Note that the ECC Comprehensive Algorithm (Fig. 2) conveys this same approach using the memory aid of the Secondary ABCD Survey. In this survey A = advanced airway (tracheal tube placement); B = confirmation of airway location, oxygenation, and ventilation; and C = circulation access via IV line and circulation medications.

6 (Fig. 1)

VF/VT refractory to initial shocks: epinephrine or vasopressin. The ILCOR Universal Algorithm indicates...
that response personnel give all cardiac arrest patients a strong vasopressor, either epinephrine IV or vasopressin. This recommendation for vasopressin is one of the more interesting new guidelines. The discussions on adding amiodarone are detailed later in this section.

Consider buffers, antiarrhythmics, pacing, atropine; search for and correct reversible causes. This short phrase covers a multitude of interventions discussed and debated during the Evidence Evaluation Conference and the international Guidelines 2000 Conference: multiple antiarrhythmics, neutralization of acidosis, and transcutaneous pacing. The word ‘consider’ has become an informal code in the resuscitation community interpreted to mean that we lack the evidence that establishes one intervention as superior to another. Whether this means that two interventions are equally effective or equally ineffective is a debate being waged constantly in resuscitation research.

Consider causes that are potentially reversible. This guideline applies primarily to non-VF/VT patients. For this group there is often a specific cause of the loss of an effective heartbeat. The International Guidelines 2000 take the innovative step of listing the 10 most common reversible causes of non-VF/VT arrest at the bottom of the algorithm.
This is discussed in detail in the section on pulseless electrical activity. *End of Algorithm Notes*

**Primary ABCD Survey**  
(Begin BLS Algorithm)  
Activate emergency response system  
Call for defibrillator  
A Airway: open airway; assess breathing (open airway, look, listen, feel)  
B Breathing: give 2 slow breaths  
C CPR: check pulse; if no pulse  
C Start Chest Compressions  
D Defibrillator: attach AED or monitor/defibrillator when available

**Secondary ABCD Survey**  
A Secure airway as soon as possible  
B Confirm tube placement; use 2 methods to confirm  
• Primary physical examination criteria plus  
• Secondary confirmation device (qualitative and quantitative measurements of end-tidal CO₂)  

B Secure tracheal tube  
• Prevents dislodgment; purpose-made tracheal tube holders recommended over tie-and-tape approaches

**B Confirm initial oxygenation and ventilation**  
• End-tidal CO₂ monitor  
• Oxygen saturation monitor

**C Oxygen, IV, monitor, fluids**  
• rhythm appropriate medications  
**C Vital signs:** temperature, blood pressure, heart rate, respirations

**D Differential Diagnoses**  
**Note:** The primary and secondary ABCD action surveys above are slightly different from the surveys in other algorithms. In subsequent algorithms the wording of the Primary and Secondary ABCD Surveys is identical. The difference in wording between the first 2 algorithms and the later algorithms allows the learners to see that the overall concept is more important than ‘getting the algorithm exactly right.’ Review these 2 surveys for Fig. 2. Notice the way in which the vocabulary of the survey changes but the overall content of the survey does not change. People learn in different styles and remember by different techniques. Under-standing is more important than repetition.

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**Fig. 2: Comprehensive ECC Algorithm**

Both the ILCOR Universal Algorithm and the Comprehensive ECC Algorithm (Fig. 2) convey the concept that all cardiac arrest victims are in 1 of 2 ‘rhythms’: VF/VT rhythms and non-VF rhythms.

• Non-VF comprises asystole and PEA, which are treated alike.  
• Therefore, there is no critical need to separate the subjects into VF, pulseless VT, PEA, or asystole.

All cardiac arrest victims receive the same 4 treatments

• CPR  
• Secure airway  
• Vasoconstrictors  
• Antiarrhythmics

The only distinguishing treatment for arrest victims is that rescuers treat VF/VT patients with defibrillatory shocks.

The algorithms in Figs. 1 and 2 demonstrate a simple concept. The ILCOR Universal Algorithm and the Comprehensive ECC Algorithm are the only teaching/learning displays rescuers will need because they treat everyone in cardiac arrest this way.

**Notes to the Comprehensive ECC Algorithm**  
(Fig. 2)

**Begin Primary ABCD Survey.** Unresponsive; not breathing. Boxes 1 and 2 cover the steps of the BLS Algorithm and cover the Primary ABCD Survey. The survey is a memory aid and conveys no therapeutic value as stated and displayed. The Primary and Secondary ABCD Surveys are simple mnemonics that assist initial learning. They also provide a useful mental ‘hook’ for later review and recall. Listing more details within the algorithm provides easy review of the steps, especially when the learner has not participated routinely in actual resuscitation attempts.

2 (Fig. 2)  
VF/VT: attempt defibrillation (up to 3 shocks if VF persists). Rhythm assessment and continued CPR are at the center of the Comprehensive ECC Algorithm. The metaphor of a clock ticking away for a cardiac arrest victim in VF is overused but accurate. With each minute of persistent VF, the probability of survival declines. Two clocks are racing. One is the clock that measures the therapeutic interval (from collapse to arrival of the defibrillator). One is the clock that measures the irreversible damage interval (from cessation of blood flow to the brain to the start of permanent, irreversible brain death).
Here is an observation that will put the racing clocks into perspective. Several experts have observed that great amounts of time and money are spent on the development of new defibrillation waveforms, novel antiarrhythmics, innovative vasopressors, and fresh approaches to ventilation and oxygenation. The total combined effect on survival of these interventions is equivalent to nothing more than cutting the interval from collapse to defibrillatory shock by 2 minutes[1].

3 (Fig. 2)

Non-VF/VT. The ILCOR recommendation is to consider the non-VF/VT rhythms as one rhythm when the patient is in cardiac arrest. Consider non-VF/VT as either asystole or PEA. The treatment in the algorithm is the same for both: epinephrine, atropine, transcutaneous pacing. Electrical activity on the monitor screen is a more positive rhythm than asystole. Later in this discussion PEA and asystole are presented in much greater detail.

Both rhythms have a ‘differential diagnosis’ in terms of what entities can produce a PEA and an asystolic rhythm. Responders must aggressively evaluate PEA victims to discover a potential reversible cause. There is a narrow diagnostic interval of just a few minutes at the discovery of PEA. Asystole, on the other hand, is rarely salvaged unless a reversible cause (eg, severe hyperkalemia, overdose of phenothiazine) is found. Only occasionally does asystole respond to epinephrine in higher doses, atropine, or pacing, because the patient is simply destined to die, given the nature of the original precipitating event.

4 (Fig. 2)

Secondary ABCD Survey. Use of a vasopressor: epinephrine for non-VF/VT, vasopressin for refractory VF. This section of the algorithm makes the same points about persistent arrest from VF/VT and non-VF/VT as the ILCOR Universal Algorithm. The ECC Comprehensive Algorithm, however, uses the memory aid of the Secondary ABCD Survey, a device repeated in all the cardiac arrest algorithms. The algorithm notes expand on these concepts.

5 (Fig. 2)

Potentially reversible causes. Sudden VF/VT arrests are straightforward in their management. Management consists of early defibrillation, which can succeed independently of other interventions and independently of discovery of the cause of the arrhythmia. With non-VF/VT arrest, however, successful restoration of a spontaneous pulse depends almost entirely on recognizing and treating a potentially reversible cause. As an aide mémoire, Fig. 1 places the following list, referred to as ‘the 5 Hs and 5 Ts,’ in the algorithm layout:

The ‘5 Hs’
- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hyperkalemia/hypokalemia and metabolic disorders
- Hypothermia/hyperthermia

The ‘5 Ts’
- Toxins/tablets (drug overdose, illicit drugs)
- Tamponade, cardiac
- Tension pneumothorax
- Thrombosis, coronary
- Thrombosis, pulmonary

Fig. 2, the Comprehensive ECC Algorithm, expands the table of reversible causes by listing possible therapeutic interventions next to each of the potential causes.

Consider: Is one of the following conditions playing a role?
- Hypovolemia (volume infusion)
- Hypoxia (oxygen, ventilation)
- Hydrogen ion–acidosis (buffer, ventilation)
- Hyperkalemia (CaCl plus others)
- Hypothermia (see Hypothermia Algorithm in Part 8)
- ‘Tablets’ (drug overdoses, accidents)
- Tamponade, cardiac (pericardiocentesis)
- Tension pneumothorax (decompress–needle decompression)
- Thrombosis, coronary (fibrinolytics)
- Thrombosis, pulmonary (fibrinolytics, surgical evacuation)

Newly Recommended Agent: Vasopressin for VF/VT

People knowledgeable about the ACLS recommendations during the 1990s will immediately notice that the recommendations for the requisite vasoconstrictor, epinephrine, have changed. The first 3 algorithms—the ILCOR Universal Algorithm, the Comprehensive ECC Algorithm, and Ventricular Fibrillation—each contain the same recommendation for vasopressin as an adrenergic agent equivalent to epinephrine for VF/VT cardiac arrest.

This is one of the most important new recommendations in the International Guidelines 2000. Vasopressin, the natural substance antidiuretic hormone, becomes a powerful vasoconstrictor when used at much higher doses than normally present in the body. Vasopressin possesses positive effects that duplicate the positive effects of epinephrine. Vasopressin does not duplicate the adverse effects of epinephrine. (See ‘Pharmacology II: Agents to Optimize Cardiac Output and Blood Pressure’ for more detailed material on vasopressin.)

Vasopressin received a Class IIb recommendation (acceptable, not harmful, supported by fair evidence) from the panel of international experts on adrenergics. Notice that vasopressin is recommended as a single, 1-time dose in humans. Vasopressin requires less frequent administration because the 10- to 20-minute half-life of vasopressin is much greater than the 3- to 5-minute half-life of epinephrine.

After the single dose of vasopressin, the algorithms allow...
a return to epinephrine if there is no clinical response to vasopressin. This return to epinephrine has no specific human evidence to provide support, although at least 1 clinical trial in Europe is under way. In an informal poll of the experts on the adrenergic panel, every person accepted this recommendation to return to epinephrine after 10 to 20 minutes. (The possibility of a second dose of vasopressin in 10 to 20 minutes was discussed and seems rational. However, this was listed as a Class Indeterminate recommendation because we lack research in humans that addresses this question.)

The rather imprecise time range between the dose of vasopressin and the administration of subsequent epinephrine allows flexibility in the decisions about when to give subsequent adrenergics. The dilemma is: give too soon and cause adverse effects from excessive vasopressin; give too late and the chances of a positive outcome vanish.

**Primary and Secondary ABCD Surveys**

In some locations, particularly in courses for ACLS providers, the learners are taught a memory aid called the Primary and Secondary ABCD Surveys. These 8 steps apply to all cardiovascular-cardiopulmonary emergencies. Course directors crafted the ABCD surveys to help ACLS providers remember the specific action steps. By memorizing the 2 surveys, ACLS students learn specific actions in a specific sequence. The surveys use the familiar mnemonic of the first 4 letters of the alphabet, and they maintain the traditional actions associated with those 4 letters:

- **A** = Airway
- **B** = Breathing
- **C** = Circulation
- **D** = Defibrillation (or Differential Diagnosis in the Secondary ABCD Survey)

Because repetition is a well-documented aid to learning, the elements of the Primary and Secondary ABCD Surveys are repeated in several other algorithms: VF/VT, PEA, and asystole.

Fig. 3, VF/pulseless VT, conveys more details about the Secondary ABCD Survey:

- **A** = Airway control with a secure airway
- **B** = Breathing effectively: verify with primary and secondary confirmation of proper airway placement
- **C** = Circulation, which incorporates vital signs, ECG monitoring, access to the circulation via IV lines, and then administration of rhythm-appropriate medications
- **D** = Differential Diagnosis

A directive to ‘consider the differential diagnoses’ improves the resuscitation protocols, because this is a recommendation to stop and think: What caused this arrest? With the addition of this step, resuscitation teams will identify more cardiac arrests with reversible causes. Although we lack evidence that supports use of this memory aid, its use has the strong appeal of common sense.

The Secondary ABCD Survey in Fig. 2 states perhaps the most important new recommendations for out-of-hospital care providers.

- We make stronger and more explicit recommendations to confirm tracheal tube placement.
- We recommend that resuscitation personnel take specific actions to prevent tube dislodgment after an initial correct placement.

During the years 1999–2000, publications about out-of-hospital pediatric resuscitation documented high rates of tube dislodgment. The researchers discovered that on arrival and evaluation in the Emergency Department, 8% to 12% of tracheal tubes were in the esophagus or hypopharynx. Given the study design, researchers were unable to determine whether these possibly lethal mishaps were due to incorrect initial tube placement or dislodgment after placement. This information has heightened concerns that ACLS providers may be committing undetected harm while performing our most critical interventions.

**Fig. 3: VF/Pulseless VT**

Fig. 3 covers the treatment of VF/pulseless VT in more depth than Figs. 1 and 2. Fig. 3 was created as a teaching aid to convey specific details about the Primary and Secondary ABCD Surveys. The treatments outlined in Figs. 1, 2, and 3 are identical: CPR, defibrillation if VF/VT, advanced airway control, intravenous access, rhythm-appropriate medications.

**Always Assume VF (Figs. 1–3)**

Note that Fig. 1, the ILCOR Universal ACLS Algorithm, Fig. 2, the ECC Comprehensive Algorithm, and Fig. 3, the Ventricular Fibrillation/Pulseless VT Algorithm, state this precept unequivocally: rescuers must assume that all adult sudden cardiac arrests are caused by VF/pulseless VT. All training efforts therefore place a strong emphasis on immediate recognition and treatment of VF/pulseless VT. Proper treatment with early defibrillatory shocks allows VF/pulseless VT to provide the majority of adult cardiac arrest survivors. Several mature EMS systems, such as Seattle/King County, Washington, USA, have collected data for >25 years. Year after year VF/VT contributes 85–95% of the survivors.

**Energy Levels for Shock and Defibrillation Waveforms**

The appearance of biphasic waveform defibrillators has generated great enthusiasm in the resuscitation community. Reaching EMS organizations in 1996, the first biphasic defibrillator approved for market shocked at only 1 energy level, approximately 170 J. Competitive market forces stirred up
considerable controversy over the efficacy of biphasic waveform shocks in general and nonescalating energy levels in particular. This unseemly chapter in the history of medical device manufacturers has been reviewed in detail in a Medical Scientific Statement from the Senior Science Editors and the chairs of the ECC subcommittees[1]. Biphasic waveform defibrillators are conditionally acceptable—regardless of initial shock energy level and regardless of the energy level of subsequent shocks (nonescalding). The condition that must be met is clinical data that confirms equivalent or superior effectiveness to monophasic defibrillators when used in the same clinical context. For example, to meet this condition manufacturers cannot compare rescue defibrillatory shocks delivered to a fibrillating heart in the Electrophysiology Stimulation Laboratory versus defibrillatory shocks delivered to patients with 12-minute-old VF in the absence of CPR efforts from bystanders. (See ‘Defibrillation’ in Part 6 for more detail on waveforms and energy levels.) The International Guidelines 2000 panel experts, the ILCOR representatives, and other delegates thought that the class of recommendation for biphasic shocks, nonescalating energy levels, should be upgraded from Class IIb in 1998 to Class IIa in 2000.

CPR, VF, and Defibrillation

After 3 unsuccessful attempts to achieve defibrillation, the first 3 algorithms instruct rescuers to provide approximately 1 minute of CPR. This produces some reoxygenation of the blood and some circulation of this blood to the heart and brain. The precise effect of this minute of CPR on refractory VF is unclear.

Stimulated by the 1999 publication of a retrospective analysis of out-of-hospital cardiac arrest data from the Seattle, Washington, EMS system, the Evidence Evaluation Conference (September 1999) included this topic on its agenda. The EMS personnel initially used a protocol in which arriving EMTs attached an AED and analyzed and shocked any VF rhythms as quickly as possible. Later the protocol directed the EMTs to perform 60 to 90 seconds of CPR before attaching the AED and shocking VF. The survival rates to hospital discharge were significantly higher during the period of prescribed preshock CPR. Other experts argued that a fibrillating myocardium suffers unrelenting deterioration as long as VF continues, CPR or no CPR. A minute or so of preshock CPR does not prevent this deterioration. This guideline recommendation was classed as Indeterminate because the quality and amount of evidence, on both sides of the question, were at lower levels: retrospective data (Level 5) and extrapolation of data from other sources (Level 7), particularly animal studies (Level 6).

Diminishing Roles for Drugs in VF Arrest

The ILCOR Universal Algorithm, the Comprehensive ECC Algorithm, and similar comments in Fig. 3 relegate adrenergic agents, antiarrhythmic agents, and buffer therapy to secondary roles for both VF and non-VF patients. This secondary role applies to time-honored agents such as epinephrine, lidocaine, procainamide, and buffer agents and to newly available agents such as amiodarone. Meticulous, systematic review reveals that relevant, valid, and credible evidence to confirm a benefit due to these agents simply does not exist. This does not mean that resuscitation drugs were selected capriciously by the pioneers of resuscitation decades ago. They applied common sense, rational conjecture, and extrapolations from animal studies to arrive at the antiarrhythmics used over the past decade. If an agent is shown in animal models to raise the fibrillation threshold and lower the defibrillation threshold, then a reasonable assumption would be that the drug would facilitate defibrillation of the human heart to a perfusing rhythm. This sort of rational conjecture produced the rather eclectic groups of drugs that have stocked resuscitation kits for more than a decade.

In addition, it was not until the 1990s that researchers discovered the dismal truth that antiarrhythmic drugs were acting more like proarrhythmic agents. Drugs given to prevent VF/VT arrest appear to generate VF/VT arrest. With critical reappraisal these disturbing discoveries undermined the validity and credibility of scores of excellently designed and executed studies. Through the use of critical appraisal, most researchers in this area realized that the only proper evaluation of new resuscitation agents had to be prospective, randomized clinical trials in which the only acceptable control group had to be placebo.

Designs of studies of new drugs versus standard therapy were unacceptable for the obvious reason—if both standard therapy and the new drug made cardiac arrest victims worse, we could never obtain valid results. The adverse effects would not be recognized unless one agent was significantly worse than the other. Ironically, the researchers would conclude that the less worse drug was actually a superior agent of positive benefit to patients. See ‘Pharmacology I: Agents for Arrhythmias’ and ‘Pharmacology II: Agents to Optimize Cardiac Output and Blood Pressure’ for more detailed material that supports these observations.

New Class of Recommendation for Epinephrine and Lidocaine: Indeterminate

An immense amount of animal research and lower-level human research exists on epinephrine in cardiac arrest. These projects are remarkable in the homogeneity of results—the findings are consistently and invariably positive. But almost no valid, consistent, and relevant human evidence exists to support epinephrine over placebo in human cardiac arrest. Clinical researchers have not conducted prospective, placebo-controlled, clinical trials in humans on this topic. Consequently, the international,
evidence-based guidelines had to conclude that epinephrine was Class Indeterminate.

Similarly, no study has shown that lidocaine is effective as an agent to use in human arrest from refractory, shock-resistant VF. Our growing awareness of the proarrhythmic effects of antiarrhythmics now requires that researchers evaluate lidocaine and other antiarrhythmics against placebo, and not against some other antiarrhythmics. No clinical differences will be observed if 2 antiarrhythmics are equally ineffective or even equally harmful. At this time, therefore, lidocaine receives a Class Indeterminate recommendation.

Notes to Fig. 3: VF/Pulseless VT Algorithm

Assume that VF/VT persists after each intervention.1 (Fig. 3)
Defibrillatory shock waveforms

- Use monophasic shocks at listed energy levels (200 J, 200–300 J, 360 J) or biphasic shocks at energy levels documented to be clinically equivalent (or superior) to the monophasic shocks.2 (Fig. 3)

2A Confirm airway placement with

- Primary physical examination criteria plus
- Secondary confirmation device (end-tidal CO₂, end-diastolic diameter) (Class IIa)

2B Secure airway

- To prevent dislodgment, especially in patients at risk for movement, use purpose-made (commercially available) tube holders, which are superior to tie-and-tape methods (Class IIb)
- Consider cervical collar and backboard for transport (Class Indeterminate)
- Consider continuous, quantitative end-tidal CO₂ monitor (Class IIa)

2C Confirm oxygenation and ventilation with

- End-tidal CO₂ monitor and
- Oxygen saturation monitor3 (Fig. 3)

3A Epinephrine (Class Indeterminate) 1 mg IV push every 3 to 5 minutes. If this fails, higher doses of epinephrine (up to 0.2 mg/kg) are acceptable but not recommended (there is growing evidence that it may be harmful).

3B Vasopressin is recommended only for VF/VT; there is no evidence to support its use in asystole or PEA. There is no evidence about the value of repeat vasopressin doses. There is no evidence about the best approach if there is no response after a single bolus of vasopressin. The following Class Indeterminate action is acceptable, but only on the basis of rational conjecture. If there is no response 5 to 10 minutes after a single IV dose of vasopressin, it is acceptable to resume epinephrine 1 mg IV push every 3 to 5 minutes.4 (Fig. 3)

4A Antiarrhythmics are indeterminate or Class IIb: acceptable; only fair evidence supports possible benefit of antiarrhythmics for shock-refractory VF/VT.

- Amiodarone (Class IIb) 300 mg IV push (cardiac arrest dose). If VF/pulseless VT recurs, consider administration of a second dose of 150 mg IV. Maximum cumulative dose: 2.2 g over 24 hours.
- Lidocaine (Class Indeterminate) 1.0 to 1.5 mg/kg IV push. Consider repeat in 3 to 5 minutes to a maximum cumulative dose of 3 mg/kg. A single dose of 1.5 mg/kg in cardiac arrest is acceptable.
- Magnesium sulfate 1 to 2 g IV in polymorphic VT (torsades de pointes) and suspected hypomagnesemic state.
- Procainamide 30 mg/min in refractory VF (maximum total dose: 17 mg/kg) is acceptable but not recommended because prolonged administration time is unsuitable for cardiac arrest.

