

Overview

Trauma anesthesia is practiced by many, but the specialty of few. Like other areas of medicine, specialization in trauma patients yields experience and insight that contribute to better patient outcomes. This refresher course will present lessons learned about this population over three decades of dedicated practice, and review the scientific evidence which supports today's standard of care and the promising therapies of tomorrow.

Admission and Triage

Pre-hospital and emergency care are important components of anesthesia practice in many parts of the world, including much of Europe. Work force issues and the rise of Emergency Medicine in the past two decades have taken most American anesthesiologists away from the Emergency Department (ED), to the detriment of severely injured patients. Participation of anesthesiologists on the Trauma Team enables early effective airway management, precise resuscitation, comprehensive analgesia and sedation, and rapid access to the operating room (OR). While certification as a "Level One" trauma center by the American College of Surgeons requires the presence of an anesthesiologist in the hospital at all times,¹ the greatest benefit is achieved when this individual is present in the ED at the time of patient admission. The term "The Golden Hour" was coined to emphasize the importance of rapid diagnosis and therapy for trauma patients. While there is nothing magical about the 60 minute mark (the term was originally presented in the lay press, without scientific support) it is clear that the speed of treatment has an important effect on outcome in many conditions caused by trauma, especially airway emergencies, ongoing hemorrhage, and acute neurologic injury. Even when the anesthesiologist can not be physically present in the ED when the patient arrives, understanding the basics of trauma will allow for informed decisions regarding OR access and emergency patient management. Risk to the patient from delay of surgery may be substantial; the frequent need to expedite surgery—without consideration for optimizing chronic medical conditions—is the most important difference between trauma anesthesia and other sub-specialties.

Anesthesiologists caring for trauma patients must be familiar with the tenets of the Advanced Trauma Life Support (ATLS) course of the American College of Surgeons.² This is a basic curriculum that provides a common language and choreography for the first minutes of diagnosis and treatment of the trauma patient. Airway, Breathing, and Circulation make up the "ABCs" of ATLS. Airway patency and adequacy of oxygenation and ventilation are assessed first and then corrected if inadequate, generally by rapid sequence endotracheal intubation (see below). Circulation is assessed by looking for the signs and symptoms of shock: pallor, diaphoresis, alterations in mental status (agitation followed by lethargy), hypotension, tachycardia, and peripheral vasoconstriction. Large bore intravenous access is obtained and blood is sent for laboratory assay (complete blood chemistry, electrolytes, coagulation studies, toxicology) and type and cross-match. "D" is for "Disability" and consists of a primary patient survey noting significant visible injuries, musculoskeletal deformities, and gross motor and sensory function. "E" is for "Exposure:" the patient's clothes are completely removed and a detailed physical examination is conducted, augmented by rapid diagnostic testing with plain radiographs (chest, pelvis, and sometimes lateral cervical spine) and ultrasound (the FAST exam: Focused Assessment by Sonography in Trauma, a rapid search for free intraperitoneal or pericardial fluid or evidence of pneumothorax).³ Assuming the patient is hemodynamically stable, the initial diagnostic work-up is completed with computed tomography (CT) of the head, cervical spine, chest, abdomen, and pelvis--as indicated by the patient's injuries--followed by plain film radiographs of injured extremities and consultation by appropriate surgical sub-specialists.

Therapeutic efforts proceed in parallel with the diagnostic stages of ATLS. Airway management is first, followed by emergent surgery to control exsanguinating hemorrhage. Life-threatening bleeding can occur in any of five compartments: the chest, the abdomen, the retroperitoneum, the thighs, and outside the body.⁴ Bleeding from open wounds is easy to diagnose and is managed by direct pressure and surgical ligation. Bleeding associated with femur fracture is brisk at the time of injury, but will resolve spontaneously through vasoconstriction and tamponade in most otherwise normal patients. Hemodynamically significant bleeding in the chest is detected by the initial radiograph and managed with tube thoracostomy for peripheral injuries and with emergent thoracotomy for central injuries and those with high (>1500 ml) or ongoing (> 100 ml/hr) chest tube output. Abdominal hemorrhage is diagnosed by FAST and unstable patients are taken immediately to the OR. Stable patients or those with a good response to an initial fluid bolus are candidates for CT and then angiographic embolization. Bleeding in the retroperitoneum may be suspected by the presence of an unstable pelvis on physical exam and confirmed by pelvic plain film; quantification of hemorrhage and specific injuries generally requires CT. Treatment of pelvic

hemorrhage is challenging, and usually requires a combination of external compression (by binder or fixator), angiographic embolization, percutaneous screw fixation, and sometimes internal packing.⁵ It is critical at this stage to discriminate between the hypotensive patient who has bled, but is now stopped (e.g. unilateral closed femur fracture), and the one who is continuing to actively bleed (e.g. high grade splenic rupture). The former patient will have a sustained response to fluid administration. The latter patient will have a transient response only, with recurrence of hypotension, and will be very sensitive to even small doses of sedative or analgesic medications.

The anesthesiologist must be aware of the indications for emergency surgery in the trauma patient, when in the diagnostic sequence they are likely to occur, and what patient information is likely to be available. Surgery to open or secure the airway is the most urgent, and is often performed at the bedside in the ED. Exploratory thoracotomy or laparotomy for exsanguinating hemorrhage is the next priority, and often occurs before the diagnostic work-up is complete. Decompressive craniotomy to relieve subdural or epidural hematoma is the next most urgent, typically arising immediately after CT scan in patients with a decreased level of consciousness. Next are surgeries to salvage extremities threatened by vascular injuries or control abdominal contamination; these cases must be accommodated as soon as possible after the diagnostic work-up is complete. Unstable orthopedic injuries are the next priority, with spinal and pelvic stabilization the most urgent, followed by irrigation and debridement of open fractures and intramedullary nail fixation of long-bones. For open fractures the rate of complications (osteomyelitis, non-union) increases linearly with time until operative debridement;⁶ for closed fractures there is less urgency for this reason, but good data to suggest that earlier repair leads to improved pulmonary outcomes (lower incidence of pneumonia and pulmonary embolus).⁷ In general, none of these procedures should be delayed to allow gastric emptying (which will occur slowly, if at all, following injury) or definitive cervical spine clearance (which may require MRI).

Airway Management

Anesthesiologists are the most experienced physicians in the hospital at airway management, and are adept at planning for difficult intubations and dealing with unexpected problems that arise during airway procedures. One advantage of being present at the time of patient arrival is that the anesthesiologist can construct and execute the intubation plan from the outset, rather than being called urgently when a disaster is already underway. Emergent intubation in the trauma patient follows the general pathway of the ASA difficult airway algorithm,⁸ with a few important caveats. First is that the patient must end up with a controlled airway: waking up and returning to spontaneous ventilation will not be possible. Second is the environment: equipment and personnel that are readily available in the OR may be lacking in the ED. Third is the increased risk of aspiration in patients who have not been fasting, and who are assumed to have delayed gastric emptying. Finally is the potential for instability of the cervical spine.

Rapid sequence intubation is the preferred approach in most situations. Use of a paralytic agent risks a “can’t intubate / can’t ventilate” scenario, but is associated with the highest overall rate of successful airway management.⁹ Sufficient personnel must be on hand to 1) provide manual in-line stabilization of the cervical spine throughout the procedure (after removing the front of the cervical collar) 2) provide cricoid pressure (the Sellick maneuver) 3) oxygenate the patient via bag-valve-mask ventilation and then perform the endotracheal intubation, and 4) administer medications and monitor the patient’s vital signs. Direct laryngoscopy during manual in-line