4B Sodium bicarbonate 1 mEq/kg IV is indicated for several conditions known to provoke sudden cardiac arrest. See Notes in the Asystole and PEA Algorithms for details.5 (Fig. 3)

Resume defibrillation attempts: use 360-J (or equivalent biphasic) shocks after each medication or after each minute of CPR. Acceptable patterns: CPR-drug-shock (repeat) or CPR-drug-shock-shock-shock (repeat).

Fig. 4: Pulseless Electrical Activity

The absence of a detectable pulse and the presence of some type of electrical activity other than VT or VF defines this group of arrhythmias. When electrical activity is organized and no pulse is detectable, clinicians traditionally have used the term electromechanical dissociation (EMD). This term, however, is too specific and narrow. Strictly speaking, EMD means that organized electrical depolarization occurs throughout the myocardium, but no synchronous shortening of the myocardial fiber occurs and mechanical contractions are absent.

In the early 1990s the international resuscitation community began to adopt the summary term pulseless electrical activity (PEA). PEA would more accurately embrace a heterogeneous group of rhythms that includes pseudo-EMD, idioventricular rhythms, ventricular escape rhythms, postdefibrillation idioventricular rhythms, and bradyasystolic rhythms. Additional research with cardiac ultrasonography and indwelling pressure catheters has confirmed that often a pulseless patient with electrical activity also has associated mechanical contractions. These contractions are too weak to produce a blood pressure detectable by the usual methods of palpation or sphygmomanometry. Of utmost importance, ACLS providers must know that PEA is often associated with specific clinical states that can be reversed when identified early and treated appropriately.

Notes to Fig. 4: Pulseless Electrical Activity

Both VF/VT and PEA are ‘rhythms of survival.’ People in VF/VT can be resuscitated by timely arrival of a defibrillator, and people in PEA can be resuscitated if a reversible cause of PEA is identified and treated appropriately. The PEA algorithm puts great emphasis on searching for specific, reversible causes of PEA. The algorithm features a table of the top 10 causes of PEA, arranged as the ‘5 H’s and 5 T’s.’ If reversible causes are not considered, rescuers will have little chance of recognition and successful treatment. Sodium bicarbonate provides a good example of how the cause of the PEA relates to the therapy. Sodium bicarbonate can vary between being a Class I intervention
and being a Class III intervention, depending on the cause.

1 (Fig. 4) Sodium bicarbonate 1 mEq/kg is used as follows:
   Class I (acceptable, supported by definitive evidence)
   - If patient has known, preexisting hyperkalemia
   - Class IIa (acceptable, good evidence supports)
   - If known, preexisting bicarbonate-responsive acidosis
   - In tricyclic antidepressant overdose
   - To alkalinize urine in aspirin or other drug overdoses
   - Class IIb (acceptable, only fair evidence provides support)
   - In intubated and ventilated patients with long arrest inter-
Emboli, tamponade, tension pneumothorax, and massive pulmonary induced vasodilation. Other causes of PEA are cardiac hypovolemia from hemorrhage or anaphylaxis—causes of hypovolemia can often be corrected, including prompt recognition and appropriate therapy, the many activity without measurable blood pressure. Through width and rate.

If one simply looks at the electrical activity often a response to a specific condition, and helpful clues for PEA is to search for possible causes. These rhythms are often seen when patients are in cardiac arrest or when there is a specific critical rhythm disturbance. For example, severe hyperkalemia, hypothermia, hypoxia, preexisting acidosis, and a large variety of drug overdoses can be wide-complex PEs. Overdoses of tricyclic antidepressants, β-blockers, calcium channel blockers, and digitalis will produce a slow, wide-complex PEA.

In contrast, a fast, narrow-complex PEA indicates a relatively normal heart responding exactly as it should for severe hypovolemia, infections, pulmonary emboli, or cardiac tamponade. These conditions have specific interventions.

The major action to take for a cardiac arrest victim in PEA is to search for possible causes. These rhythms are often a response to a specific condition, and helpful clues can appear if one simply looks at the electrical activity width and rate.

Hypovolemia is the most common cause of electrical activity without measurable blood pressure. Through prompt recognition and appropriate therapy, the many causes of hypovolemia can often be corrected, including hypovolemia from hemorrhage or from anaphylaxis-induced vasodilation. Other causes of PEA are cardiac tamponade, tension pneumothorax, and massive pulmonary embolism.

Nonspecific therapeutic interventions for PEA include epinephrine and (if the rate is slow) atropine, administered as presented in Fig. 4. In addition, personnel should provide proper airway management and aggressive hyperventilation because hypoventilation and hypoxemia are frequent causes of PEA. Clinicians can give a fluid challenge because the PEA may be due to hypovolemia.

Immediate assessment of blood flow by Doppler ultrasound may reveal an actively contracting heart and significant blood flow. The blood pressure and flow, however, may fall below the threshold of detection by simple arterial palpation. Any PEA patient with a Doppler-detectable blood flow should be aggressively treated. These patients need volume expansion, norepinephrine, dopamine, or some combination of the three. They might benefit from early transcutaneous pacing because a healthy myocardium exists and only a temporarily disturbed cardiac conduction system stands between survival and death. Although in general PEA has poor outcomes, reversible causes should always be targeted and never missed when present.

**Fig. 5: Asystole: The Silent Heart Algorithm**

Patients in cardiac arrest discovered on the defibrillator’s monitor screen to be in asystole have a dismal rate of survival—usually as low as 1 or 2 people out of 100 cardiac arrests. During a resuscitation attempt, brief periods of an organized complex may appear on the monitor screen, but spontaneous circulation rarely emerges. As with PEA, the only hope for resuscitation of a person in asystole is to identify and treat a reversible cause.

Fig. 5, the Asystole Algorithm, outlines an approach much more in keeping with our current understanding of the issues surrounding asystole. The Asystole Algorithm focuses on ‘not starting’ and ‘when to stop.’ With prolonged, refractory asystole the patient is making the transition from life to death. ACLS providers who try to make that transition as sensitive and dignified as possible serve their patients well.

**Notes to Fig. 5: Asystole**

1 (Fig. 5)


- Any *clinical* indicators that resuscitation attempts are not indicated, eg, signs of death? If Yes: do not start/attempt resuscitation.

2 (Fig. 5)

**Confirm true asystole**

- Check lead and cable connections
- Monitor power on?
Fig. 5. Asystole: The Silent Heart Algorithm
Monitor gain up?
Verify asystole in another lead?

3 (Fig. 5)
**Sodium bicarbonate** 1 mEq/kg
- Indications for use include the following: overdose of tricyclic antidepressants; to alkalinize urine in overdoses; patients with tracheal intubation plus long arrest intervals; on return of spontaneous circulation if there is a long arrest interval.
- Ineffective or harmful in hypercarbic acidosis.

4 (Fig. 5)
**Transcutaneous pacing**
- To be effective, must be performed early, combined with drug therapy. Evidence does not support routine use of transcutaneous pacing for asystole.

5 (Fig. 5)
**Epinephrine**
- Recommended dose is 1 mg IV every 3 to 5 minutes. If this approach fails, higher doses of epinephrine (up to 0.2 mg/kg) may be used but are not recommended.
- We currently lack evidence to support routine use of vasopressin in treatment of asystole.

6 (Fig. 5)
**Atropine**
- Use the shorter dosing interval (every 3 to 5 minutes) in asystolic arrest.

7 (Fig. 5)
**Review the quality of the resuscitation attempt**
- Was there an adequate trial of BLS? of ACLS? Has the team done the following:
  - Achieved secure airway?
  - Performed effective ventilation?
  - Shocked VF if present?
  - Obtained IV access?
  - Given epinephrine IV? atropine IV?
  - Ruled out or corrected reversible causes?
  - Continuously documented asystole >5 to 10 minutes after all of the above have been accomplished?

8 (Fig. 5)
**Reviewed for atypical clinical features?**
- Not a victim of drowning or hypothermia?
- No reversible therapeutic or illicit drug overdose?
  - ‘Yes’ to the questions in Notes 7 and 8 means the resuscitation team complies with recommended criteria to terminate resuscitative efforts where the patient lies (Class IIa)
  - If the response team and patient meet the above criteria, then withhold urgent field-to-hospital transport with continuing CPR = Class III (harmful; no benefit)

9 (Fig. 5)
**Withholding or stopping resuscitative efforts out-of-hospital**
If criteria in 7 and 8 are fulfilled:
- Field personnel, in jurisdictions where authorized, should start protocols to cease resuscitative efforts or to pronounce death outside the hospital (Class IIa).
- In most US settings, the medical control official must give direct voice-to-voice or on-scene authorization.
- Advance planning for these protocols must occur. The planning should include specific directions for
  - Leaving the body at scene
  - Death certification
  - Transfer to funeral service
  - On-scene family advocate–Religious or nondenominational counseling

Asystole most often represents a confirmation of death rather than a ‘rhythm’ to be treated. Team leaders can cease efforts to resuscitate the patient from confirmed and persistent asystole when the resuscitation team has done the following:
- Provided suitable basic CPR
- Eliminated VF
- Achieved a successful secure airway with primary and secondary confirmation of tube placement
- Confirmed throughout the efforts that the tube was secure and had not been dislodged
- Monitored oxygen saturation and end-tidal CO₂ to ensure that the best possible oxygenation and ventilation were achieved
- Established successful IV access
- Maintained these interventions for >10 minutes, during which time the confirmed rhythm was asystole
- Administered all rhythm-appropriate medications
- Updated waiting family members, spouses, or available friends about the severity of the patient’s condition and lack of response to interventions
- Discussed the concept of programs to support family presence during resuscitative attempts and offered that option to appropriate family members. Note that family presence at resuscitative efforts is not a spur-of-the-moment offer, extended or not extended at the whim of supervising physicians. Rather, family presence at resuscitative efforts requires a formal program, with advance planning, assigned roles, and even rehearsals.
When to Stop?

Is it possible to state a specific time interval beyond which rescuers have never resuscitated patients? Does every resuscitation attempt have to continue for that length of time to guarantee that every salvageable person will be identified and saved? As outlined in the algorithm notes, the resuscitation team must make a conscientious and competent effort to give patients ‘a trial of CPR and ACLS,’ provided that the person had not expressed a decision to forego resuscitative efforts. The final decision to stop efforts can never be as simple as an isolated time interval, but clinical judgment and a respect for human dignity must enter the decision making. Many people among the resuscitation community strongly believe that we have erred greatly in the tendency to try prolonged, excessive resuscitative efforts.
Emergency medical response systems should not require the field personnel to transport every victim of cardiac arrest back to a hospital or Emergency Department (ED). In European countries, most out-of-hospital ALS care is provided by medical doctors, so decisions about stopping CPR, transportation back to the ED, and pronouncing death are handled by an authorized medical doctor in the field. Transportation with continuing CPR is justified if there are interventions available in the ED that cannot be performed in the field (such as central core rewarming equipment) or field interventions (such as tracheal intubation) that were unsuccessful in the field.

In the United States, outdated concepts of EMS care can linger for years. For example, many systems still dictate the practice of ‘scoop and run’ on all major medical patients, not just major trauma. For nontraumatic cardiac arrest, solid evidence confirms that ACLS care in the ED offers no advantage over ACLS care in field. Stated succinctly—if ACLS care in the field cannot resuscitate the victim, neither will ED care. Civil rules, administrative concerns, medical insurance requirements, and even reimbursement enhancement have frequently led to requirements to transport all cardiac arrest victims back to a hospital or ED. If these are unselective requirements, they are inappropriate, futile, and ethically unacceptable. There should be no requirements for ambulance transport of all patients who suffer an out-of-hospital cardiac arrest. This is especially true when the patient is pulseless and CPR is continued during transport. Researchers and EMS experts continue to publish observational studies on this practice of transporting all field resuscitations back to an ED, most often for pronouncement of death. To have the resuscitation team succeed with one of these victims and then have the victim survive to hospital discharge is extremely rare—usually <1%.

Likewise, it is inappropriate for clinicians to apply routine ‘stopping rules’ without thinking about the particular situation. ‘Part 2: Ethical Aspects of ECC and CPR’ provides a more detailed discussion of these issues. Cessation of efforts in the prehospital setting, following system-specific criteria and under direct medical control, should be standard practice in all EMS systems.

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**Fig. 6: Bradycardia**

**Notes to Fig. 6: Bradycardia**

1 (Fig. 6)
   If the patient has **serious signs or symptoms**, make sure they are related to the slow rate.

2 (Fig. 6)
   Clinical manifestations include

- Symptoms (chest pain, shortness of breath, decreased level of consciousness)
- Signs (low blood pressure, shock, pulmonary congestion, congestive heart failure)

3 (Fig. 6)
   If the patient is asymptomatic, do not delay transcutaneous pacing while awaiting IV access or for atropine to take effect.

4 (Fig. 6)
   *Denervated transplanted hearts* will not respond to atropine. Go at once to pacing, catecholamine infusion, or both.

5 (Fig. 6)
   **Atropine** should be given in repeat doses every 3 to 5 minutes up to a total of 0.03 to 0.04 mg/kg. Use the shorter dosing interval (3 minutes) in severe clinical conditions.

6 (Fig. 6)
   Never treat the combination of **third-degree heart block** and ventricular escape beats with lidocaine (or any agent that suppresses ventricular escape rhythms).

7 (Fig. 6)
   Verify patient tolerance and mechanical capture. Use analgesia and sedation as needed.

**Transcutaneous pacing** is a Class I intervention for all symptomatic bradycardias. If clinicians are concerned about the use of atropine in higher-level blocks, they should remember that transcutaneous pacing is always appropriate, although not as readily available as atropine. If the bradycardia is severe and the clinical condition is unstable, implement transcutaneous pacing immediately.

There are several other cautions to remember about treatment of symptomatic bradycardias. Lidocaine may be *lethal* if the bradycardia is a ventricular escape rhythm and unwary clinicians think they are treating preventricular contractions or slow VT. In addition, transcutaneous pacing can be painful and may fail to produce effective mechanical contractions. Sometimes the patient’s ‘symptom’ is not due to the bradycardia. For example, hypotension, associated with bradycardia, may be due to myocardial dysfunction or hypovolemia rather than to conducting system or autonomic problems.

Fig. 6 lists interventions in a sequence based on the assumption of worsening clinical severity. Give patients who are ‘precardiac arrest,’ or moving in that direction, multiple interventions in rapid sequence. Begin preparations for pacing, IV atropine, and administration of an epinephrine infusion. If the patient displays only mild problems due to the bradycardia, then **atropine 0.5 to 1.0 mg IV** can be given in a repeat dose every 3 to 5 minutes, to a total of 0.03 mg/kg. (For severe bradycardia or asystole, a maximum dose of 0.04 mg/kg is advisable.) Selection of the dosing interval (3 to 5 minutes) requires judgment about the severity of the patient’s symptoms. The provider should repeat atropine at shorter intervals for more distressed patients. Dopamine (at rates of 2 to 5 μg/kg per minute) can be added and increased quickly to 5 to 20 μg/kg per minute if low blood pressure is associated with the bradycardia. If the patient displays severe symptoms, clinicians can go directly to an epinephrine infusion.
Transcutaneous pacing should be initiated quickly in patients who do not respond to atropine or who are severely symptomatic, especially when the block is at or below the His-Purkinje level. Newer defibrillator/monitors have the capability to perform transcutaneous pacing. This intervention, unlike insertion of transvenous pacemakers, is available to and can be performed by almost all ECC providers. This gives transcutaneous pacing enormous advantages over transvenous pacing because transcutaneous pacing can be started quickly and conveniently at the bedside.

References

Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock. (N Engl J Med 2001;345:1368-77.)

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The systemic inflammatory response syndrome can be self-limited or can progress to severe sepsis and septic shock. Along this continuum, circulatory abnormalities (intravascular volume depletion, peripheral vasodilatation, myocardial depression, and increased metabolism) lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock. An indicator of serious illness, global tissue hypoxia is a key development preceding multiorgan failure and death. The transition to serious illness occurs during the critical “golden hours,” when definitive recognition and treatment provide maximal benefit in terms of outcome. These golden hours may elapse in the emergency department, hospital ward, or the intensive care unit.

Early hemodynamic assessment on the basis of physical findings, vital signs, central venous pressure, and urinary output fails to detect persistent global tissue hypoxia. A more definitive resuscitation strategy involves goal-oriented manipulation of cardiac preload, afterload, and contractility to achieve a balance between systemic oxygen delivery and oxygen demand. End points used to confirm the achievement of such a balance (hereafter called resuscitation end points) include normalized values for mixed venous oxygen saturation, arterial lactate concentration, base deficit, and pH. Mixed venous oxygen saturation has been shown to be a surrogate for the cardiac index as a target for hemodynamic therapy. In cases in which the insertion of a pulmonary-artery catheter is impractical, venous oxygen saturation can be measured in the central circulation.

Whereas the incidence of septic shock has steadily increased during the past several decades, the associated mortality rates have remained constant or have decreased only slightly. Studies of interventions such as immunotherapy, hemodynamic optimization, or pulmonary-artery catheterization enrolled patients up to 72 hours after admission to the intensive care unit. The negative results of studies of the use of hemodynamic variables as end points (“hemodynamic

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*The members of the Early Goal-Directed Therapy Collaborative Group are listed in the Appendix.
optimization”), in particular, prompted suggestions that future studies involve patients with similar causes of disease or with global tissue hypoxia (as reflected by elevated lactate concentrations) and that they examine interventions begun at an earlier stage of disease.

We examined whether early goal-directed therapy before admission to the intensive care unit effectively reduces the incidence of multiorgan dysfunction, mortality, and the use of health care resources among patients with severe sepsis or septic shock.

METHODS

Approval of Study Design

This prospective, randomized study was approved by the institutional review board for human research and was conducted under the auspices of an independent safety, efficacy, and data monitoring committee.

![Figure 1. Overview of Patient Enrollment and Hemodynamic Support.](image)

SIRS denotes systemic inflammatory response syndrome, CVP central venous pressure, MAP mean arterial pressure, ScvO₂ central venous oxygen saturation, SaO₂ arterial oxygen saturation, and VO₂ systemic oxygen consumption. The criteria for a diagnosis of SIRS were temperature greater than or equal to 38°C or less than 36°C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute or partial pressure of arterial carbon dioxide less than 32 mm Hg, and white-cell count greater than 12,000 per cubic millimeter or less than 4000 per cubic millimeter or the presence of more than 10 percent immature band forms.
Eligibility

Eligible adult patients who presented to the emergency department of an 850-bed academic tertiary care hospital with severe sepsis, septic shock, or the sepsis syndrome from March 1997 through March 2000 were assessed for possible enrollment according to the inclusion and exclusion criteria (Fig. 1). The criteria for inclusion were fulfillment of two of four criteria for the systemic inflammatory response syndrome and a systolic blood pressure no higher than 90 mm Hg (after a crystalloid-fluid challenge of 20 to 30 ml per kilogram of body weight over a 30-minute period) or a blood lactate concentration of 4 mmol per liter or more. The criteria for exclusion from the study were an age of less than 18 years, pregnancy, or the presence of an acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhythmias (as a primary diagnosis), contraindication to central venous catheterization, active gastrointestinal hemorrhage, seizure, drug overdose, burn injury, trauma, a requirement for immediate surgery, uncured cancer (during chemotherapy), immunosuppression (because of organ transplantation or systemic disease), do-not-resuscitate status, or advanced directives restricting implementation of the protocol.

The clinicians who assessed the patients at this stage were unaware of the patients’ treatment assignments. After written informed consent was obtained (in compliance with the Helsinki Declaration), the patients were randomly assigned either to early high-demand therapy or to standard (control) therapy in computer-generated blocks of two to eight. The study-group assignments were placed in sealed, opaque, randomly assorted envelopes, which were opened by a hospital staff member who was not one of the study investigators.

Treatment

The patients were treated in a nine-bed unit in the emergency department by an emergency physician, two residents, and three nurses. The study was conducted during the routine treatment of other patients in the emergency department. After arterial and central venous catheterization, patients in the standard-therapy group were treated at the clinicians’ discretion according to a protocol for hemodynamic support (Fig. 1), with critical-care consultation, and were admitted for inpatient care as soon as possible. Blood, urine, and other relevant specimens for culture were obtained in the emergency department before the administration of antibiotics. Antibiotics were given at the discretion of the treating clinicians. Antimicrobial therapy was deemed adequate if the in vitro sensitivities of the identified microorganisms matched the particular antibiotic ordered in the emergency department.

The patients assigned to early goal-directed therapy received a central venous catheter capable of measuring central venous oxygen saturation (Edwards Lifesciences, Irvine, Calif.); it was connected to a computerized spectrophotometer for continuous monitoring. Patients were treated in the emergency department according to a protocol for early goal-directed therapy (Fig. 2) for at least six hours and were transferred to the first available inpatient beds. Monitoring of central venous oxygen saturation was then discontinued. Critical-care clinicians (intensivists, fellows, and residents providing 24-hour in-house coverage) assumed the care of all the patients; these physicians were unaware of the patients’ study-group assignments. The study investigators did not influence patient care in the intensive care unit.

The protocol was as follows. A 500-ml bolus of crystalloid was given every 30 minutes to achieve a central venous pressure of 8 to 12 mm Hg. If the mean arterial pressure was less than 65 mm Hg, vasopressors were given to maintain a mean arterial pressure of at least 65 mm Hg. If the mean arterial pressure was greater than 90 mm Hg, vasodilators were given until it was 90 mm Hg or below. If the central venous oxygen saturation was less than 70 percent or did not be achieved received mechanical ventilation and sedatives.

Outcome Measures

The patients’ temperature, heart rate, urine output, blood pressure, and central venous pressure were measured continuously for the first 6 hours of treatment and assessed every 12 hours for 72 hours. Arterial and venous blood gas values (including central venous oxygen saturation measured by in vitro co-oximetry; Nova Biomedical, Waltham, Mass.), lactate concentrations, and coagulation-related variables and clinical variables required for determination of the Acute Physiology and Chronic Health Evaluation (APACHE II) score (on a scale from 0 to 71, with higher scores indicating more severe organ dysfunction), the Simplified Acute Physiology Score II (SAPS II, on a scale from 0 to 174, with higher scores indicating more severe organ dysfunction), and the Multiple Organ Dysfunction Score (MODS, on a scale from 0 to 24, with higher scores indicating more severe organ dysfunction) were obtained at base line (0 hours) and at 3, 6, 12, 24, 36, 48, 60, and 72 hours. The results of laboratory tests required only for purposes of the study were made known only to the study investigators. Patients were followed for 60 days or until death. The consumption of health care resources (indicated by the duration of vasopressor therapy and mechanical ventilation and the length of the hospital stay) was also examined.

Statistical Analysis

In-hospital mortality was the primary efficacy end point. Secondary end points were the resuscitation end points, organ-dysfunction scores, coagulation-related variables, administered treatments, and the consumption of health care resources. Assuming a rate of refusal or exclusion of 10 percent, a two-sided type I error rate of 5 percent, and a power of 80 percent, we calculated that a sample size of 260 patients was required to permit the detection of a 15 percent reduction in in-hospital mortality. Kaplan–Meier estimates of mortality, along with risk ratios and 95 percent confidence intervals, were used to describe the relative risk of death. Differences between the two groups at base line were tested with the use of Student’s t-test, the chi-square test, or Wilcoxon’s rank-sum test. Incremental analyses of the area under the curve were performed to quantify differences during the interval from base line to six hours after the start of treatment. For the data at six hours, analysis of covariance was used with the base-line values as the covariates. Mixed models were used to assess the effect of treatment on prespecified secondary variables during the interval from 7 to 72 hours after the start of treatment. An independent, 12-member external safety, efficacy, and data monitoring committee reviewed interim analyses of the data after one third and two thirds of the patients had been enrolled and at both times recommended that the trial be continued. To adjust for the two interim analyses, the alpha spending function of DeMets and Lan was used to determine that a P value of 0.04 or less would be considered to indicate statistical significance.

RESULTS

Base-Line Characteristics

We evaluated 288 patients; 87 percent were excluded or did not consent to participate. The 263 patients enrolled were randomly assigned to undergo either standard therapy or early goal-directed therapy; 236 patients completed the initial six-hour study period.
All 263 were included in the intention-to-treat analyses. The patients assigned to standard therapy stayed a significantly shorter time in the emergency department than those assigned to early goal-directed therapy (mean [±SD], 6.3±3.2 vs. 8.0±2.1 hours; \( P<0.001 \)). There was no significant difference between the groups in any of the base-line characteristics, including the adequacy and duration of antibiotic therapy (Table 1). Vital signs, resuscitation end points, organ-dysfunction scores, and coagulation-related variables were also similar in the two study groups at base line (Table 2).

Twenty-seven patients did not complete the initial six-hour study period (14 assigned to standard therapy and 13 assigned to early goal-directed therapy), for the following reasons: discontinuation of aggressive medical treatment (in 5 patients in each group), discontinuation of aggressive surgical treatment (in 2 patients in each group), a need for immediate surgery (in 4 patients assigned to standard therapy and in 3 assigned to early goal-directed therapy), a need for interventional urologic, cardiologic, or angiographic procedures (in 2 patients in each group), and refusal to continue participation (in 1 patient in each group) (\( P=0.99 \) for all comparisons). There were no significant differences between the patients who completed

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Figure 2. Protocol for Early Goal-Directed Therapy.
CVP denotes central venous pressure, MAP mean arterial pressure, and ScvO\(_2\) central venous oxygen saturation.
The New England Journal of Medicine

TABLE 1. Base-Line Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>STANDARD THERAPY (N=133)</th>
<th>EARLY GOAL-DIRECTED THERAPY (N=130)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
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<td>67.1±17.4</td>
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<tr>
<td>Sex (%)</td>
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<td>Female</td>
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<td>Male</td>
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<td>Time from arrival at emergency department to enrollment</td>
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<td>Mean (hr)</td>
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<tr>
<td>Median (min)</td>
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<td>59.0</td>
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<tr>
<td>Entry criteria</td>
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<tr>
<td>Temperature (°C)</td>
<td>36.6±2.3</td>
<td>35.9±3.2</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>114±27</td>
<td>117±31</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>109±34</td>
<td>106±36</td>
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<td>Respiratory rate (breaths/min)</td>
<td>30.2±10.6</td>
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<td>Partial pressure of carbon dioxide (mm Hg)</td>
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<td>White-cell count (per mm³)</td>
<td>14,200±9,600</td>
<td>13,600±8,300</td>
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<td>Lactate (mmol/liter)</td>
<td>6.9±4.5</td>
<td>7.7±4.7</td>
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<td>Base-line laboratory values</td>
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<td>Anion gap (mmol/liter)</td>
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<td>21.7±7.6</td>
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<td>Creatinine (mg/dl)</td>
<td>2.6±2.0</td>
<td>2.6±2.0</td>
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<td>Blood urea nitrogen (mg/dl)</td>
<td>45.4±33.0</td>
<td>47.1±31.3</td>
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<td>Total bilirubin (mg/dl)</td>
<td>1.9±3.0</td>
<td>1.3±1.7</td>
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<tr>
<td>y-Glutamyltransferase (U/liter)</td>
<td>123±130</td>
<td>117±159</td>
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<td>Albumin (g/dl)</td>
<td>2.8±0.7</td>
<td>2.8±0.7</td>
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<tr>
<td>Chronic coexisting conditions (%)†</td>
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<tr>
<td>Alcohol use</td>
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<td>38.5</td>
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<tr>
<td>Congestive heart failure</td>
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<td>Coronary artery disease</td>
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<td>26.5</td>
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<td>Chronic obstructive pulmonary disease or emphysema</td>
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<td>Diabetes</td>
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<td>30.8</td>
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<td>Human immunodeficiency virus infection</td>
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<td>Hypertension</td>
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<td>68.4</td>
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<td>Liver disease</td>
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<td>23.1</td>
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<td>History of cancer</td>
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<td>Neurologic disease</td>
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<td>Renal insufficiency</td>
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<td>Smoking</td>
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<td>Diagnosis (%)†</td>
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<td>Medical condition</td>
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<td>90.6</td>
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<td>Pneumonia</td>
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<td>Urosepsis</td>
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<td>Peritonitis</td>
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<td>Surgical condition</td>
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<td>Intraabdominal process</td>
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<td>Abscess of the arms or legs</td>
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<tr>
<td>Types and features of sepsis (%)</td>
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<td></td>
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<tr>
<td>Severe sepsis</td>
<td>48.7</td>
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<td>Septic shock</td>
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<td>Sepsis syndrome</td>
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<td>Culture positive</td>
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<td>Culture negative</td>
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<tr>
<td>Blood culture positive</td>
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<tr>
<td>Antibiotic therapy</td>
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<td>Antibiotics given in the first 6 hr (%)</td>
<td>92.4</td>
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<tr>
<td>Antibiotics adequate (%)</td>
<td>94.3</td>
<td>96.7</td>
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<tr>
<td>Duration (days)</td>
<td>11.3±15.8</td>
<td>11.7±16.2</td>
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*Plus–minus values are means ±SD. There were no significant differences between groups in any of the variables. To convert the values for creatinine to micromoles per liter, multiply by 88.4; to convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357; and to convert the values for total bilirubin to micromoles per liter, multiply by 17.1.

†Values sum to more than 100% because patients could have more than one condition.
### Table 2. Vital Signs, Resuscitation End Points, Organ-Dysfunction Scores, and Coagulation Variables.*

<table>
<thead>
<tr>
<th>VARIABLE AND TREATMENT GROUP</th>
<th>BASE LINE (0 hr)</th>
<th>HOURS AFTER START OF THERAPY</th>
<th>VARIABLE AND TREATMENT GROUP</th>
<th>BASE LINE (0 hr)</th>
<th>HOURS AFTER START OF THERAPY</th>
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<td></td>
<td>0</td>
<td>0–6†</td>
<td>7–72‡</td>
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<td>0–6†</td>
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<tr>
<td>P value</td>
<td>0.45</td>
<td>0.12</td>
<td>0.25</td>
<td>0.04</td>
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<tr>
<td>Central venous pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>6.1±7.7</td>
<td>11.8±6.8</td>
<td>10.5±6.8</td>
<td>11.6±6.1</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>5.3±9.3</td>
<td>13.8±4.4</td>
<td>11.7±5.1</td>
<td>11.9±5.6</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.57</td>
<td>0.007</td>
<td>0.22</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>76±24</td>
<td>81±18</td>
<td>81±16</td>
<td>80±15</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>74±27</td>
<td>95±19</td>
<td>88±16</td>
<td>87±15</td>
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<tr>
<td>P value</td>
<td>0.60</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>Central venous oxygen saturation (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>49.2±13.3</td>
<td>66.0±15.5</td>
<td>65.4±14.2</td>
<td>65.3±11.4</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>48.6±11.2</td>
<td>77.3±10.0</td>
<td>71.6±10.2</td>
<td>70.4±10.7</td>
<td></td>
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<tr>
<td>P value</td>
<td>0.49</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Lactate (mmp/liter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>6.9±4.5</td>
<td>4.9±4.7</td>
<td>5.9±4.2</td>
<td>3.9±4.4</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>7.7±4.7</td>
<td>4.3±4.2</td>
<td>5.5±4.2</td>
<td>3.0±4.4</td>
<td></td>
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<tr>
<td>P value</td>
<td>0.17</td>
<td>0.01</td>
<td>0.62</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Base deficit (mmp/liter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>8.9±7.5</td>
<td>8.0±6.4</td>
<td>8.6±6.0</td>
<td>5.1±6.7</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>8.9±8.1</td>
<td>4.7±5.8</td>
<td>6.7±5.6</td>
<td>2.0±6.6</td>
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</tr>
<tr>
<td>P value</td>
<td>0.81</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td>&lt;0.001</td>
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<tr>
<td>Arterial pH</td>
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<tr>
<td>Standard therapy</td>
<td>7.32±0.19</td>
<td>7.31±0.15</td>
<td>7.31±0.12</td>
<td>7.36±0.12</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>7.31±0.17</td>
<td>7.35±0.11</td>
<td>7.33±0.13</td>
<td>7.40±0.12</td>
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</tr>
<tr>
<td>P value</td>
<td>0.40</td>
<td>&lt;0.001</td>
<td>0.26</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>20.4±7.4</td>
<td>17.6±6.2</td>
<td>—</td>
<td>15.9±6.4</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>21.4±6.9</td>
<td>16.0±6.9</td>
<td>—</td>
<td>13.0±6.3</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.27</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>SAPS II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>48.8±11.1</td>
<td>45.5±12.3</td>
<td>—</td>
<td>42.6±11.5</td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>51.2±11.1</td>
<td>42.1±13.2</td>
<td>—</td>
<td>36.9±11.3</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.08</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. EGDT denotes early goal-directed therapy; APACHE II Acute Physiology and Chronic Health Evaluation, SAPS II Simplified Acute Physiology Score II, and MODS Multiple Organ Dysfunction Score.
†For the period from base line (0 hours) to 6 hours, the area under the curve was calculated, except for noncontinuous variables (as indicated by dashes).
‡For the period from 7 to 72 hours, the adjusted mean value was obtained from a mixed model.

The initial six-hour study period and those who did not in any of the base-line characteristics or base-line vital signs, resuscitation end points, organ-dysfunction scores, or coagulation-related variables (data not shown).

**Vital Signs and Resuscitation End Points**

During the initial six hours after the start of therapy, there was no significant difference between the two study groups in the mean heart rate (P = 0.25) or central venous pressure (P = 0.22) (Table 2). During this period, the mean arterial pressure was significantly lower in the group assigned to standard therapy than in the group assigned to early goal-directed therapy (P < 0.001), but in both groups the goal of 65 mm Hg or higher was met by all the patients. The goal of 70 percent or higher for central venous oxygen saturation was met by 60.2 percent of the patients in the standard-therapy group, as compared with 94.9 percent of those in the early-therapy group (P < 0.001). The combined hemodynamic goals for central venous pressure, mean arterial pressure, and urine output (with adjustment for patients with end-stage renal failure) were achieved in 86.1 percent of the standard-therapy group, as compared with 99.2 percent of the early-therapy group (P < 0.001). During this period, the patients assigned to standard therapy had a significantly lower central venous oxygen saturation (P < 0.001) and a greater base deficit (P = 0.006) than those assigned to early goal-directed therapy; the two
groups had similar lactate concentrations ($P=0.62$) and similar pH values ($P=0.26$).

During the period from 7 to 72 hours after the start of treatment, the patients assigned to standard therapy had a significantly higher heart rate ($P=0.04$) and a significantly lower mean arterial pressure ($P<0.001$) than the patients assigned to early goal-directed therapy; the two groups had a similar central venous pressure ($P=0.68$). During this period, those assigned to standard therapy also had a significantly lower central venous oxygen saturation than those assigned to early goal-directed therapy ($P<0.001$), as well as a higher lactate concentration ($P=0.02$), a greater base deficit ($P<0.001$), and a lower pH ($P<0.001$).

**Organ Dysfunction and Coagulation Variables**

During the period from 7 to 72 hours, the APACHE II score, SAPS II, and MODS were significantly higher in the patients assigned to standard therapy than in the patients assigned to early goal-directed therapy ($P<0.001$ for all comparisons) (Table 2). During this period, the prothrombin time was significantly greater in the patients assigned to standard therapy than in those assigned to early goal-directed therapy ($P=0.001$), as was the concentration of fibrin-split products ($P<0.001$) and the concentration of D-dimer ($P=0.006$). The two groups had a similar partial thromboplastin time ($P=0.06$), fibrinogen concentration ($P=0.21$), and platelet count ($P=0.51$) (Table 2).

**Mortality**

In-hospital mortality rates were significantly higher in the standard-therapy group than in the early-therapy group ($P=0.009$), as was the mortality at 28 days ($P=0.01$) and 60 days ($P=0.03$) (Table 3). The difference between the groups in mortality at 60 days primarily reflected the difference in in-hospital mortality. Similar results were obtained after data from the 27 patients who did not complete the initial six-hour study period were excluded from the analysis (data not shown). The rate of in-hospital death due to sudden cardiovascular collapse was significantly higher in the standard-therapy group than in the early-therapy group ($P=0.02$); the rate of death due to multiorgan failure was similar in the two groups ($P=0.27$).

**Administered Treatments**

During the initial six hours, the patients assigned to early goal-directed therapy received significantly more fluid than those assigned to standard therapy ($P<0.001$) and more frequently received red-cell transfusion ($P<0.001$) and inotropic support ($P<0.001$), whereas similar proportions of patients in the two groups required vasopressors ($P=0.62$) and mechanical ventilation ($P=0.90$) (Table 4). During the period from 7 to 72 hours, however, the patients assigned to standard therapy received significantly more fluid than those assigned to early goal-directed therapy ($P=0.01$) and more often received red-cell transfusion ($P<0.001$) and vasopressors ($P=0.03$) and underwent mechanical ventilation ($P<0.001$) and pulmonary-artery catheterization ($P=0.04$); the rate of use of inotropic agents was similar in the two groups ($P=0.14$) (Table 4). During the overall period from base line to 72 hours after the start of treatment, there was no significant difference between the two groups in the total volume of fluid administered ($P=0.73$) or the rate of use of inotropic agents ($P=0.15$), although a greater proportion of the patients assigned to standard therapy than of those assigned to early goal-direct-

---

**Table 3. Kaplan–Meier Estimates of Mortality and Causes of In-Hospital Death.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>STANDARD THERAPY (N=133)</th>
<th>EARLY GOAL-DIRECTED THERAPY (N=130)</th>
<th>RELATIVE RISK (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality†</td>
<td>59 (46.5)</td>
<td>38 (30.5)</td>
<td>0.58 (0.38–0.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>Patients with severe sepsis</td>
<td>19 (30.0)</td>
<td>9 (14.9)</td>
<td>0.46 (0.21–1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Patients with septic shock</td>
<td>40 (56.8)</td>
<td>29 (42.3)</td>
<td>0.60 (0.36–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with sepsis syndrome</td>
<td>44 (45.4)</td>
<td>35 (35.1)</td>
<td>0.66 (0.42–1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>28-Day mortality†</td>
<td>61 (49.2)</td>
<td>40 (33.3)</td>
<td>0.58 (0.39–0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>60-Day mortality†</td>
<td>70 (56.9)</td>
<td>50 (44.3)</td>
<td>0.67 (0.46–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Causes of in-hospital death‡</td>
<td>25/119 (21.0)</td>
<td>12/117 (10.3)</td>
<td>—</td>
<td>0.02</td>
</tr>
<tr>
<td>Sudden cardiovascular collapse</td>
<td>26/119 (21.8)</td>
<td>19/117 (16.2)</td>
<td>—</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.
†Percentages were calculated by the Kaplan–Meier product-limit method.
‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.
ed therapy received vasopressors (P=0.02) and mechanical ventilation (P=0.02) and underwent pulmonary-artery catheterization (P=0.01), and a smaller proportion required red-cell transfusion (P<0.001). Though similar between the groups at base line (P=0.91), the mean hematocrit during this 72-hour period was significantly lower in the standard-therapy group than in the early-therapy group (P<0.001). Despite the transfusion of red cells, it was significantly lower than the value obtained at base line in each group (P<0.001 for both comparisons) (Table 2).

### Consumption of Health Care Resources

There were no significant differences between the two groups in the mean duration of vasopressor therapy (2.4±4.2 vs. 1.9±3.1 days, P=0.49), the mean duration of mechanical ventilation (9.0±13.1 vs. 9.0±11.4 days, P=0.38), or the mean length of stay in the hospital (13.0±13.7 vs. 13.2±13.8 days, P=0.54). However, of the patients who survived to hospital discharge, those assigned to standard therapy stayed a significantly longer time in the hospital than those assigned to early goal-directed therapy (18.4±15.0 vs. 14.6±14.5 days, P=0.04).

### DISCUSSION

Severe sepsis and septic shock are common and are associated with substantial mortality and substantial consumption of health care resources. There are an estimated 751,000 cases (3.0 cases per 1000 population) of sepsis or septic shock in the United States each year, and they are responsible for as many deaths each year as acute myocardial infarction (215,000, or 9.3 percent of all deaths).29 In elderly persons, the incidence of sepsis or septic shock and the related mortality rates are substantially higher than those in younger persons. The projected growth of the elderly population in the United States will contribute to an increase in incidence of 1.5 percent per year, yielding an estimated 934,000 and 1,110,000 cases by the years 2010 and 2020, respectively.29 The present annual cost of this disease is estimated to be $16.7 billion.29

The transition from the systemic inflammatory response syndrome to severe sepsis and septic shock involves a myriad of pathogenic changes, including circulatory abnormalities that result in global tissue hypoxia.1,2 These pathogenic changes have been the therapeutic target of previous outcome studies.12 Although this transition occurs over time, both out of the hospital and in the hospital, in outcome studies interventions have usually been initiated after admission to the intensive care unit.12 In studies of goal-directed hemodynamic optimization, in particular, there was no benefit in terms of outcome with respect to normal and supranormal hemodynamic end points, as well as those guided by mixed venous oxygen saturation.9,13 In contrast, even though we enrolled patients with lower central venous oxygen saturation and lower central venous pressure than those studied by Gattinoni et al.9 and with a higher lactate concentration than those studied by Hayes et al.,13 we found significant benefits with respect to outcome when goal-directed therapy was applied at an earlier stage of disease. In patients with septic shock, for example, Hayes et al. observed a higher in-hospital mortality rate with aggressive hemodynamic optimization in the intensive care unit (71 percent) than with control therapy (52 percent), whereas we observed a lower mortality rate in patients with septic shock assigned to early goal-directed therapy (42.3 percent) than in those assigned to standard therapy (56.8 percent).

The benefits of early goal-directed therapy in terms of outcome are multifactorial. The incidence of death due to sudden cardiovascular collapse in the standard-therapy group was approximately double that in the group assigned to early goal-directed therapy, suggesting that an abrupt transition to severe disease is an important cause of early death. The early identification...
of patients with insidious illness (global tissue hypoxia accompanied by stable vital signs) makes possible the early implementation of goal-directed therapy. If sudden cardiovascular collapse can be prevented, the subsequent need for vasopressors, mechanical ventilation, and pulmonary-artery catheterization (and their associated risks) diminishes. In addition to being a stimulus of the systemic inflammatory response syndrome, global tissue hypoxia independently contributes to endothelial activation and disruption of the homeostatic balance among coagulation, vascular permeability, and vascular tone. These are key mechanisms leading to microcirculatory failure, refractory tissue hypoxia, and organ dysfunction. When early therapy is not comprehensive, the progression to severe disease may be well under way at the time of admission to the intensive care unit. Aggressive hemodynamic optimization and other therapy undertaken thereafter may be incompletely effective or even deleterious.

The value of measurements of venous oxygen saturation at the right atrium or superior vena cava (central venous oxygen saturation) instead of at the pulmonary artery (mixed venous oxygen saturation) has been debated, in particular, when saturation values are above 65 percent. In patients in the intensive care unit who have hyperdynamic septic shock, the mixed venous oxygen saturation is rarely below 65 percent. In contrast, our patients were examined during the phase of resuscitation in which the delivery of supplemental oxygen is required (characterized by a decreased mixed venous oxygen saturation and an increased lactate concentration), when the central venous oxygen saturation generally exceeds the mixed venous oxygen saturation. The initial central venous oxygen saturation was less than 50 percent in both study groups. The mixed venous oxygen saturation is estimated to be 5 to 13 percent lower in the pulmonary artery and 15 percent lower in the splanchnic bed.

Though not numerically equivalent, these ranges of values are pathologically equivalent and are associated with high mortality. Among all the patients in the current study in whom the goals with respect to central venous pressure, mean arterial pressure, and urine output during the first six hours were met, 39.8 percent of those assigned to standard therapy were still in this oxygen-dependent phase of resuscitation at six hours, compared with 5.1 percent of those assigned to early goal-directed therapy. The combined 56.5 percent in-hospital mortality of this 39.8 percent of patients, who were at high risk for hemodynamic compromise, is consistent with the results of previous studies in the intensive care unit.

In an open, randomized, partially blinded trial, there are unavoidable interactions during the initial period of the study. As the study progressed, the patients in the standard-therapy group may have received some form of goal-directed therapy, reducing the treatment effect. This reduction may have been offset by the slight but inherent bias resulting from the direct influence of the investigators on the care of the patients in the treatment group. The potential period of bias was 9.9 ± 19.5 percent of the overall hospital stay in the standard-therapy group and 7.2 ± 12.0 percent of that in the group assigned to early goal-directed therapy (P = 0.20). This interval was minimal in comparison with those in previous studies, because the clinicians who assumed responsibility for the remainder of hospitalization were completely blinded to the randomization order.

We conclude that goal-directed therapy provided at the earliest stages of severe sepsis and septic shock, though accounting for only a brief period in comparison with the overall hospital stay, has significant short-term and long-term benefits. These benefits arise from the early identification of patients at high risk for cardiovascular collapse and from early therapeutic intervention to restore a balance between oxygen delivery and oxygen demand. In the future, investigators conducting outcome trials in patients with sepsis should consider the quality and timing of the resuscitation before enrollment as an important outcome variable.

Supported by the Henry Ford Health Systems Fund for Research, a Weithersby Healthcare Resuscitation Fellowship, Edwards Lifesciences (which provided oximetry equipment and catheters), and Nova Biomedical (which provided equipment for laboratory assays).

We are indebted to the nurses, residents, senior staff attending physicians, pharmacists, patient advocates, technicians, and billing and administrative personnel of the Department of Emergency Medicine; to the nurses and technicians of the medical and surgical intensive care units; and to the staff members of the Department of Respiratory Therapy, Department of Pathology, Department of Medical Records, and Department of Admitting and Discharge for their patience and their cooperation in making this study possible.

APPENDIX


REFERENCES


Copyright © 2001 Massachusetts Medical Society.
Vasopressor and inotropic support in septic shock: An evidence-based review

Richard J. Beale, MBBS; Steven M. Hollenberg, MD, FCCM; Jean-Louis Vincent, MD, PhD, FCCM; Joseph E. Parrillo, MD, FCCM

Objective: In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for vasopressor and inotropic support in septic shock that would be of practical use for the bedside clinician, under the auspices of the Surviving Sepsis Campaign, an international effort to increase awareness and to improve outcome in severe sepsis.

Design: The process included a modified Delphi method, a consensus conference, several subsequent smaller meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee.

Methods: The modified Delphi methodology used for grading recommendations built on a 2001 publication sponsored by the International Sepsis Forum. We undertook a systematic review of the literature graded along five levels to create recommendation grades from A to E, with A being the highest grade. Pediatric considerations to contrast adult and pediatric management are in the article by Parker et al. on p. S591.

Conclusion: An arterial catheter should be placed as soon as possible in patients with septic shock. Vasopressors are indicated to maintain mean arterial pressure of <65 mm Hg, both during and following adequate fluid resuscitation. Norepinephrine or dopamine are the vaspressors of choice in the treatment of septic shock. Norepinephrine may be combined with dobutamine when cardiac output is being measured. Epinephrine, phenylephrine, and vasopressin are not recommended as first-line agents in the treatment of septic shock. Vasopressin may be considered for salvage therapy. Low-dose dopamine is not recommended for the purpose of renal protection. Dobutamine is recommended as the agent of choice to increase cardiac output but should not be used for the purpose of increasing cardiac output above physiologic levels. (Crit Care Med 2004; 32[Suppl.]:S455–S465)

S
tshock may be defined as an impairment of the normal relationship between oxygen demand and oxygen supply. As a consequence, there are detrimental alterations in tissue perfusion, resulting in a reduction in the delivery of oxygen and other nutrients to tissue beds and causing cellular and then organ dysfunction. In hypovolemic, cardiogenic, and obstructive forms of shock, the primary defect is a fall in cardiac output, leading to hypoperfusion, hypotension, and anaerobic metabolism. In septic shock, however, there is a complex interaction between pathologic vasodilatation, relative and absolute hypovolemia, direct myocardial depression, and altered blood flow distribution, which occur as a consequence of the inflammatory response to infection. Even after the restoration of circulating volume, maldistribution of a normal or increased cardiac output typically persists as a consequence of microvascular abnormalities. In addition, cellular and organ injury also occur as direct consequences of the inflammatory response in sepsis and as a consequence of hypoperfusion.

Making recommendations about the choice of individual vasopressor agents in septic shock is made difficult by the paucity of controlled trials and by the clinical reality that agents are frequently used in combination. In modern practice, norepinephrine and dopamine are the vaspressors used most frequently, although dopamine has more marked inotropic effects. The relatively small inotropic effect of norepinephrine, and concerns about regional blood flow, mean that it is frequently used in combination with dobutamine. Epinephrine may also be used as an alternative and, again, combines vasopressor and inotropic effects. Phenylephrine, which has virtually only vasopressor actions, is also sometimes used. Dopamine and epinephrine in particular have important metabolic and endocrine effects that may complicate their use and be potentially detrimental. This review of the literature enables recommendations to be established and graded according to the strength of the available evidence.

End Points of Resuscitation and Monitoring in Septic Shock

The complexity of the pathophysiology and the limitations of routinely used hemodynamic monitoring techniques have made defining the end points of hemodynamic management of sepsis difficult. Nevertheless, the available literature does provide important guidance as to a basic approach to the use of vasopressors and inotropes in sepsis, although this will undoubtedly change as our understanding improves further. Septic shock is characterized by hypotension, which in adults generally refers to a mean arterial pressure below 65–70 mm Hg, and altered tissue perfusion. Poor tissue perfusion may be manifest clinically by reduced capillary refill, oliguria, and altered sensorium. Some caution is necessary in interpreting these signs, however, because signs of peripheral vasoconstriction may be absent in some patients who may seem...
deceptively well in the early phases of severe sepsis.

Other global markers of tissue perfusion that are used clinically include the acid-base status (base excess and blood lactate) and the mixed venous or central venous oxygen saturations. The adequacy of regional perfusion is usually assessed by evaluating indices of specific organ function, although none of these alone has been validated as a reliable indicator of adequate resuscitation. These include coagulation abnormalities (disseminated intravascular coagulation); altered renal function with increased blood urea nitrogen and creatinine; altered liver parenchymal function with increased serum levels of transaminases, lactate dehydrogenase, and bilirubin; and altered gut perfusion, manifest by ileus and malabsorption. A number of approaches may be employed to monitor the hemodynamic and perfusion status of patients with septic shock. The variables measured provide potential end points for the resuscitation process and information about the progress of the patient in response to treatment.

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

**Intravascular Volume Status.** Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock. Ideally, this should be achieved before vasopressors and inotropes are used, although it is frequently necessary to employ vasopressors early as an emergency measure in patients with severe shock. In fluid-responsive hearts, in which the Frank-Starling mechanism is intact, fluid administration increases preload and therefore stroke volume and cardiac output. Depending on the degree of vasodilatation, there may also be an increase in blood pressure. There are a number of approaches to monitoring intravascular filling that are employed currently. These include the use of traditional cardiac filling pressures (central venous pressure and pulmonary artery occlusion pressure), which are limited by errors in routine measurement, the confounding effects of mechanical ventilation, and uncertainties about the compliance of the left ventricle. Alternatives employed with increasing frequency in modern practice include central blood volume measurements using the transpulmonary indicator dilution technique and analysis of patterns of dynamic changes in the arterial waveform in response to mechanical ventilation (systolic pressure variation, stroke volume variation) as a predictor of volume responsiveness. This issue is addressed in more detail in the section on fluid resuscitation.

**Cardiac Output.** Cardiac output is frequently measured in patients with septic shock, both as a guide to the adequacy of resuscitation and to allow calculation of oxygen transport variables. It is also useful diagnostically in confirming the typical hyperdynamic picture of septic shock, although this is not always present, especially if the patient is still hypovolemic or has co-existing cardiac disease.

**Mixed Venous Oxygen Saturation and Central Venous Oxygen Saturation.** Mixed venous oxygen saturation (S\textsubscript{V\text{O}}\textsubscript{2}) can be measured in patients with a pulmonary artery catheter in place. S\textsubscript{V\text{O}}\text{2} is dependent on cardiac output, oxygen demand, hemoglobin, and arterial oxygen saturation. The normal S\textsubscript{V\text{O}}\text{2} value is 70–75% in critically ill patients but can be elevated in septic patients due to maldistribution of blood flow. Frequently, however, it may be low or even normal, and the value must be interpreted carefully in the context of the wider hemodynamic picture. Nevertheless, it is useful to measure S\textsubscript{V\text{O}}\text{2} because if cardiac output becomes inadequate, S\textsubscript{V\text{O}}\text{2} decreases. Moreover, if S\textsubscript{V\text{O}}\text{2} remains low even though other end points of resuscitation have been corrected, this suggests increased oxygen extraction and therefore potentially incomplete resuscitation. Ronco et al. (1) studied terminally ill patients in whom treatment was withdrawn; S\textsubscript{V\text{O}}\text{2} decreased dramatically before oxygen consumption started to fall, indicating that oxygen extraction capabilities are not necessarily profoundly altered even in patients in the final stage of the disease process. Hence, S\textsubscript{V\text{O}}\text{2}, if normal or high, does not necessarily indicate adequate resuscitation, whereas a low S\textsubscript{V\text{O}}\text{2} should prompt rapid intervention to increase oxygen delivery to the tissues. The advent of continuous S\textsubscript{v\text{O}}\text{2} monitoring using fiberoptic pulmonary artery catheters has greatly increased the value of this variable as a real-time monitor, so long as the systems are recalibrated appropriately.

Central venous oxygen saturation is becoming increasingly popular as an alternative to S\textsubscript{v\text{O}}\text{2} because the measurement provides a clinically useful approximation to S\textsubscript{V\text{O}}\text{2} and can be obtained from a central venous catheter without the need for pulmonary artery catheterization. In a recent study in patients with severe sepsis presenting to the emergency department, Rivers et al. (2) randomized 263 patients with severe sepsis or septic shock to receive either standard resuscitation or early goal-directed therapy for the first 6 hrs after admission. Central venous oxygen saturation was used as an intrinsic part of the early goal-directed therapy protocol, targeting a value of 70%. The mortality in the early goal-directed therapy group was 30.5% compared with 46.5% in the standard care group (p = .009).

**Blood Lactate Levels.** Hyperlactatemia (>2 mEq/L) is typically present in patients with septic shock and may be secondary to anaerobic metabolism due to hypoperfusion. However, the interpretation of blood lactate levels in septic patients is not always straightforward. Experimental studies have not always been able to show a reduction in high-energy phosphate levels in animal models of sepsis (3). The differences between studies may be related to the severity of the septic model, with more severe sepsis being associated with depletion of adenosine triphosphate, despite maintenance of systemic oxygen delivery and tissue oxygenation. Also, measurements of tissue PO\textsubscript{2} in septic patients have not demonstrated tissue hypoxia in the presence of lactic acidosis (4). However, if inhomoogeneity in blood flow distribution is a real phenomenon, it is likely that cell hypoperfusion also exists with ischemia/reperfusion. A number of studies have suggested that elevated lactate levels may result from cellular metabolic failure rather than from global hypoperfusion in sepsis. Some organs may produce more lactate than others, in particular, the lungs in acute lung injury or acute respiratory distress syndrome (5, 6). Elevated lactate levels can also result from decreased clearance by the liver, and patients with septic shock may have a more severe liver injury than conventional liver function.
tests may suggest (7). Nonetheless, the prognostic value of raised blood lactate levels has been well established in septic shock patients (8), particularly if the high levels persist (9, 10). It is also of interest to note that blood lactate levels are of greater prognostic value than oxygen-derived variables (11).

**Gut Tonometry.** The measurement of regional perfusion as a means of detecting inadequate tissue oxygenation has focused on the splanchnic circulation, as the hepatosplanchnic circulation is particularly sensitive to changes in blood flow and oxygenation for several reasons. First, under normal conditions, the gut mucosa receives the majority of total intestinal blood flow. However, in sepsis, there is a redistribution of flow away from the mucosa toward the serosa and muscularis (12), resulting in mucosal hypoxia. Any further reduction in splanchnic flow has a correspondingly greater effect on gut hypoxia. Second, the gut may have a higher critical oxygen delivery threshold than other organs (13). Third, the tip of the villus is supplied by a central arteriole and drained by venules passing away from the tip. A countercurrent exchange mechanism operates in the villus, whereby a base-to-tip PO2 gradient exists, making the tip particularly sensitive to changes in regional flow and oxygenation. Fourth, constriction of the villus arteriole occurs during sepsis (14), rendering the villus even more sensitive to reductions in blood flow. Fifth, the capillary density at the villus tip is reduced during sepsis (15), impeding the transfer of oxygen. Finally, gut ischemia increases intestinal permeability, which may increase translocation of bacteria or cytokines. This mechanism is frequently suggested as a possible trigger or "motor" of the sepsis response and multiple organ failure, and recent work has suggested that the lymphatic drainage of the gut may be an important route by which inflammatory mediators released by injured gut reach the systemic circulation (16).

Gastric tonometry has been proposed as a method to assess regional perfusion in the gut by measuring intragastric ΔPCO2. Originally, the PCO2 value was used, together with the arterial bicarbonate, to calculate gastric intramucosal pH (pHi), but arterial bicarbonate represents global conditions, is nonspecific, and is measured only intermittently. Consequently, pHi measurement has become obsolete, and the change in the PCO2 signal itself is considered more representative of conditions in the gut. Gastric mucosal PCO2 is influenced directly by systemic arterial PCO2, and some clinicians have proposed using the gastric−arterial PCO2 difference as the primary tonometric variable of interest (17). Even this measure is not a simple measure of gastric mucosal hypoxia because either anaerobic metabolism, decreased gastric blood flow in the absence of anaerobic metabolism, or a combination of the two can increase gastric mucosal PCO2 (17). An early trial suggested that tonometry-derived variables might be useful in guiding therapy (18), but these findings were not confirmed recently (19), and many investigators have emphasized the limited sensitivity and specificity of these measurements. Various vasoactive agents have been shown to have divergent effects on gastric PCO2 and pHi that are neither consistent nor predictable (20). Perhaps most problematic, tonometric PCO2 measurement is confounded by enteral feeding, which is often started relatively early in modern intensive care practice. Taken together, these limitations make gastric tonometry of interest largely as a research tool rather than as a useful clinical monitor for routine use.

**Sublingual Capnometry.** Sublingual capnometry is a new technique beginning the process of clinical evaluation. It is based on the principle that reduced perfusion leading to an increase in tissue PCO2 occurs in areas of the gastrointestinal tract other than just the stomach, including the readily accessible sublingual mucosa (21). The device itself uses a PCO2-sensitive optode placed under the tongue to detect changes in the local CO2 tension. Recently, in an observational study of 54 unstable critically ill patients, of whom 21 had either severe sepsis or septic shock and 27 died, Marik and Bankov (22) demonstrated that the initial sublingual PCO2−PCO2 gap was the best predictor of outcome (p = .0004), followed by the initial sublingual PCO2 reading itself (p = .004). The area under the receiver operating characteristic curve for the sublingual PCO2−PCO2 gap was 0.75, and the best threshold for discriminating between survivors and nonsurvivors was a gap of <25 mm Hg. Data were obtained at admission (after insertion of a pulmonary artery catheter), at 4 hrs, and at 8 hrs, and there were no differences between either blood lactate or SVO2 between survivors and nonsurvivors during this period. Clearly, although initial re-

**Rationale:** Adequate fluid resuscitation is a prerequisite for the successful and appropriate use of either vasopressors or inotropes in patients with septic shock, and in general, the end points of fluid resuscitation are the same as those for the use of pharmacologic hemodynamic support. Sometimes, fluid resuscitation alone may suffice. The choice of fluid remains a matter of debate, but patients with septic shock can be successfully resuscitated with either crystalloid or colloid, or a combination of both. It is also
necessary to maintain a minimum hemoglobin concentration to ensure adequate blood oxygen carriage and oxygen dispatch to the tissues. These aspects of the management of the patient with septic shock are discussed in detail elsewhere.

Four agents with vasopressor activity are commonly used in the treatment of patients with septic shock. These are dopamine, norepinephrine, epinephrine, and phenylephrine. More recently, there has been an increasing trend to use low-dose hydrocortisone as an adjunct to vasopressor therapy, especially in patients who exhibit a poor response to the primary vasopressor agent. The other recent change in practice is the increasing interest in the possible role of vasopressin as an alternative vasopressor agent in patients with septic shock.

Although all the vasopressor agents mentioned generally result in an increase in blood pressure, concerns remain in clinical practice about their potentially inappropriate or detrimental use. The most obvious of these relates to the inadequately volume-resuscitated patient, in whom vasopressor use may worsen already inadequate organ perfusion. Even when volume resuscitation has been performed, discussion continues as to whether vasopressor agents may raise blood pressure at the expense of the perfusion of vulnerable organs, most particularly, the kidneys and the gut. A further concern relates to the possibility that overenthusiastic use, especially if an unnecessarily high blood pressure is targeted, may increase left ventricular work to an unsustainable degree and so worsen cardiac output and end-organ perfusion. Although this is much more likely to occur in patients with cardiogenic shock, cardiac depression is a feature of severe sepsis, and a number of patients presenting with septic shock may already have significant underlying cardiac disease.

The precise level of mean arterial pressure to aim for is not certain and is likely to vary between individual patients. In animal studies, a mean arterial pressure of $\geq 60$ mm Hg is associated with compromised autoregulation in the coronary, renal, and central nervous system vascular beds, and blood flow may be reduced. Some patients, however, especially the elderly, may require higher blood pressures to maintain adequate organ perfusion. To address this question specifically, LeDoux et al. (24) studied ten patients with septic shock who had been fluid resuscitated to a pulmonary artery occlusion pressure of $\geq 12$ mm Hg and were requiring vasopressors to maintain mean arterial pressures of $\geq 60$ mm Hg. Norepinephrine infusions were used to raise the blood pressure incrementally from 65 to 75 mm Hg and then to 85 mm Hg, with detailed global and regional hemodynamic and metabolic measurements being taken at each stage. Cardiac index increased from $4.7 \pm 0.5$ L.min$^{-1}$m$^{-2}$ to $5.5 \pm 0.5$ L.min$^{-1}$m$^{-2}$ ($p = .07$), and left ventricular stroke work index increased accordingly ($p = .01$). There were no significant changes in urine output, blood lactate, tonometric PCO$_2$ gap, skin capillary blood flow, or red blood cell velocity and, thus, no suggestion of either harm or benefit from the maneuver. Although fascinating, the wider applicability of these results is limited by the small number of patients and the short-term nature of the norepinephrine infusion. Nevertheless, it further reinforces the need to assess perfusion in patients on an individualized basis by a combination of the methods outlined previously.

Question: Is the combination of norepinephrine and dobutamine superior to dopamine in the treatment of septic shock?

Uncertain; Grade D

Recommendations: Either norepinephrine or dopamine (through a central catheter as soon as possible) is the first-choice vasopressor agent to correct hypotension in septic shock.

Grade D

Rationale: The effects of dopamine on cellular oxygen supply in the gut remain incompletely defined, and the effects of norepinephrine alone on splanchnic circulation may be difficult to predict. The combination of norepinephrine and dobutamine seems to be more predictable and more appropriate to the goals of septic shock therapy than norepinephrine alone. Dopamine is the natural precursor of norepinephrine and epinephrine, and it possesses several dose-dependent pharmacologic effects. Generally, at doses of $< 5 \mu$g·kg$^{-1}$·min$^{-1}$, dopamine stimulates dopaminergic DAI receptors in the renal, mesenteric, and coronary beds, resulting in vasodilation. Infusion of low doses of dopamine causes an increase in glomerular filtration rate, renal blood flow, and sodium excretion. At doses of $5-10 \mu$g·kg$^{-1}$·min$^{-1}$, $\beta$-adrenergic effects become predominant, resulting in an increase in cardiac contractility and heart rate. Dopamine also causes the release of norepinephrine from nerve terminals, contributing to its cardiac effects. At higher doses ($> 10 \mu$g·kg$^{-1}$·min$^{-1}$), $\alpha$-adrenergic effects predominate, leading to arterial vasoconstriction and an increase in blood pressure.

The systemic hemodynamic effects of dopamine in patients with septic shock are well established. Dopamine increases mean arterial pressure primarily by increasing cardiac index with minimal effects on systemic vascular resistance. The increase in cardiac index is due to an increase in stroke volume and, to a lesser extent, to increased heart rate (25–36). Patients receiving dopamine at rates of $> 20 \mu$g·kg$^{-1}$·min$^{-1}$ show increases in right heart pressures and in heart rate, and therefore, doses should not usually exceed $20 \mu$g·kg$^{-1}$·min$^{-1}$, at least not without adequate hemodynamic monitoring.

Splanchnic perfusion and the integrity of the gut mucosa may play an important role in the pathogenesis of multiple organ failure. The effect of dopamine on gastric tonometric and splanchnic variables has been evaluated with mixed results. At low doses, dopamine increases splanchnic oxygen delivery by 65% but splanchnic oxygen consumption by only 16%. Despite this, dopamine may decrease pH, perhaps by a direct effect on the gastric mucosal cell. The effects of dopamine on cellular oxygen supply in the gut remain incompletely defined. Ruokonen et al. (33) and Meier-Hellmann et al. (36) have documented that dopamine increases splanchnic blood flow. Niviere et al. (37) reported that dopamine is associated with a reduction in gastric mucosal blood flow; there were changes in gastric PCO$_2$, gastric-arterial PCO$_2$, difference, and calculated pH. They (37) concluded that they could not determine whether the reduction in gastric mucosal blood flow was critical because there were no changes in the acid-base variables of the patients. More recently, Jakob et al. (38) demonstrated that dopamine increased splanchnic blood flow in septic patients but that this did not correlate with changes in monoethylglycinexylidide formation (the cytochrome P450-dependent conversion of lidocaine to monoethylglycinexylidide in the liver). The same group also demonstrated that the dopamine infusion resulted in a decrease in splanchnic oxygen consumption, despite the increase in blood flow. They then performed a post hoc compar-
ison with septic patients receiving dobutamine infusions, in whom splanchnic blood flow also increased, but without any change in splanchnic oxygen consumption, leading the authors to conclude that dopamine resulted in an impairment of hepatosplanchnic metabolism that may be detrimental (39).

In contrast, De Backer et al. (40) compared the effects of dopamine, norepinephrine, and epinephrine on measures of splanchnic perfusion in ten patients with a moderate degree of septic shock. The gradient between mixed-venous and hepatic-venous oxygen saturations was lower with dopamine, although there were no other significant differences, leading to the authors to conclude that overall effects of all three drugs were similar in the small study group, although, if anything, dopamine had the most beneficial profile of effects on splanchnic circulation.

Recent studies have shown that dopamine may alter the inflammatory response in septic shock by decreasing the release of a number of hormones, including prolactin (41). Other potentially harmful endocrine effects have been demonstrated in trauma patients (42–45). In a study of 12 stable mechanically ventilated patients, Dive et al. (46) used intestinal manometry to demonstrate that dopamine infused at 4 μg·kg⁻¹·min⁻¹ achieved the target blood pressure. Only if this regime failed was norepinephrine added (33, 47–53). In older studies, norepinephrine was added after the use of metaraminol, methoxamine, or isoproterenol (25, 54). A few studies have used norepinephrine as the only adrenergic agent to correct sepsis-induced hemodynamic abnormalities (32, 33, 35, 56). In most studies, the mean dose of norepinephrine was 0.2–1.3 μg·kg⁻¹·min⁻¹, although the initial dose can be as low as 0.01 μg·kg⁻¹·min⁻¹ (48), and the highest reported norepinephrine dose was up to 5.0 μg·kg⁻¹·min⁻¹ (57). Thus, large doses of the drug can be required in some patients with septic shock, which may be due to adrenergic receptor “down-regulation” in sepsis (58).

Norepinephrine therapy usually causes a statistically and clinically significant increase in mean arterial pressure due to the vasoconstrictive effects, with little change in heart rate or cardiac output, leading to increased systemic vascular resistance. Several studies have demonstrated increases in cardiac output ranging from 10% to 20% and increases in stroke volume index of 10% to 15% (25, 35, 50), which may have been due to β-receptor agonist effects or to improved cardiac performance as a result of a better coronary perfusion pressure. Other studies, however, have observed no significant changes in cardiac output or stroke volume index after the use of norepinephrine in the presence of a significant increase in vascular resistance, suggesting that norepinephrine is exerting predominantly agonist effects against β-receptor agonist effects (47–49, 53, 59, 60). Obviously, because cardiac index is either increased or unchanged and mean arterial pressure is consistently increased, left ventricular stroke work index is always statistically increased with norepinephrine. With regard to pulmonary artery occlusion pressure, no clinically significant changes are reported.

Norepinephrine should be used only to restore adequate values of mean arterial blood pressure, which might be regarded as values sufficient to restore urine output (being cognizant of the pre-morbid blood pressure) or toward the lower part of the normal range. Higher values should be avoided during norepinephrine therapy because elevated cardiac afterload may be deleterious, especially in cases of severe underlying cardiac dysfunction. Mean arterial pressure is a better target for the titration of therapy than systemic vascular resistance due to the methodologic problems of the use of systemic vascular resistance as the sole measurement of peripheral resistance.

Norepinephrine seems to be more effective than dopamine at reversing hypotension in septic shock patients. Martin et al. (32) carried out a study with the most striking findings. They prospectively randomized 32 volume-resuscitated patients with hyperdynamic sepsis syndrome to receive either dopamine (2.5–25 μg·kg⁻¹·min⁻¹) or norepinephrine (0.5–5.0 μg·kg⁻¹·min⁻¹) to achieve and maintain normal hemodynamic and oxygen transport variables for at least 6 hrs. If the goals were not achieved with one agent, the other was added. The groups were similar at baseline. Dopamine administration (10–25 μg·kg⁻¹·min⁻¹) was successful in only 31% of patients (5 of 16), whereas norepinephrine (0.5–1.2 μg·kg⁻¹·min⁻¹) resulted in success in 93% of patients (15 of 16; p < .001). Of the 11 patients who did not respond to dopamine, ten responded when norepinephrine was added. In contrast, the one patient who did not respond to norepinephrine failed to respond to dopamine. The survival rate differed between the two groups (59% for norepinephrine vs. 17% for dopamine), although the study was not statistically designed to examine this issue. In a recent larger study from the same group, 97 patients with septic shock were entered into an observational study, in which they were treated in a standardized fashion. After antibiotic treatment, respiratory support, and fluid resuscitation, dopamine (5–15 μg·kg⁻¹·min⁻¹) was used to support the blood pressure, and dobutamine (5–25 μg·kg⁻¹·min⁻¹) was added if the SV.O₂ was <70%. If hypotension, oliguria, or lactic acidosis persisted, patients then received either high-dose dopamine (16–25 μg·kg⁻¹·min⁻¹) or norepinephrine (0.5–5.0 μg·kg⁻¹·min⁻¹), although this choice was left to the discretion of the individual clinician and was not randomized. If the patients remained in shock, epinephrine could then be added. The results were analyzed statistically with the aim of establishing which aspects of therapy were associated with outcome. Four factors were significantly associated with a poor outcome (pneumonia as the cause of septic shock, organ
system failure index of \( \leq 3 \), low urine output at study entry, and admission blood lactate level of \( \geq 4 \) mmol/L. The only factor that was associated with a favorable outcome was the use of norepinephrine as part of the hemodynamic support of the patient, with these 57 patients having a significantly lower hospital mortality (62% vs. 82%; \( p < .001 \); relative risk, 0.68; 95% confidence interval, 0.54 – 0.87) than the 40 patients who received support with high-dose dopamine or epinephrine, or both.

Concern is frequently expressed with regard to the effect of norepinephrine on the kidney. In patients with hypotension and hypovolemia during hemorrhagic shock, for example, norepinephrine and other vasoconstrictor agents may have severe detrimental effects on renal hemodynamics. Despite the improvement in blood pressure, renal blood flow does not increase, and renal vascular resistance continues to rise (61). However, in hyperdynamic septic shock, during which urine flow is believed to decrease mainly as a result of lowered renal glomerular perfusion pressure, the situation is different. In an elegant study in a dog model, Bellomo et al. (62) were able to demonstrate that during endotoxic shock, norepinephrine infused at 0.3 \( \mu g\cdot kg^{-1}\cdot min^{-1} \) resulted in an increase in renal blood flow. Under baseline conditions, however, the effect of norepinephrine was to reduce renal blood flow.

The effects of norepinephrine on renal function in patients with sepsis have been reported in several studies. Four studies (33, 35, 50, 52) in which vascular resistance and urine flow were increased in patients with elevated lactate concentrations (as high as 4.8 \( \pm \) 1.6 mmol/L) (32). Redl-Wenzl et al. (50) studied 56 patients with septic shock treated with norepinephrine (0.1 – 2.0 \( \mu g\cdot kg^{-1}\cdot min^{-1} \)) and dopamine (2.5 \( \mu g\cdot kg^{-1}\cdot min^{-1} \)). During norepinephrine infusion, creatinine clearance increased significantly from 75 \( \pm \) 37 to 102 \( \pm \) 43 mL/min after 48 hrs of treatment. The authors concluded that mean arterial pressure could be increased by norepinephrine with a positive effect on organ perfusion and oxygenation.

The effects of norepinephrine on serum lactate concentrations have been assessed in several studies. Four studies assessed changes in serum lactate concentrations over a relatively short period of time (i.e., 1–3 hrs). Hesselvik and Brodin (49) reported unchanged lactate levels during norepinephrine therapy, but the actual values were not given. In the other three studies (33, 35, 52), mean values of serum lactate concentrations did not change over the 1- to 3-hr study period. It should be noted that initial values were not very high (1.8 –2.3 mmol/L). Because blood flow tended to improve significantly and lactate acid concentrations decreased (but not significantly) in one study, it is unclear whether sufficient time elapsed between measurements to see a significant norepinephrine-induced change in serum lactate concentrations. Martin et al. (32) infused norepinephrine into patients with septic shock in whom initial lactate concentrations were elevated (4.8 \( \pm \) 1.6 mmol/L), and a statistically and clinically significant decrease in lactate levels was observed at the end of the 6-hr study period. Zhou et al. (63) infused dopamine into 16 patients with septic shock and then switched to norepinephrine, epinephrine, and a norepinephrine-dobutamine combination to maintain the same blood pressure in a random fashion. There was a trend toward a lower lactate level with norepinephrine compared with dopamine or epinephrine, and this difference became significant with the norepinephrine-dobutamine combination. Once again, however, the lactate values were already low (all were \( \leq 2.6 \) mmol/L), and the infusion of each drug was for only 120 mins. Norepinephrine thus does not worsen, and may even improve, tissue oxygenation, as assessed by serum lactate levels, in patients with septic shock. Very recently, De Backer et al. (40) compared norepinephrine, epinephrine, and dopamine in patients with moderate and severe septic shock and found no effect of norepinephrine on arterial lactate levels.

The effects of norepinephrine alone on the splanchnic circulation are difficult to predict. The combination of norepinephrine and dobutamine seems to be more predictable and more appropriate to the goals of septic shock therapy than the effects of epinephrine alone. Ruokonen et al. (33) measured splanchnic blood flow and splanchnic oxygen consumption in septic shock patients receiving either norepinephrine (0.07 – 0.23 \( \mu g\cdot kg^{-1}\cdot min^{-1} \)) or dopamine (7.6 – 33.8 \( \mu g\cdot kg^{-1}\cdot min^{-1} \)) to correct hypotension. With norepinephrine, no overall changes in splanchnic blood flow and splanchnic oxygen consumption or extraction were noted, and in individual patients, its effects on splanchnic blood flow were unpredictable (increased in three patients, decreased in two). Dopamine caused a consistent and statistically significant increase in splanchnic blood flow. Meier-Hellmann et al. (36) studied patients changed from dobutamine to norepinephrine. They observed a significant decrease in hepatic venous oxygen saturation. In another group of patients, they studied the effects of switching from dobutamine plus norepinephrine to the latter drug alone. They observed the previously reported changes in hepatic venous...
the results of studies of norepinephrine, it can be concluded that norepinephrine markedly improves mean arterial pressure and glomerular filtration. This is particularly true in the high-output–low-resistance state of many septic shock patients. After restoration of systemic hemodynamics, urine flow reappears in most patients and renal function improves without the use of low-dose dopamine or furosemide. This fact supports the hypothesis that the renal ischemia observed during hyperdynamic septic shock is not worsened by norepinephrine infusion and even suggests that this drug may be effective in improving renal blood flow and renal vascular resistance. Clinical experience with norepinephrine in septic shock patients suggests that this drug can successfully increase blood pressure without causing deterioration in cardiac index or organ function. Norepinephrine (at doses of 0.01–3 \( \mu \)g·kg\(^{-1} \cdot \text{min}^{-1} \)) consistently improves hemodynamic variables in the large majority of patients with septic shock. The effects of norepinephrine on oxygen transport variables remain undefined from the available data, but most studies find other clinical variables of peripheral perfusion to be significantly improved. There is some evidence that outcome may be better with norepinephrine than with high-dose dopamine. Unfortunately only one published study was controlled (32), and a prospective, randomized clinical trial is still required to assess whether the use of norepinephrine in septic shock patients affects mortality compared with other vasopressors.

**Question:** Should low-dose dopamine be routinely administered for renal protection?

**No:** Grade B

**Recommendations:** Low-dose dopamine should not be used for renal protection as part of the treatment of severe sepsis.

**Grade B**

**Rationale:** Although no prospective, randomized studies have demonstrated a significant improvement in renal function with vasopressors, a number of open-label clinical series support an increase in renal perfusion pressure (47–50, 55, 56, 59, 63, 66). Excessive doses of vasopressors may shift the renal autoregulation curve to the right, necessitating a greater perfusion pressure for a specified renal blood flow. The precise target mean blood pressure level depends on the premorbid blood pressure, but it can be as high as 75 mm Hg (47, 49, 50, 55, 56, 59, 65, 66). However, individual levels should be kept at the minimum needed to reestablish urine flow, and in some patients, this can be achieved with a mean arterial pressure of 60 or 65 mm Hg. Certain patients may remain oliguric, despite normalization of systemic hemodynamic variables (48, 50, 55, 56, 59). This may be due to the absence of an increase in renal blood flow, a decrease in glomerular perfusion pressure, or because renal failure has become established.

Although in nonseptic conditions combination therapy with the use of low-dose dopamine (1–4 \( \mu \)g·kg\(^{-1} \cdot \text{min}^{-1} \)) in addition to norepinephrine in an anesthetized dog model and in healthy volunteers resulted in significantly higher renal blood flow and lower renal vascular resistance (67, 68), such effects have not been conclusively demonstrated in septic shock. The Australian and New Zealand Intensive Care Society Clinical Trials Group (69) recently performed the only large randomized, clinical trial of the effect of low-dose dopamine on the development of renal failure in a general intensive care unit population of patients with systemic inflammatory response syndrome and early renal dysfunction. A total of 328 patients, including patients with sepsis, were randomized either to receive dopamine at 2 \( \mu \)g·kg\(^{-1} \cdot \text{min}^{-1} \) or placebo, but no protective effect on renal function or other outcomes was found.

**Question:** Should epinephrine or phenylephrine be administered as first-line vasopressors in septic shock?

**No:** Grade D

**Recommendations:** Epinephrine or phenylephrine should not be used as first-line vasopressors as part of the treatment of septic shock. Epinephrine decreases splanchnic blood flow, increases gastric mucosal PCO\(_2\) production, and decreases pH\(_i\), suggesting that the drug alters oxygen supply in the splanchnic circulation. Phenylephrine was reported to reduce splanchnic blood flow and oxygen delivery in septic shock patients.

**Grade D**

**Rationale:** Epinephrine can increase arterial pressure in patients who fail to respond to fluid administration or other vasopressors, primarily by increasing cardiac index and stroke volume (66, 70–72). Moran et al. (72) reported a linear relationship between epinephrine dose and heart rate, mean arterial pressure, cardiac index, left ventricular stroke index, and oxygen delivery and consumption. Epinephrine, however, has variable and often detrimental effects on splanchnic blood flow and causes transient de-
increases in pH and increases in the Pco₂ gap (51, 63, 73). De Backer et al. (40) demonstrated in septic patients with severe shock that epinephrine increased cardiac index when compared with norepinephrine but that splanchnic blood flow was reduced and the mixed-venous–to–hepatic venous oxygenation gradient was increased, although Pco₂ gap remained unchanged, leading these authors to conclude that epinephrine was potentially detrimental.

Epinephrine administration has also been associated with increases in systemic and regional lactate concentrations (51, 71, 74), although the cause of these increases is unclear. As the monitoring periods in all these studies were short, it is unclear whether these increases are a transient phenomenon. In an animal sepsis model, Levy et al. (75) demonstrated that these changes may well be due to a direct effect on carbohydrate metabolism. Other adverse effects of epinephrine include tachyarrhythmias. In summary, epinephrine clearly increases blood pressure and cardiac output in patients unresponsive to other agents. However, because of its potentially negative effects on gastric blood flow and blood lactate concentrations, its use should be limited.

Phenylephrine is a selective α-adrenergic agonist and has been used in septic shock, although there are concerns about its potential to reduce cardiac output and lower heart rate in these patients. Doses of phenylephrine start at 0.5 μg·kg⁻¹·min⁻¹ and reach a maximum dose of 5–8 μg·kg⁻¹·min⁻¹. A few studies have evaluated the clinical use of phenylephrine in septic shock (76–78). Reinelt et al. (78) reported reduced splanchnic blood flow and oxygen delivery in six septic shock patients treated with phenylephrine compared with norepinephrine.

**Question: Should vasopressin be administered as vasopressor in septic shock when conventional vasopressor therapy fails?**

Uncertain; Grade E

**Recommendations:** Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors. Pending the outcome of ongoing trials, it is not recommended as a replacement for norepinephrine or dopamine as a first-line agent. If used in adults, it should be administered at infusion rates of 0.01–0.04 units/min. It may decrease stroke volume.

Grade E

**Rationale:** There is increasing interest in the possible role of vasopressin as a therapeutic vasopressor in patients with septic shock. Landry et al. (79) reported that patients with severe septic shock had reduced vasopressin levels and demonstrated a marked response to exogenous infusion. Subsequently, there have been several small case series of the use of vasopressin to raise the blood pressure in septic patients (80, 81). Recently, Dunser et al. (82) prospectively randomized 48 patients with vasodilatory shock to receive either norepinephrine or norepinephrine plus vasopressin at 4 units/hr for 48 hrs. Mean arterial pressure, cardiac index, and left ventricular stroke work index were all significantly higher in the vasopressin group. Splanchnic perfusion as assessed by tonometry was better preserved in the vasopressin group, although serum bilirubin levels were also higher and increased significantly during the infusion period. However, in a separate report, the same group described a 30.2% rate (19 of 63 patients) of ischemic skin lesions in patients with septic shock receiving vasopressin infusions (83). Although these preliminary results are fascinating, there is still inadequate understanding as to the mechanisms and potential therapeutic risk/benefit ratio of the use of vasopressin in septic shock. At this stage, vasopressin should only be used as part of properly constructed clinical trials until more information is available.

**Question:** Is dobutamine the pharmacologic agent of choice to increase cardiac output in the treatment of septic shock?

Yes; Grade E

**Recommendations:** In patients with low cardiac output despite adequate fluid resuscitation, dobutamine may be used to increase cardiac output. If used in the presence of low blood pressure, it should be combined with vasopressor therapy.

Grade E

**Rationale:** Although the cardiac index is usually maintained in the volume-resuscitated septic shock patient, cardiac function is impaired (84). Characterized by ventricular dilation, a decreased ejection fraction, an impaired contractile response to volume loading, and a low peak systolic pressure/end-systolic volume (85, 86), the mechanism of the myocardial dysfunction is complex. Coronary blood flow is usually normal, and there is no net lactate production across the coronary vascular bed, so myocardial ischemia is not implicated. Alterations in intracellular calcium homeostasis and in β-adrenergic signal transduction may be contributory factors. Several inflammatory mediators have been shown to cause myocardial depression in various animal models, including cytokines (87), platelet-activating factor, and nitric oxide (88). Inotropic therapy in septic shock is thus not straightforward. Cardiac output is usually not decreased, and multiple factors may be involved in the depressed cardiac function.

Dobutamine is an adrenergic agonist that stimulates β₁ and β₂-adrenergic receptors. A number of studies have investigated the effect of dobutamine on cardiac function during sepsis or septic shock (89–93). The doses utilized ranged from 2 to 28 μg·kg⁻¹·min⁻¹. The majority of these studies found increases in cardiac index combined with increases in stroke volume and heart rate.

Dopexamine is a dopamine analog that stimulates adrenergic and dopamine 1 and 2 receptors. It is not approved for use in the United States. Several studies have evaluated short-term infusions of dopexamine in sepsis or septic shock and demonstrated significant improvements in cardiac index and left ventricular stroke work index (94–96). In addition, mesenteric perfusion, as assessed by gastric tonometry, was improved compared with baseline values in initial studies (95), but this has not been confirmed in subsequent studies (97).

Phosphodiesterase inhibitors alone, such as amrinone and milrinone, have little place in the treatment of septic shock. They may be considered in combination with adrenergic agents. One study evaluating milrinone in pediatric patients with sepsis observed that cardiac index and right and left ventricular stroke work indices improved significantly, with little change in heart rate (98).

Calcium supplementation has been proposed in the management of myocardial dysfunction in septic shock. However, no consistent beneficial hemodynamic effect of calcium administration in septic patients has been reported (99), and increased mortality has been reported in animal models (100, 101). Digoxin has been reported to significantly
improve cardiac performance in hypodynamic septic patients (102). The new calcium-sensitizing agent levosimendan may also prove to have a role in the future, but there are no available data at present.

Question: Is it recommended to use inotropic agents for increasing cardiac output above physiologic levels?

No; Grade A

Recommendations: A strategy of increasing cardiac index to achieve an arbitrarily predefined elevated level is not recommended.

Grade A

Rationale: In patients with decreased cardiac output, the goals of therapy are relatively clear and are aimed at restoring normal physiology. Because of the complexity of assessment of clinical variables in septic patients, direct measurement of cardiac output by invasive hemodynamic monitoring is advisable, but other end points of global perfusion should be followed as well. When global hypoperfusion is manifest by a decreased SV$_{O_2}$, monitoring of SV$_{O_2}$ can be helpful to guide response to therapy. Similarly, although lactate production in sepsis is complex, a fall in blood lactate levels during inotropic therapy is a good prognostic sign (103).

In contrast to former reports (104, 105), two large prospective clinical trials that included critically ill patients who had severe sepsis failed to demonstrate benefit from increasing oxygen delivery to supranormal levels by use of dobutamine (106, 107). The goal of resuscitation should instead be to achieve adequate levels of oxygen delivery to avoid flow-dependent tissue hypoxia.

REFERENCES

16. Deitch EA: Bacterial translocation or lymphatic drainage of toxic products from the gut: What is important in human beings? Surgery 2002; 131:241–244
21. Deitch EA: Bacterial translocation or lymphatic drainage of toxic products from the gut: What is important in human beings? Surgery 2002; 131:241–244

Crit Care Med 2004 Vol. 32, No. 11 (Suppl.)
A goal-directed therapy using volume loading, dobutamine and/or norepinephrine. Acta Anaesthesiol Scand 1990; 34:413–417


VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*

ABSTRACT

Background  Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 ml per kilogram of body weight and may cause stretch-induced lung injury in patients with acute lung injury and the acute respiratory distress syndrome. We therefore conducted a trial to determine whether ventilation with lower tidal volumes would improve the clinical outcomes in these patients.

Methods  Patients with acute lung injury and the acute respiratory distress syndrome were enrolled in a multicenter, randomized trial. The trial compared traditional ventilation treatment, which involved an initial tidal volume of 12 ml per kilogram of predicted body weight and an airway pressure measured after a 0.5-second pause at the end of inspiration (plateau pressure) of 50 cm of water or less, with ventilation with a lower tidal volume, which involved an initial tidal volume of 6 ml per kilogram of predicted body weight and a plateau pressure of 30 cm of water or less. The first primary outcome was death before a patient was discharged home and was breathing without assistance. The second primary outcome was the number of days without ventilator use from day 1 to day 28.

Results  The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0 percent vs. 39.8 percent, \( P = 0.007 \)), and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean \( \pm SD \), 12 \( \pm \) 11 vs. 10 \( \pm \) 11; \( P = 0.007 \)). The mean tidal volumes on days 1 to 3 were 6.2 \( \pm \) 0.8 and 11.8 \( \pm \) 0.8 ml per kilogram of predicted body weight (\( P < 0.001 \)), respectively, and the mean plateau pressures were 25 \( \pm \) 6 and 33 \( \pm \) 8 cm of water (\( P < 0.001 \)), respectively.

Conclusions  In patients with acute lung injury and the acute respiratory distress syndrome, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use. (N Engl J Med 2000;342:1301-8.)

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*Members of the Acute Respiratory Distress Syndrome (ARDS) Network are listed in the Appendix.
The use of lower tidal volumes during ventilation in patients with acute lung injury and the acute respiratory distress syndrome may reduce injuries to lung stretch and the release of inflammatory mediators. However, this approach may cause respiratory acidosis and decrease arterial oxygenation and may therefore require changes in the priority of some objectives in the care of these patients. With the traditional approach, the attainment of normal partial pressure of arterial carbon dioxide and pH is given a higher priority than the protection of the lung from excessive stretch. With an approach that involves lower tidal volumes, the reverse is true. Uncontrolled studies suggested that the use of a lower tidal volume would reduce mortality in patients with acute lung injury and the acute respiratory distress syndrome, but the results of four randomized trials of lung-protecting ventilation strategies have been conflicting. The present trial was conducted to determine whether the use of a lower tidal volume with mechanical ventilation would improve important clinical outcomes in such patients.

METHODS

Patients

Patients were recruited from March 1996 through March 1999 at the 10 university centers of the Acute Respiratory Distress Syndrome Network of the National Heart, Lung, and Blood Institute (the centers are listed in the Appendix). The protocol was approved by the institutional review board at each hospital, and informed consent was obtained from the patients or surrogates at all but one hospital, where this requirement was waived. A complete description of the methods is available on the World Wide Web (at www.ardsnet.org) or from the National Auxiliary Publications Service (NAPS).

Patients who were intubated and receiving mechanical ventilation were eligible for the study if they had an acute decrease in the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen to 300 or less (indicating the onset of hypoxemia; values were adjusted for altitude in Denver and Salt Lake City), bilateral pulmonary infiltrates on a chest radiograph consistent with the presence of edema, and no clinical evidence of left atrial hypertension or (if measured) a pulmonary-capillary wedge pressure of 18 mm Hg or less. Patients were excluded if 36 hours had elapsed since they met the first three criteria; they were younger than 18 years of age; they had participated in other trials within 30 days before the first three criteria were met; they were pregnant; they had increased intracranial pressure, neuromuscular disease that could impair spontaneous breathing, sickle cell disease, or severe chronic respiratory disease; they weighed more than 1 kg per centimeter of height; they had burns over more than 30 percent of their body-surface area; they had other conditions with an estimated 6-month mortality rate of more than 50 percent; they had undergone bone marrow or lung transplantation; they had chronic liver disease (as defined by Child–Pugh class C); or their attending physician refused or was unwilling to agree to the use of full life support.

A centralized interactive voice system was used for randomization. Patients were randomly assigned to receive mechanical ventilation involving either traditional tidal volumes or lower tidal volumes.

Ventilator Procedures

The volume-assist–control mode was used for the ventilator until the patient was weaned from the device or for 28 days after randomization on day 0. Because normal lung volumes are predicted on the basis of sex and height, a predicted body weight was calculated for each patient from these data. The predicted body weight of male patients was calculated as equal to 50 + 0.91(centimeters of height − 152.4); that of female patients was calculated as equal to 45.5 + 0.91(centimeters of height − 152.4). In the group treated with traditional tidal volumes, the initial tidal volume was 12 ml per kilogram of predicted body weight. This was subsequently reduced stepwise by 1 ml per kilogram of predicted body weight if necessary to maintain the airway pressure measured after a 0.5-second pause at the end of inspiration (plateau pressure) at a level of 50 cm of water or less. The minimal tidal volume was 4 ml per kilogram of predicted body weight. If the plateau pressure dropped below 45 cm of water, the tidal volume was increased in steps of 1 ml per kilogram of predicted body weight until the plateau pressure was at least 45 cm of water or the tidal volume was 12 ml per kilogram of predicted body weight.

In the group treated with lower tidal volumes, the tidal volume was reduced to 6 ml per kilogram of predicted body weight within four hours after randomization and was subsequently reduced stepwise by 1 ml per kilogram of predicted body weight if necessary to maintain plateau pressure at a level of no more than 30 cm of water. The minimal tidal volume was 4 ml per kilogram of predicted body weight. If plateau pressure dropped below 25 cm of water, tidal volume was increased in steps of 1 ml per kilogram of predicted body weight until the plateau pressure was at least 25 cm of water or the tidal volume was 6 ml per kilogram of predicted body weight. For patients with severe dyspnea, the tidal volume could be increased to 7 to 8 ml per kilogram of predicted body weight if the plateau pressure remained 30 cm of water or less.

Plateau pressures were measured with a half-second inspiratory pause at four-hour intervals and after changes in the tidal volume or positive end-expiratory pressure. Plateau pressures of more than 50 cm of water in the patients in the group treated with traditional tidal volumes and of more than 30 cm of water in patients in the group treated with lower tidal volumes were allowed if the tidal volume was 4 ml per kilogram of predicted body weight or if arterial pH was less than 7.15.

All other objectives and ventilation procedures, including weaning, were identical in the two study groups (Table 1). If a patient became able to breathe without assistance but subsequently required additional mechanical ventilation within a period of 28 days, the same tidal-volume protocol was resumed.

Organ or System Failure

Patients were monitored daily for 28 days for signs of the failure of nonpulmonary organs and systems. Circulatory failure was defined as a systolic blood pressure of 90 mm Hg or less or the need for treatment with any vasopressor; coagulation failure as a platelet count of 80,000 per cubic millimeter or less; hepatic failure as a serum bilirubin concentration of at least 2 mg per deciliter (34 µmol per liter); and renal failure as a serum creatinine concentration of at least 2 mg per deciliter (177 µmol per liter). We calculated the number of days without organ or system failure by subtracting the number of days per organ failure from the lesser of 28 days or the number of days to death. Organs and systems were considered failure-free after patients were discharged from the hospital.

Plasma Interleukin-6 Concentrations

Blood samples were obtained from 204 of the first 234 patients on day 0 and on day 3 for measurement of plasma interleukin-6 by immunoassay (R & D Systems, Minneapolis). Blood samples were stored in sterile EDTA-treated glass tubes.

Data Collection

Data on demographic, physiologic, and radiographic characteristics, coexisting conditions, and medications were recorded with...
unassisted breathing lasted at least 48 consecutive hours. A differ-

tor-free days, defined as the number of days from day 1 to day 28

sidered to have been discharged from the hospital and to be breath-

were in other types of health care facilities at 180 days were con-

Statistical Analysis

these data from each of the 10 centers were used by investigators

Assessment of Compliance

randomly selected ventilator and blood gas variables were an-

Statistical Analysis

The first primary outcome was death before a patient was dis-

in four hours before the ventilator settings were changed on day 0.

Assessment of Compliance

Randomly selected ventilator and blood gas variables were an-

Statistical Analysis

The first primary outcome was death before a patient was dis-

Table 1. Summary of Ventilator Procedures.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>GROUP RECEIVING TRADITIONAL TIDAL VOLUMES</th>
<th>GROUP RECEIVING LOWER TIDAL VOLUMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial tidal volume (ml/kg of predicted body weight)</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Plateau pressure (cm of water)</td>
<td>≤50</td>
<td>≤30</td>
</tr>
<tr>
<td>Ventilator rate setting needed to achieve a pH goal of 7.3 to 7.45 (breaths/min)</td>
<td>6–35</td>
<td>6–35</td>
</tr>
<tr>
<td>Ratio of the duration of inspiration to the duration of expiration</td>
<td>1:1–1:3</td>
<td>1:1–1:3</td>
</tr>
<tr>
<td>Oxygenation goal</td>
<td>PaO2 55–80 mm Hg, or SpO2 88–95%</td>
<td>PaO2 55–80 mm Hg, or SpO2 88–95%</td>
</tr>
<tr>
<td>Allowable combinations of FiO2 and PEEP (cm of water)</td>
<td>0.3 and 5</td>
<td>0.3 and 5</td>
</tr>
<tr>
<td>0.4 and 5</td>
<td>0.4 and 5</td>
<td></td>
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<tr>
<td>0.4 and 8</td>
<td>0.4 and 8</td>
<td></td>
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<tr>
<td>0.5 and 8</td>
<td>0.5 and 8</td>
<td></td>
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<tr>
<td>0.6 and 10</td>
<td>0.6 and 10</td>
<td></td>
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<tr>
<td>0.7 and 10</td>
<td>0.7 and 10</td>
<td></td>
</tr>
<tr>
<td>0.7 and 12</td>
<td>0.7 and 12</td>
<td></td>
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<tr>
<td>0.7 and 14</td>
<td>0.7 and 14</td>
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<tr>
<td>0.8 and 14</td>
<td>0.8 and 14</td>
<td></td>
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<tr>
<td>0.9 and 14</td>
<td>0.9 and 14</td>
<td></td>
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<tr>
<td>0.9 and 16</td>
<td>0.9 and 16</td>
<td></td>
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<tr>
<td>0.9 and 18</td>
<td>0.9 and 18</td>
<td></td>
</tr>
<tr>
<td>1.0 and 18</td>
<td>1.0 and 18</td>
<td></td>
</tr>
<tr>
<td>1.0 and 20</td>
<td>1.0 and 20</td>
<td></td>
</tr>
<tr>
<td>1.0 and 22</td>
<td>1.0 and 22</td>
<td></td>
</tr>
<tr>
<td>1.0 and 24</td>
<td>1.0 and 24</td>
<td></td>
</tr>
<tr>
<td>Weaning</td>
<td>By pressure support; required by protocol when FiO2&lt;0.4</td>
<td>By pressure support; required by protocol when FiO2&lt;0.4</td>
</tr>
</tbody>
</table>

*PaO2 denotes partial pressure of arterial oxygen, SpO2 oxyhemoglobin saturation measured by pulse oximetry, FiO2 fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

‡Subsequent adjustments in tidal volume were made to maintain a plateau pressure of ≤50 cm of water and in the group receiving traditional tidal volumes and ≤30 cm of water in the group receiving lower tidal volumes.

Further increases in PEEP, to 34 cm of water, were allowed but were not required.
tality to compare the proportion of patients in each group who died before being discharged home and breathing without assistance,\(^2\) after stratification for other experimental interventions: treatment with kerosomazole, the kerosomazole placebo, lisofylline, the lisofylline placebo, or no other agent. We used a chi-square test to determine whether there was an interaction between the study group and the other experimental interventions with respect to the mean (±SE) mortality rates at 180 days. All P values are two-sided.

RESULTS

The trial was stopped after the fourth interim analysis because the use of lower tidal volumes was found to be efficacious (\(P=0.005\) for the difference in mortality between groups; \(P\) value for the stopping boundary, 0.023). The base-line characteristics of the 861 patients who were enrolled were similar, except that minute ventilation was slightly but significantly higher (\(P=0.01\)) in the group treated with lower tidal volumes (Table 2).

The tidal volumes and plateau pressures were significantly lower on days 1, 3, and 7 in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (Table 3). The mean (±SD) tidal volumes on days 1 to 3 were 6.2±0.8 and 11.8±0.8 ml per kilogram of predicted body weight (\(P<0.001\)), respectively, and the mean plateau pressures were 25±6 and 33±8 cm of water (\(P<0.001\)), respectively. The partial pressure of arterial oxygen was similar in the two groups at all three times, but the positive end-expiratory pressure and fraction of inspired oxygen were significantly higher and the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen was significantly lower in the group treated with lower tidal volumes on days 1 and 3. On day 7, positive end-expiratory pressure and the fraction of inspired oxygen were significantly higher in the group treated with traditional tidal volumes. The respiratory rate was significantly higher in the group treated with lower tidal volumes on days 1 and 3, but minute ventilation was similar in the two groups on these days. The partial pressure of arterial carbon dioxide was significantly higher on days 1, 3, and 7 and arterial pH was significantly lower on days 1 and 3 in the group treated with lower tidal volumes.

The probability of survival and of being discharged home and breathing without assistance during the first 180 days after randomization is shown in Figure 1. The mortality rate was 39.8 percent in the group treated with traditional tidal volumes and 31.0 percent in the group treated with lower tidal volumes (\(P=0.007\); 95 percent confidence interval for the difference between groups, 2.4 to 15.3 percent). The interaction between the study group and stratification for other experimental interventions was not significant (\(P=0.16\)).

Data were available to calculate the static compliance of the respiratory system at base line in 517 patients (Fig. 2). The interaction between the quartile of static compliance at base line and the study group with respect to the risk of death was not significant (\(P=0.49\)).

The number of ventilator-free days was significantly higher in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (Table 4). The median duration of ventilation was 8 days among patients in both groups who were discharged from the hospital after weaning and 10.5 and 10 days, respectively, among those who died in the group treated with lower tidal volumes and the group treated with traditional tidal volumes. The number of days without nonpulmonary organ or system failure was significantly higher in the group treated with lower tidal volumes (\(P=0.006\)). This group had more days without circulatory failure (mean [±SD], 19±10 vs. 17±11 days; \(P=0.004\)), coagulation failure (21±10 vs. 19±11 days, \(P=0.004\)), and renal failure (20±11 vs. 18±11 days, \(P=0.005\)) than did the group treated with traditional tidal volumes. The

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**Table 2. Base-Line Characteristics of the Patients.**

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>GROUP RECEIVING LOWER TIDAL VOLUMES (N=429)</th>
<th>GROUP RECEIVING TRADITIONAL TIDAL VOLUMES (N=429)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51±17</td>
<td>52±18</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Race or ethnic group (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>Black</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>APACHE III score†</td>
<td>81±28</td>
<td>84±28</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>138±64</td>
<td>134±58‡</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ≤200 (%)</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>Tidal volume (ml)§</td>
<td>676±119</td>
<td>665±125</td>
</tr>
<tr>
<td>Minute ventilation (l/min)</td>
<td>13.4±4.3§</td>
<td>12.7±4.3</td>
</tr>
<tr>
<td>No. of nonpulmonary organ or system failures</td>
<td>1.8±1.1</td>
<td>1.8±1.0</td>
</tr>
</tbody>
</table>

†APACHE III denotes Acute Physiology, Age, and Chronic Health Evaluation. Scores can range from 0 to 299, with higher scores indicating more severe illness.\(^3\)

§Data were available for 300 patients in the group treated with lower tidal volumes and for 290 patients in the group treated with traditional tidal volumes.

*Plus–minus values are means ±SD. Because of rounding, not all percentages total 100. PaO₂ denotes partial pressure of arterial oxygen, and FiO₂ fraction of inspired oxygen.

*Data were missing for one patient.

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incidence of barotrauma after randomization was similar in the two groups.

There were no significant differences between groups in the percentages of days on which neuromuscular-blocking drugs were used among patients who were discharged home and breathing without assistance (6±14 percent in the group treated with lower tidal volumes and 6±15 percent in the group treated with traditional tidal volumes) or among those who died (20±32 percent and 16±28 percent, respectively), or in the percentages of days on which sedatives were used among patients who were discharged home and breathing without assistance (65±26 percent and 65±24 percent, respectively) or those who died (73±24 percent and 71±28 percent, respectively). Investigational treatments for acute lung injury and the acute respiratory distress syndrome that were not included in the factorial design of the experimental interventions were given to 15 patients in the group treated with lower tidal volumes and 12 patients in the group treated with traditional tidal volumes. These included prone positioning in 14 and 9 patients, respectively.

The mean log-transformed plasma interleukin-6 values decreased from 2.5±0.7 pg per milliliter on day 0 to 2.3±0.7 pg per milliliter on day 3 in the group treated with traditional tidal volumes and from 2.5±0.7 pg per milliliter to 2.0±0.5 pg per milliliter in the group treated with lower tidal volumes. The decrease was greater in the group treated with lower tidal volumes (P<0.001), and the day 3 plasma interleukin-6 concentrations were also lower in this group (P=0.002).

**DISCUSSION**

In this large study of patients with acute lung injury and the acute respiratory distress syndrome, mortality was reduced by 22 percent and the number of ventilator-free days was greater in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes. These differences were maintained during the first 7 days of treatment (P<0.01).

| TABLE 3. Respiratory Values during the First Seven Days of Treatment in Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome.* |
|------------------------------|------------------|------------------|------------------|
| VARIABLE                     | DAY 1            | DAY 2            | DAY 7            |
|                              | GROUP REceiving LOWER TIDAL VOLUMES | GROUP REceiving TRADITIONAL TIDAL VOLUMES | GROUP REceiving LOWER TIDAL VOLUMES | GROUP REceiving TRADITIONAL TIDAL VOLUMES |
| Tidal volume (ml/kg of predicted body weight) | 6.2±0.9 | 11.8±0.8 | 6.2±1.1 | 11.8±0.8 | 6.5±1.4 | 11.4±1.4 |
| No. of patients               | 387             | 405             | 384             | 399             | 382 | 401 |
| Plateau pressure (cm of water) | 25±7            | 33±9            | 26±7            | 34±9            | 26±7 | 37±9 |
| No. of patients               | 387             | 405             | 384             | 399             | 382 | 401 |
| Peak inspiratory pressure (cm of water) | 32±8            | 39±10           | 32±9            | 40±10           | 33±9 | 44±10 |
| No. of patients               | 387             | 405             | 384             | 399             | 382 | 401 |
| Mean airway pressure (cm of water) | 17±13           | 17±12           | 17±14           | 19±17           | 17±14 | 20±10 |
| No. of patients               | 387             | 405             | 384             | 399             | 382 | 401 |
| Respiratory rate (breaths/min) | 29±7            | 16±6            | 30±7            | 17±7            | 30±7 | 20±7 |
| No. of patients               | 387             | 405             | 384             | 399             | 382 | 401 |
| Minute ventilation (liters/min) | 12.9±3.6       | 12.6±4.5       | 13.4±3.5       | 13.4±4.8       | 13.7±3.8 | 14.9±5.3 |
| FiO₂                          | 0.56±0.19       | 0.51±0.17       | 0.54±0.18       | 0.51±0.18       | 0.50±0.17 | 0.54±0.20 |
| No. of patients               | 387             | 405             | 384             | 399             | 382 | 401 |
| PEEP (cm of water)            | 9.4±3.6         | 8.6±3.6         | 9.2±3.6         | 8.6±4.2         | 8.1±3.4 | 9.1±4.2 |
| No. of patients               | 387             | 405             | 384             | 399             | 382 | 401 |
| PaO₂ (mm Hg)                  | 158±73          | 176±76          | 160±68          | 177±81          | 165±71 | 164±88 |
| No. of patients               | 387             | 405             | 384             | 399             | 382 | 401 |
| PaCO₂ (mm Hg)                 | 76±23           | 77±19           | 74±22           | 76±23           | 73±17 | 75±21 |
| No. of patients               | 387             | 405             | 384             | 399             | 382 | 401 |
| Arterial pH                   | 7.38±0.08       | 7.41±0.07       | 7.38±0.08       | 7.41±0.07       | 7.40±0.07 | 7.41±0.08 |
| No. of patients               | 387             | 405             | 384             | 399             | 382 | 401 |

*Plus–minus values are means (±SD) of the values recorded between 6 and 10 a.m. on days 1, 3, and 7 after enrollment. The numbers of patients refers to those who were receiving ventilation and for whom data were available. FiO₂ denotes fraction of inspired oxygen, PEEP positive end-expiratory pressure, PaO₂ partial pressure of arterial oxygen, and PaCO₂ partial pressure of arterial carbon dioxide. All differences between study groups were significant on each day (P<0.05) except for mean airway pressure on days 1, 3, and 7; the PaO₂, FiO₂ on day 7; minute ventilation on days 1 and 3; pH on day 7; and PaO₂ on days 1, 3, and 7.
The results are consistent with the results of experiments in animals and observational studies in humans.16,17 These benefits occurred despite the higher requirements for positive end-expiratory pressure and fraction of inspired oxygen and the lower ratio of partial pressure of arterial oxygen to fraction of inspired oxygen in the group treated with lower tidal volumes on days 1 and 3. These results, coupled with the greater reductions in plasma interleukin-6 concentrations, suggest that the group treated with lower tidal volumes had less lung inflammation.35 The greater reductions in plasma interleukin-6 concentrations may also reflect a reduced systemic inflammatory response to lung injury, which could contribute to the higher number of days without organ or system failure and the lower mortality in the group treated with lower tidal volumes.35

Several factors could explain the difference in results between our trial and other trials of ventilation using lower tidal volumes in patients with acute lung injury and the acute respiratory distress syndrome.22-24 First, our study had a greater difference in tidal volumes between groups. In one earlier trial, the traditional tidal volume was equivalent to approximately 12.2 ml per kilogram of predicted body weight and the lower tidal volume was equivalent to approximately 8.1 ml per kilogram of predicted body weight.23 In a second study, the traditional and lower tidal volumes were approximately 10.3 and 7.1 ml per kilogram of dry body weight (calculated as the measured weight minus the estimated weight gain from fluid retention), respectively.22 In the present trial, measured weight exceeded predicted body weight by approximately 20 percent. Assuming a similar difference, and assuming that half the difference was dry weight in excess of predicted body weight, tidal volumes in the second trial would have been approximately 11.3 and 7.8 ml per kilogram of predicted body weight. Therefore, the traditional tidal volume of 11.8 ml per kilogram of predicted body weight in our study was similar to the values in the previous two trials.

### Table 4. Main Outcome Variables.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group Receiving Lower Tidal Volumes</th>
<th>Group Receiving Traditional Tidal Volumes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before discharge and breathing without assistance (%)</td>
<td>31.0</td>
<td>39.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Breathing without assistance by day 28 (%)</td>
<td>65.7</td>
<td>55.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of ventilator-free days, days 1 to 28</td>
<td>12±11</td>
<td>10±11</td>
<td>0.007</td>
</tr>
<tr>
<td>Barotrauma, days 1 to 28 (%)</td>
<td>10</td>
<td>11</td>
<td>0.43</td>
</tr>
<tr>
<td>No. of days without failure of nonpulmonary organs or systems, days 1 to 28</td>
<td>15±11</td>
<td>12±11</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. The number of ventilator-free days is the mean number of days from day 1 to day 28 on which the patient had been breathing without assistance for at least 48 consecutive hours. Barotrauma was defined as any new pneumothorax, pneumomediatinum, or subcutaneous emphysema, or a pneumatocele that was more than 2 cm in diameter. Organ and system failures were defined as described in the Methods section.

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However, the tidal volume of 6.2 ml per kilogram of predicted body weight in the group receiving lower tidal volumes was lower than the values in the previous two trials.

If one assumes that measured weights also exceeded predicted body weights by 20 percent in the earlier trials, the tidal volumes in the traditional groups were approximately 10.2 and 9.4 ml per kilogram of measured weight, respectively, as compared with 9.9 ml per kilogram of measured weight in our study. Therefore, the tidal volumes in the traditional groups in each of the three trials were consistent with traditional recommendations.

A second possible explanation for the different results is that the previous trials were designed to detect larger differences in mortality between groups. Hence, they lacked the statistical power to demonstrate the moderate effects of lower tidal volumes that we found.

A third difference in the trials was in the treatment of acidosis. Increases in the ventilator rate were required and bicarbonate infusions were allowed to correct mild-to-moderate acidosis in our study, which resulted in smaller differences in the partial pressure of arterial carbon dioxide and pH between the study groups than in the previous trials. The deleterious effects of acidosis in the previous studies may have counteracted a protective effect of the lower tidal volumes.

In addition to being caused by excessive stretch, lung injury may also result from repeated opening and closing of small airways or from excessive stress at margins between aerated and atelectatic regions of the lungs. These types of lung injury may be prevented by the use of a higher positive end-expiratory pressure. A slightly higher positive end-expiratory pressure was necessary in the group treated with lower tidal volumes during the first few days to maintain arterial oxygenation at a level similar to that in the group treated with traditional tidal volumes, but positive end-expiratory pressure was not increased as a means of protecting the lungs.

In a recent trial in 53 patients with acute respiratory distress syndrome, 28-day mortality was significantly lower with a ventilation strategy that used a higher positive end-expiratory pressure combined with limited peak inspiratory pressure than with a strategy of traditional ventilation. These results suggest that both increased positive end-expiratory pressure and reduced inspiratory stretch could have beneficial effects.

Stretch-induced lung injury may not occur if lung compliance is not greatly reduced. However, the benefit of ventilation with a lower tidal volume was independent of the static compliance of the respiratory system at baseline, suggesting that the lower tidal volume was advantageous regardless of lung compliance. Variations in chest-wall compliance, which contribute to compliance of the respiratory system and is reduced in many patients with acute lung injury and the acute respiratory distress syndrome, may have obscured a true interaction between tidal volume and base-line lung compliance.

Barotrauma occurred with similar frequency in the two study groups, a finding consistent with the results of other studies in which the incidence of barotrauma was independent of airway pressures. The most common manifestation of barotrauma was pneumothorax, which could have been the result of invasive procedures. Pneumothorax is not a sensitive or specific marker of stretch-induced injury with the tidal volumes used in this study.

The similarity in the number of days of ventilator use among the survivors in both groups suggests that the higher number of ventilator-free days in the group treated with lower tidal volumes resulted from reduced mortality rather than from a reduced number of days of ventilation among the survivors. However, the comparison of the number of days of ventilator use among the survivors could be misleading. Some patients who would have survived in the group treated with traditional tidal volumes might have needed the ventilator on fewer days had they been in the group treated with lower tidal volumes. This beneficial effect would have been obscured if prolonged ventilation was required before recovery among patients who otherwise would have died in the group treated with traditional tidal volumes. For similar reasons, it is also difficult to compare the number of days with organ or system failure among the survivors in the two study groups.

We found that treatment with a ventilation approach designed to protect the lungs from excessive stretch resulted in improvements in several important clinical outcomes in patients with acute lung injury and the acute respiratory distress syndrome. On the basis of these results, high priority should be given to preventing excessive lung stretch during adjustments to mechanical ventilation, and this lower-tidal-volume protocol should be used in patients with acute lung injury and the acute respiratory distress syndrome.

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APPENDIX

In addition to the members of the Writing Committee, the members of the National Heart, Lung, and Blood Institute ARDS Network were as follows: Network Participants: Cleveland Clinic Foundation — H.P. Wiedemann, A.C. Arroliga, C.J. Fisher, Jr., J.J. Komara, Jr., P. Perez-Trepubio,
REFERENCES


**SPECIAL ARTICLE**

**Difficult Airway Society guidelines for management of the unanticipated difficult intubation**

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**Summary**

Problems with tracheal intubation are infrequent but are the most common cause of anaesthetic death or brain damage. The clinical situation is not always managed well. The Difficult Airway Society (DAS) has developed guidelines for management of the unanticipated difficult tracheal intubation in the non-obstetric adult patient without upper airway obstruction. These guidelines have been developed by consensus and are based on evidence and experience. We have produced flow-charts for three scenarios: routine induction; rapid sequence induction; and failed intubation, increasing hypoxaemia and difficult ventilation in the paralysed, anaesthetised patient. The flow-charts are simple, clear and definitive. They can be fully implemented only when the necessary equipment and training are available. The guidelines received overwhelming support from the membership of the DAS.

**Disclaimer:** It is not intended that these guidelines should constitute a minimum standard of practice, nor are they to be regarded as a substitute for good clinical judgement.

**Keywords**  Intubation, intratracheal. Practice guidelines. Cricothyroidotomy. Laryngeal mask airway.

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Problems with tracheal intubation were the most frequent causes of anaesthetic death in the published analyses of records of the UK medical defence societies [1, 2]. The true number is likely to be substantially greater than those published.

Most cases of unanticipated difficult intubation are managed satisfactorily, but problems with tracheal intubation can cause serious soft tissue damage [3] and are the principal cause of hypoxaemic anaesthetic death and brain damage [1, 2, 4]. Management of the unanticipated difficult tracheal intubation must therefore concentrate on maintenance of oxygenation and prevention of airway trauma.

Guidelines for management of the difficult airway have been published recently by North American [5, 6], French [7], Canadian [8] and Italian [9] national societies or groups. A limitation of the American guidelines is the use of flow-charts which allow a wide choice of techniques at each stage. This wide choice makes them less useful for management of airway emergencies than simple and definitive flow-charts such as those in the European [10, 11] or American Heart Association [12] Advanced Life Support guidelines.

In the UK there are no national guidelines for management of unanticipated difficult intubation in the non-obstetric patient. The Royal College of Anaesthetists...
has encouraged individual departments to display national guidelines for management of a number of emergencies. In the case of failed intubation and ventilation they suggest that guidelines are developed locally. However, general concern has been expressed about the quality of local guidelines [13, 14].

The Difficult Airway Society (DAS) has developed guidelines for the management of the unanticipated difficult intubation in an adult non-obstetric patient. The purpose of this article is to present these guidelines, to justify the choice of techniques, and to discuss alternative management strategies. Paediatric and obstetric patients, and patients with upper airway obstruction, are excluded.

**Methods**

The need for airway guidelines was first discussed at the Annual Scientific Meeting of DAS in 1999. The following year, members of DAS considered a structured approach to airway guidelines and initiated development of such guidelines for the management of unanticipated difficult intubation. The aim was to produce simple, clear and definitive guidelines, similar in structure to those of the Advanced Life Support groups. Such guidelines could be used in training drills and could be followed easily in an emergency situation. Definitive guidelines imply the use of recommended techniques at every stage. These techniques must be of proven value and relatively easy to learn.

A prototype flow-chart was presented at the DAS Annual Scientific Meeting in November 2000. There was debate and criticism, and constructive suggestions were received at the meeting and subsequently by electronic mail. The DAS executive committee examined the flow-charts in detail at several meetings. Development was based on evidence, experience and consensus. The published literature on difficult and failed tracheal intubation was reviewed with extensive Medline searches and use of personal bibliographies. Advice was sought from members who had particular expertise or knowledge. Revised flow-charts were presented at the DAS Annual Scientific Meetings in November 2001 and 2002. There was overwhelming support for the concept and content of the flow-charts. A late version of the paper was sent for comments to 27 DAS members who had been particularly involved in the guidelines discussions. Their comments were considered during preparation of the final version.

These guidelines are concerned primarily with difficulty with tracheal intubation when the larynx cannot be seen with conventional direct laryngoscopy. Even when the larynx can be visualised, it is sometimes difficult to pass the tracheal tube. Use of optimum shape of the tracheal tube, with [15–19] or without [20] a stylet, or passage of an introducer (‘bougie’) under vision (‘visual bougie’ technique) with subsequent ‘railroading’ of the tube into the trachea, are recommended [21].

**The Difficult Airway Society guidelines**

The essence of the DAS guidelines for management of unanticipated difficult tracheal intubation is a series of flow-charts. They should be used in conjunction with this paper.

The DAS flow-charts are based on a series of plans. The philosophy of having a series of plans is well established in airway management as no single technique is always effective [22, 23]. Effective airway management requires careful planning so that back up plans (plan B, C, D) can be executed when the primary technique (plan A) fails. This philosophy forms the basis of the DAS guidelines. It is hoped that anaesthetists will always make back up plans before performing primary techniques so that adequate expertise, equipment and assistance are available.

Two other principles are particularly important. Maintenance of oxygenation takes priority over everything else during the execution of each plan. Anaesthetists should seek the best assistance available as soon as difficulty with laryngoscopy is experienced.

The basic structure of the DAS flow-charts is shown in Fig. 1. This contains the plans and core techniques, and shows the possible outcomes. The plans are labelled A–D:

- **Plan A** Initial tracheal intubation plan.
- **Plan B** Secondary tracheal intubation plan, when Plan A has failed.
- **Plan C** Maintenance of oxygenation and ventilation, postponement of surgery, and awakening the patient, when earlier plans fail.
- **Plan D** Rescue techniques for ‘can’t intubate, can’t ventilate’ (CICV) situation.

Not all these plans are appropriate to every possible scenario *(vide infra)*. The outcome of each plan determines progress to subsequent plans. In some situations, progress depends upon clinical factors, such as the best view of the larynx. Subdivision [24] of the Cormack & Lehane [25] grade 3 into 3a (epiglottis can be lifted) and 3b (epiglottis cannot be lifted from the posterior pharyngeal wall) has a significant effect on the success of the introducer (bougie) [24] and fiberoptic techniques [26].

It was not possible to develop a single detailed flow-chart to cover all clinical scenarios. Detailed flow-charts have therefore been developed for each of the following:

2. Unanticipated difficult tracheal intubation – during rapid sequence induction of anaesthesia (with succinylcholine) in a non-obstetric patient.
Failed intubation, increasing hypoxaemia, and difficult ventilation in the paralysed, anaesthetised patient, the ‘can’t intubate, can’t ventilate’ situation.

The principal points of these plans are discussed in more detail. Practical details of some techniques are outlined, but full descriptions should be sought in the references and textbooks. The techniques should be practised under supervision in elective situations, where appropriate, and in manikins.

**Scenario 1: Unanticipated difficult tracheal intubation – during routine induction of anaesthesia in an adult patient (Fig. 2)**

This is the clinical scenario of difficult intubation in an adult patient after induction of general anaesthesia and muscle paralysis, usually with a non-depolarising neuromuscular blocking drug.

**Plan A: Initial tracheal intubation plan**

The first attempt at direct laryngoscopy should always be performed in optimal conditions after ensuring adequate muscle relaxation and appropriate position of the head and neck (normally the ‘sniffing’ position of head extension and neck flexion) [27]. Use of optimum external laryngeal manipulation (OELM) [28–32] or BURP (backward, upward, and rightward pressure on the thyroid cartilage) [33–35], if required, applied with the anaesthetist’s right hand, should be an integral part of this first attempt [27]. If, despite these measures, there is still a grade 3 or 4 [25] view, then alternative techniques will be needed. These techniques include use of an introducer (‘gum elastic bougie’) [21] and/or a different laryngoscope. Alternative direct laryngoscopes of proven value include the McCoy [36–40] and straight [41, 42] laryngoscopes. The choice of technique depends upon the experience of the anaesthetist with a particular technique. Oxygenation is maintained with mask ventilation between intubation attempts.

The Eschmann tracheal tube introducer (‘gum elastic bougie’) was designed for multiple use and was marketed in the UK in the early 1970s [43]. It differs from previous introducers in its greater length (60 cm), angled tip and the combination of flexibility and malleability. It is inexpensive and readily available and the technique combines simplicity of operation with a high success rate. It is passed blindly into the trachea when the laryngeal inlet is not visible. The most widely used technique in the UK is the combination of the multiple-use bougie (introducer) with the Macintosh laryngoscope [44]. There is evidence that the bougie is more effective than the stylet when the best view of the larynx is grade 3 [45].

The bougie technique should be used in an optimal way. The Macintosh laryngoscope is left in the mouth
and attempts are made to insert the bougie blindly into the trachea. It is important to maximise the chance of the bougie entering the trachea. The anaesthetist will not see the bougie entering the larynx when the laryngoscopy view is grade 3 or 4. Therefore it is important to be able to recognise whether the bougie is in the trachea or the oesophagus. Clicks can often be felt by the anaesthetist when the bougie is passed into the trachea [46–48]. These are caused by the tip of the bougie hitting the tracheal cartilages. Clicks are more likely to be elicited if the distal end of the bougie is bent into a curve of about 60° [49]. If clicks are present, proceed with intubation by passing (‘railroading’) the tube over the bougie (vide infra). Clicks will not be present if the bougie goes down the centre of the tracheal lumen or is in the oesophagus. If clicks are not elicited, the bougie should be advanced gently to a maximum distance of 45 cm. If distal hold-up is sensed as slight resistance to further advancement, indicating that the bougie is held up in the bronchial tree, proceed with intubation [47]. If the patient is not fully paralysed, coughing may indicate the presence of the bougie in the trachea [46]. If neither clicks, hold-up nor coughing are elicited, the bougie is probably in the oesophagus. Remove the bougie and consider another attempt at passing the bougie blindly into the trachea – if the laryngeal view is 3a [47].

Once the bougie is in the trachea, the tracheal tube is railroaded over the bougie. Railroading is facilitated if the laryngoscope is kept in the mouth [50] and the tube is

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**Plan A:** Initial tracheal intubation plan

- **Direct laryngoscopy**
  - Check: Neck flexion and head extension
  - Laryngoscope technique and vector
  - External laryngeal manipulation - by laryngoscopist
  - Vocal cords open and immobile
  - If poor view: Introducer (bougie) - seek clicks or hold-up
  - and/or Alternative laryngoscope

**Plan B:** Secondary tracheal intubation plan

- **ILMA® or LMA®**
  - Not more than 2 insertions
  - Oxygenate and ventilate

**Plan C:** Maintenance of oxygenation, ventilation, postponement of surgery and awakening

- **Revert to face mask**
  - Oxygenate and ventilate
  - Reverse non-depolarising relaxant
  - 1 or 2 person mask technique (with oral ± nasal airway)

**Plan D:** Rescue techniques for “can’t intubate, can’t ventilate” situation

- **Confirm:** ventilation, oxygenation, anaesthesia, CVS stability and muscle relaxation - then fiberoptic tracheal intubation through IMILA® or LMA® - 1 attempt
  - If LMA®, consider long flexometallic, nasal RAE or microlaryngeal tube
  - Verify intubation and proceed with surgery

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**Figure 2** Management of unanticipated difficult tracheal intubation – during routine induction of anaesthesia in an adult patient.
rotated 90° anticlockwise [50, 51]. Use of a small tube [52–54], reinforced tube [55, 56], the tube (Euromedical
ILM) supplied with the Intubating Laryngeal Mask [57, 58] and the Parker tube [59] have all facilitated railroading in flexible fibreoptic intubation. By analogy, it is probable that these tube factors will facilitate railroading with the Eschmann introducer.

Success rates with the original reusable Eschmann introducer in prospective studies have varied between 94.3% [24], 99.5% [48] and 100% [49]. Optimum results depend on regular use and experience [48]. However, the technique is of limited value when it is not possible to elevate (grade 3b) [24] or visualise (grade 4) [25] the epiglottis. There are concerns that some recently introduced single-use disposable introducers are not as effective as and may cause more trauma than the original multiple-use bougie [60–62].

Alternative techniques of laryngoscopy, of proven value, may be used by those experienced in these techniques. In particular there is considerable evidence of the value of the following techniques in experienced hands:

- direct use of the flexible fibreoptic laryngoscope [63, 64];
- Bullard-type laryngoscope [65–75].

There are situations in which these techniques can offer unique advantages. The lighted stylet is not a visual technique, but may be successful in experienced hands [76].

Multiple and prolonged attempts at laryngoscopy and tracheal intubation are associated with morbidity [77–81] and mortality [3, 77, 78, 82]. The extent of laryngeal oedema may not become apparent until fibreoptic examination [83] or extubation [84]. An essential component of Plan A is therefore to limit the number and duration of attempts at laryngoscopy in order to prevent trauma and development of a ‘can’t ventilate’ situation. It is difficult to justify use of the same direct laryngoscope more than twice and the maximum number of laryngoscope insertions should be limited to four. However, tracheal intubation may be successful when it is performed by a more experienced anaesthetist and one such additional attempt is worthwhile [85, 86].

When these attempts at tracheal intubation have been unsuccessful, Plan B should be implemented.

Plan B: Secondary tracheal intubation plan

A different approach is required when direct laryngoscopy has failed. Alternative techniques can allow continuous ventilation and oxygenation both during and between intubation attempts. This is best achieved by using a ‘dedicated airway device’, defined as ‘an upper airway device which maintains airway patency while facilitating tracheal intubation’ [87]. Although the classic laryngeal mask airway (LMA™) has been recommended as a ventilation and intubation device in patients with a difficult airway [88], it was not designed as a conduit for tracheal intubation and has clear limitations when used for this purpose (vide infra). Any other supraglottic airway device could be used, but the intubating laryngeal mask (ILMA™) [89, 90] was designed specifically to facilitate tracheal intubation while maintaining ventilation. Each of these devices has advantages and disadvantages.

ILMA™ for secondary tracheal intubation: Numerous reports have confirmed the effectiveness of the ILMA™ for both ventilation and blind intubation in patients without airway difficulties [89, 91–98]. The overall intubation success rate in 1100 patients in these studies was 95.7% [90]. Further studies have confirmed its value in management of patients with known or anticipated difficult tracheal intubation [99–107]. The ILMA™ has also proved to be a useful device in the management of unanticipated difficult intubation. In one study, blind intubation was performed in 20 out of 23 patients with a 75% success rate at the first attempt (10% required two or three attempts and 5% required four attempts) and 100% overall success rate [104]. Fibreoptic guided intubation was successful at the first attempt in the remaining three patients.

Although high success rates can be achieved with a blind technique, several attempts may be required and the incidence of oesophageal intubation can be up to 5% [108, 109]. Transillumination techniques may improve first-attempt success rates [110] and certainly reduce the number of manoeuvres required, the incidence of oesophageal intubation and the time required to achieve intubation [111, 112]. However, intubation under vision through the ILMA™ using a flexible fibreoptic laryngoscope has real advantages. The first-attempt [104] and overall [113] success rates are higher than blind techniques, and it nearly always succeeds when blind intubation fails [103].

The techniques of insertion and intubation through the ILMA™ differ in many respects from the classic LMA™, and training and practice are essential if it is to be used to achieve a high success rate and minimise trauma in the unanticipated difficult tracheal intubation. A learning curve of about 20 insertions has been described [95, 114]. The manufacturer’s instruction manual describes the insertion and intubation techniques, the adjustments necessary for ideal positioning of the device and an approach to problem-solving [115]. The ‘Chandy manoeuvre’ (alignment of the internal aperture of ILMA™ and the glottic opening by finding the degree of sagittal rotation which produces optimal ventilation, and then applying a slight anterior lift with the ILMA™ handle) facilitates correct positioning and blind intubation.
through the ILMA\textsuperscript{TM} and has been shown to reduce the number of intubation attempts [104]. Use of the dedicated silicone tracheal tube is strongly recommended [115]. The fibrescope can be used to visualise the ‘Epiglottic Elevator Bar’ lifting the epiglottis and observe passage of the tracheal tube through the glottis [90, 116] or it can be passed into the trachea after glottic visualisation and then used to railroad the tube [104]. We prefer the latter technique. The lubricated silicone tracheal tube is first inserted into the shaft of the ILMA\textsuperscript{TM} until its tip reaches the mask aperture (indicated by the transverse line on the tube). The fibrescope is then inserted through the tracheal tube so that its tip is just within the tip of the tube. The tube and fibrescope are then advanced together for about 1.5 cm so that the ‘Epiglottic Elevator Bar’ is seen to elevate the epiglottis. Once the tip of the tube is in the larynx, the fibrescope is advanced into the trachea and the tube is then railroaded over it [90, 104]. Finally, the position of the tube is checked with the fibrescope during withdrawal. Oxygen and anaesthetic gases can be delivered continuously if a self-sealing bronchoscope connector is attached between the 15-mm tracheal tube connector and the anaesthetic breathing system [104].

Ventilation is maximised by using a wide tracheal tube with a narrow fibrescope [117]. The ILMA\textsuperscript{TM} should be removed when tracheal intubation has been verified and the tracheal tube secured [118, 119].

**Classic ILMA\textsuperscript{TM} for secondary tracheal intubation:** Fibreoptic tracheal intubation through the classic ILMA\textsuperscript{TM} (the role of the single-use ILMA\textsuperscript{TM} in management of the difficult airway patient has not been established) should be considered when an ILMA\textsuperscript{TM} is not available. Although Heath [120] reported a 93% success rate for blind intubation through the LMA\textsuperscript{TM} (in the absence of cricoid pressure), others have achieved much lower success rates [121, 122] and blind intubation cannot be recommended. Success rates of 90–100% (depending on technique, equipment, number of attempts allowed and experience of user) can be achieved with fibreoptic intubation through the classic ILMA\textsuperscript{TM} [113, 123, 124]. The limitations of the classic ILMA\textsuperscript{TM} as a conduit for intubation are well known [125, 126] and include the following:

- The LMA\textsuperscript{TM} tube connector is narrow and will only allow a 6 mm (ID) tracheal tube through a size 3 or 4 LMA\textsuperscript{TM} and 7 mm (ID) through a size 5 LMA\textsuperscript{TM}.
- The LMA\textsuperscript{TM} tube is so long that the cuff of an uncut normal tracheal tube (26–27 cm) may lie between the vocal cords so that it is ineffective and potentially traumatic. A long flexometallic tube [127], nasal RAE [128] or a microlaryngeal tube [129–131] is recommended.
- The mask aperture bars may obstruct the passage of the tracheal tube.
- Manipulation requires head and neck movement and/or finger insertion, both of which may worsen difficulties.

Difficulties may be encountered during subsequent removal of the LMA\textsuperscript{TM}. The LMA\textsuperscript{TM} may be left in situ if its presence does not interfere with surgical access. Techniques of LMA\textsuperscript{TM} removal without dislodging the tracheal tube have been described, but they may fail and expose the patient to avoidable danger [132].

The problems mentioned above can be avoided by using a two-stage technique with a flexible fiberoptic laryngoscope and an Aintree Intubation Catheter [87, 133, 134].

Whatever technique of tracheal intubation through a ‘dedicated airway’ is used, the vocal cords should be open and non-reactive before attempting to advance the fibrescope or tracheal tube into the trachea. If two attempts at the secondary tracheal intubation technique fail, surgery should be postponed and the patient awakened, i.e. Plan C should be implemented.

**Plan C:** Maintenance of oxygenation and ventilation, postponement of surgery and awakening the patient – if Plans A and B have failed

If Plan B (secondary tracheal intubation technique) fails, it remains important to avoid trauma to the airway and to maintain ventilation and oxygenation with the dedicated airway device. Elective surgery should be cancelled and the airway device should be removed only after muscle relaxation has been reversed, spontaneous ventilation is adequate, and the patient is awake. An alternative plan for anaesthesia can then be made. Although it may be possible to perform surgery under regional anaesthesia, the safest plan is to secure the airway with the patient awake [135]. If adequate ventilation and oxygenation cannot be achieved with the dedicated airway device, ventilation should be performed using a face mask with or without an oral or nasal airway.

If ventilation is impossible and serious hypoxaemia is developing, then Plan D (Rescue techniques for ‘can’t intubate, can’t ventilate’ situation) should be implemented without delay (*vide infra*).

**Scenario 2: Unanticipated difficult tracheal intubation – during rapid sequence induction of anaesthesia (with succinylcholine) in a non-obstetric patient (Fig. 3)**

**Plan A:** Initial tracheal intubation plan

In scenario 2, in contrast to scenario 1, there is an increased likelihood of regurgitation or vomiting, with a
consequent risk of pulmonary aspiration. The change in management involves the use of pre-oxygenation and the application of cricoid pressure. It is particularly important to use a pre-oxygenation technique which maximises oxygen stores [136].

Cricoid pressure has played an important role in the prevention of pulmonary aspiration since its introduction by Sellick [137]. It is an integral part of the flowchart for the patient having rapid sequence induction. However, it can impair insertion of the laryngoscope [138], passage of an introducer [139] and can cause airway obstruction [140–146]. A force of 30 N provides good airway protection, while minimising the risk of airway obstruction [147], but is not well tolerated by the conscious patient. Cricoid pressure should be applied with an initial force of 10 N when the patient is awake, increasing to 30 N as consciousness is lost [139]. The force should be reduced, with suction at hand, if it impedes laryngoscopy or causes airway obstruction.

The principles of optimising the initial tracheal intubation technique, and use of the Eschmann introducer and alternative direct laryngoscopes, are the same as in Plan A in the elective patient. If intubation fails despite a maximum of three attempts, a failed intubation plan with the aim of maintaining oxygenation and awakening the patient (Plan C) is initiated immediately. Further doses of succinylcholine should not be given.
Plan C: Maintenance of oxygenation and ventilation and postponement of surgery, if possible

Plan B is omitted from airway management of the patient having rapid sequence induction for two reasons. The risk of regurgitation or vomiting is greater in the elective patient, so that the risk of aspiration during further attempts at tracheal intubation is higher. The short duration of suxamethonium increases the risk of laryngospasm and difficulty with laryngoscopy during recovery of neuromuscular function, so that further tracheal intubation attempts increase the risk to the patient. When initial attempts at tracheal intubation in this scenario fail, the safest plan in most patients is to postpone surgery and awaken the patient.

Plan C of this scenario contains two subsidiary scenarios, in which the urgency of proceeding with surgery differs. A risk-benefit assessment balances the risks of delaying surgery against the risk of proceeding with a suboptimal airway. If it is essential to proceed with surgery, the traditional technique has been to continue with a face mask and oral airway, maintaining cricoid pressure [148, 149]. Continuation of anaesthesia with a classic LMATM is now an established technique [150, 151], although not always effective [152] or accepted [149, 153] (effect of cricoid pressure on LMA™ insertion – vide infra). If it proves difficult to ventilate the lungs as a consequence of gas leakage past the cuff of the classic LMATM, use of the ProSeal LMA™ should be considered. The ProSeal LMA™ forms a better seal [154–160] than the classic LMA™ and provides improved protection against aspiration [161–164]. The potential advantages of the ProSeal LMA™ have to be offset against increased complexity of insertion [157, 160, 165, 166] (not a problem when a precise technique [166] and the insertion tool are used [156, 167]). The risk (about 5%) of airway obstruction [168] may be lower than that with the classic LMA™ [158]. Airway obstruction may be overcome by reinsertion [169], use of a smaller size [170], withdrawal of air from the cuff [167, 170] and/or moving the head and neck into the sniffing position [167]. However, poor seal and airway obstruction may be significant problems in some obese patients [171].

Wherever possible the aim should be to postpone surgery and awaken the patient. Maintenance of ventilation and oxygenation with a face mask is a conventional technique. This may include the one- or two-person technique and the use of an oral or nasal airway. A narrow, soft, lubricated nasopharyngeal airway may be inserted gently [172, 173] if this can be done without trauma [174, 175]. It may be necessary to reduce cricoid force in order to achieve satisfactory ventilation. If satisfactory oxygenation (e.g. $S_{\text{PO}_2} > 90\%$ with $F_{\text{O}_2}$ 1.0) cannot be achieved with a face mask, the LMA™ should be used. Cricoid force impedes positioning of [176–180] and ventilation through [180–183] the LMA™. It may be necessary to reduce cricoid force during LMA™ insertion when it is used in an emergency [177, 178].

If ventilation is impossible and serious hypoxaemia is developing, then Plan D (Rescue techniques for ‘can’t intubate, can’t ventilate’ situation) should be implemented without delay.

Scenario 3: Failed intubation, increasing hypoxaemia and difficult ventilation in the paralysed anaesthetised patient

Plan D: Rescue techniques for ‘can’t intubate, can’t ventilate’ situation (Fig. 4)

This scenario may develop rapidly, but often occurs after repeated unsuccessful attempts at intubation in scenarios 1 and 2, where a ‘can ventilate’ situation develops into a ‘can’t intubate, can’t ventilate’ (CICV) situation [77, 78, 81, 82]. It is probable that most patients who suffer hypoxic damage pass through a CICV stage [77, 184]. In situations where mask ventilation fails to oxygenate the patient, the upper airway is normally sufficiently patent to allow gas to escape upwards [185–189]. This has an important bearing on the efficacy of different airway rescue techniques (vide infra).

Before resorting to invasive rescue techniques, it is essential that a maximum effort has been made to achieve ventilation and oxygenation with non-invasive techniques, such as optimum mask ventilation and the LMA™.

Other supraglottic airway devices, particularly the Combitube™, have been used in the CICV situation. Satisfactory placement of the Combitube is not always possible, even when inserted with a laryngoscope [190]. When properly positioned, it allows ventilation with a higher seal pressure than the classic LMA™, protects against regurgitation [191], and allows subsequent attempts [192] at intubation while the inflated oesophageal cuff maintains airway protection. Although there have been failures [193, 194], the Combitube has been used successfully in the difficult intubation [191, 195] and the CICV situation [196–199], including failure with the LMA™ [200]. Adjustment of cuff pressure may be necessary [201]. The Combitube is a large and bulky device, and there have been some reports of oesophageal damage with the original product [202–205], but the risk should be lower with the SA (Small Adult) size [192, 206]. The decision to use the Combitube will depend on availability, experience and the clinical situation.

The risks of an invasive rescue technique must be constantly weighed against the risks of hypoxic brain...
Failed intubation, increasing hypoxaemia and difficult ventilation in the paralysed anaesthetised patient: Rescue techniques for the "can't intubate, can't ventilate" situation

failed intubation and difficult ventilation (other than laryngospasm)

- Face mask
- Oxygenate and Ventilate patient
- Maximum head extension
- Maximum jaw thrust
- Assistance with mask seal
- Oral – 6mm nasal airway
- Reduce cricoid force - if necessary

failed oxygenation with face mask (e.g. SpO₂ < 90% with FiO₂ 1.0)

call for help

LMA™ Oxygenate and ventilate patient
- Maximum 2 attempts at insertion
- Reduce any cricoid force during insertion

Oxygenation satisfactory and stable: Maintain oxygenation and awaken patient

"can't intubate, can't ventilate" situation with increasing hypoxaemia

Plan D: Rescue techniques for "can't intubate, can't ventilate" situation

Cannula cricothyroidotomy
- Equipment: Kink-resistant cannula, e.g. Patil (Cook) or Ravussin (VBM)
- High-pressure ventilation system, e.g. Manujet III (VBM)
- Technique:
  1. Insert cannula through cricothyroid membrane
  2. Maintain position of cannula - assistant’s hand
  3. Confirm tracheal position by air aspiration - 20ml syringe
  4. Attach ventilation system to cannula
  5. Commence cautious ventilation
  6. Confirm ventilation of lungs, and exhalation through upper airway
  7. If ventilation fails, or surgical emphysema or any other complication develops - convert immediately to surgical cricothyroidotomy

Surgical cricothyroidotomy
- Equipment: Scalpel - short and rounded (no. 20 or Minitrach scalpel)
- Small (e.g. 6 or 7 mm) cuffed tracheal or tracheostomy tube
- 4-step Technique:
  1. Identify cricothyroid membrane
  2. Stab incision through skin and membrane
  3. Caudal traction on cricoid cartilage with tracheal hook
  4. Insert tube and inflate cuff

Ventilate with low-pressure source
Verify tube position and pulmonary ventilation

Notes:
1. These techniques can have serious complications - use only in life-threatening situations
2. Convert to definitive airway as soon as possible
3. Postoperative management - see other difficult airway guidelines and flow-charts
4. 4mm cannula with low-pressure ventilation may be successful in patient breathing spontaneously

Figure 4 Management of failed intubation, increasing hypoxaemia and difficult ventilation in the paralysed anaesthetised patient.

damage or death [207]. Rapid development of severe hypoxaemia, particularly associated with bradycardia, is an indication for imminent intervention with an invasive technique. Once the decision to perform an invasive technique is made, it is essential to use an effective technique. Rapid reoxygenation is now necessary, and this is best achieved with a combination of an invasive airway device and a ventilation technique which is capable of reliably delivering a large minute volume with an \( F_{iO_2} \) of 1.0. Many cricothyroidotomy techniques have been criticised because they are not capable of providing effective ventilation [4, 208–213].

Classical emergency surgical tracheostomy involves incision through skin and platysma, division of the isthmus of the thyroid gland, haemostasis, incision of tracheal cartilage, and insertion of a cuffed tracheostomy tube [214]. Emergency tracheostomy can be very difficult and have serious complications [215–217]. A few surgeons may succeed in 3 min [85, 218], but most will take longer [217, 219]. Delay in completion of tracheostomy in this situation results in death of the patient [77, 219–224].

There are a few case reports of successful use of percutaneous tracheostomy techniques in the failed intubation [225–227] and CICV situation [228]. However, percutaneous tracheostomy techniques include a number of steps and can take time.

The anaesthetist must be prepared to use invasive techniques to secure the airway via the cricothyroid membrane. Success depends on understanding the anatomy of the cricothyroid membrane [229–231] and of the

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factors which determine efficacy of ventilation with different airway devices.

Invasive airway devices which are frequently recommended include:
- cuffed tracheal or tracheostomy tubes;
- narrow (4–6 mm ID) uncuffed tubes;
- cannulae.

These must be matched to the ventilation technique in order to provide a system which can deliver a large minute volume. When a cuffed tube is used, a low-pressure ventilation system is satisfactory. When a 4-mm (ID) uncuffed tube is used, successful ventilation is less certain [232–235]. The ‘inflated’ gas may enter the lungs or flow out through the upper airway. Factors which promote entry of gas into the lungs include high resistance in the upper airway, high lung compliance, high flow rate and long inflation time. The limitations of uncuffed tubes in the CICV situation are well summarised by Walls [236]. When a cannula is used, a high-pressure ventilation source is necessary. This system is discussed clearly by Dworkin [237].

All current airway guidelines [5–8,12] recommend management of the CICV situation using:
- cannula cricothyroidotomy with percutaneous transtracheal jet ventilation (TTJV) or;
- surgical cricothyroidotomy.

They remain the standard techniques.

Cannula cricothyroidotomy: Cannula cricothyroidotomy involves the combination of insertion of a cannula through the cricothyroid membrane with high-pressure ventilation. It can provide effective ventilation [4, 209, 238–241], although low success rates have been reported [242]. We recommend use of kink-resistant cannulae because standard intravenous cannulae are easily kinked [243–245]. The technique is summarised in the flow-chart and is described in detail by Nenunof [246] and Stewart [247]. Verification of correct cannula placement by aspiration of air into a large syringe, before the use of high-pressure ventilation, is essential. Subsequent dislodgement of the cannula must be prevented.

A high-pressure source is needed to achieve effective ventilation through a cannula. The oxygen flush systems of most modern anaesthesia machines do not provide sufficient pressure [211, 248, 249] and an adjustable high-pressure device (driven by gas pipeline pressure) with a Luer Lock connection is recommended. Barotrauma [188, 238, 250, 251] is less likely if an initial inflation pressure of less than 4 kPa (55 psi) is used [213, 251, 252]. Some have recommended insertion of a second cannula to facilitate exhalation [185, 186, 253]. However, the driving pressure for exhalation is relatively low and use of a second cannula is not a reliable means of relieving high airway pressure [254, 255]. Initial high-pressure ventilation should be performed particularly cautiously. It is important to keep the upper airway as open as possible and to verify deflation of the lungs and exhalation through the upper airway. If an LMA has been used, it should be kept in place to facilitate exhalation.

Surgical cricothyroidotomy: Surgical (‘stab’) cricothyroidotomy can allow rapid restoration of ventilation and oxygenation in the CICV situation [77, 242, 256–260] and is included in ATLS and military [261] training. Anaesthetic deaths could be prevented by appropriate use of surgical cricothyroidotomy [207]. Emergency cricothyroidotomy can result in serious complications [216, 262], although these are infrequent when staff are well trained [263–267]. The technique uses low-pressure ventilation through a cuffed tube in the trachea.

A simplified cricothyroidotomy technique can be performed in 30 s [268–270]. This 4-step technique consists of:

Step 1 Identification of the cricothyroid membrane.

Step 2 Horizontal stab incision (No. 20 scalpel) through skin and membrane.

Step 3 Caudal traction on the cricoid membrane with a tracheal hook.

Step 4 Intubation of the trachea.

The ATLS cricothyroidotomy technique includes blunt dilation of the incision made in step 2. It is important to avoid endobronchial intubation [271] when a tracheal tube is used.

Cricothyroidotomy is sometimes particularly difficult in the obese patient. Insertion of the tube can be facilitated by passage of an introducer (bougie) through the incision [272] or use of a tracheal retractor [270, 273–277].

Guidewire techniques of cricothyroidotomy have been developed. Some claim that these can restore the airway as quickly as the standard surgical technique [278], while others have found the guidewire technique to take longer [279], and to be less satisfactory, as a consequence of kinking of the wires [280]. It has recently been shown that the technique can be performed in 40 s after practice in a manikin [281]. The Melker™ guidewire intubation set is now available with a cuffed tube. This technique seems promising but further reports are needed before it can be considered a core rescue technique.

Cannula and surgical cricothyroidotomy each have advantages and disadvantages. Cannula cricothyroidotomy involves a smaller incision with less risk of bleeding. It may be the technique of choice when dedicated equipment is immediately available and staff are trained in its use. If it cannot be performed rapidly, is ineffective [242, 245, 258] or causes complications [258, 282], surgical
cricothyroidotomy should be performed immediately [242, 245, 258, 282]. Surgical cricothyroidotomy is more invasive. It can be performed very rapidly and will allow effective ventilation with low-pressure sources.

Invasive airway access is a temporary measure to restore oxygenation. Definitive airway management will follow. This may be a formal tracheostomy, but tracheal intubation will be possible in some patients [257, 283].

**Discussion**

A major impetus for the development of clinical guidelines was the finding of marked variations in medical practice and the belief that guidelines could be used to improve standards [284–286]. Guidelines have much to offer in the management of infrequent, life-threatening situations [287, 288]. In particular, following the resuscitation guidelines improves outcome [12, 289, 290]. There is evidence that use of airway guidelines has improved airway management in France [291].

Unanticipated difficult intubation will continue to occur. A new approach is needed to ensure optimal management of infrequent airway problems. Medicine has lagged behind the military [292–297] and the airline industry [298–300], which use guidelines and regular practice of drills to train staff to deal with infrequent emergencies. Allnutt states that ‘there is no excuse for poorly designed procedures when human life is at risk’ [301].

Tunstall first described a failed intubation drill [148] for use in obstetric anaesthesia. Although of proven value [302, 303], some components such as the lateral position are no longer widely supported [146, 304–306] and new devices such as the LMA™ have changed management [307]. There are now new failed intubation drills in obstetrics [308].

There is a need for definitive national airway guidelines for management of unanticipated difficult intubation in the non-obstetric adult patient [309]. They should be easy to learn and to implement as simple drills [310]. They should include a minimum number of techniques of proven value. They should be based on a practical approach to airway management, using skills which are widely available. The DAS guidelines are designed to fulfil these requirements. Simple, clear and definitive flow-charts have been produced to cover three important clinical scenarios. They do not proscribe the use of other techniques by those experienced in their use, provided oxygenation is maintained and airway trauma is prevented.

The DAS guidelines have been developed by consensus and are based on experience and evidence. The principles applied are maintenance of oxygenation and prevention of trauma. Maintenance of oxygenation is achieved primarily by using the face mask and LMA™. Prevention of trauma is achieved by limiting the number of attempts at intubation and by using the ILMA™ as a dedicated airway to allow oxygenation, while tracheal intubation is achieved under vision with the fibroscope.

Controlled studies cannot be performed in unanticipated difficult intubation. The evidence basis of these guidelines best fits the description of expert committee reports, opinions and experience, and is defined as category IV evidence [311]. The DAS recommendations are therefore officially strength D. All DAS recommendations are supported by at least two case reports or series, the strongest evidence available for infrequent emergency situations.

We hope that implementation of these guidelines will reduce the incidence of airway trauma and hypoxaemic damage associated with unanticipated difficult intubation and result in better outcomes for our patients.

The techniques which have been recommended in these plans should be an integral part of initial and continuing airway training. This can be achieved by acquisition of knowledge in classroom teaching, learning practical skills using manikins in workshops [281], and use in clinical practice, when appropriate [312, 313].

There are equipment implications in these guidelines. All the equipment described should be available for regular practice. A cart containing the equipment should be located no more than a couple of minutes from every location where anaesthesia is administered. Recommended equipment lists will be published on the DAS Web Site (http://www.das.uk.com).

We hope that these guidelines will be tested in a clinical environment [314] and further modifications will certainly follow. We seek constructive suggestions.

*Notes on figures:* Figures 2–4 in this paper contain a considerable amount of detail in order to maximise their value for training. Both these and simpler versions will be available from the DAS Web Site (http://www.das.uk.com) in the future. Others may wish to produce different versions for their own purposes.

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References

55 Calder I. When the endotracheal tube will not pass over the flexible fiberoptic bronchoscope. Anaesthesia 1992; 77: 398.
60 Wilkes AR, Hodzovic I, Latto IP. Comparison of the peak forces that can be exerted by multiple-use and single-use bougies in vitro. British Journal of Anaesthesia 2002; 89: 671.


81 Miller CG. Management of the Difficult Intubation in Closed Malpractice Claims. ASA Newsletter June 2000


92 Ferson DZ, Supkis DE, Rahlfis TF, Jones RL. Evaluation of the intubating laryngeal mask as a primary airway device and a guide for blind endotracheal intubation. Anesthesiology 1997; 87: A485.


99 Cros AM, Colombani S. Preliminary study of intubation with a new laryngeal mask for difficult intubation. Anesthesiology 1997; 87: A482.


Pandit JJ, Maclachlan K, Dravid RM, Popat MT. Comparison of times to achieve tracheal intubation with three techniques using the laryngeal mask or intubating laryngeal mask airway. Anaesthesia 2002; 57: 128–32.


143 Shorten GD. Airway obstruction on cricoid pressure is not glottic. *Anaesthesia and Analgesia* 1994; 78: 1203.


170 Brain A. Esophageal breathing and upper airway obstruction with the ProSeal laryngeal mask. *Anaesthesia and Analgesia* 2002; 94: 1669–70.


240 Patel RG. Percutaneous transtracheal jet ventilation. a safe, quick, and temporary way to provide oxygenation and ventilation when conventional methods are unsuccessful. *Chest* 1999; 116: 1689–94.


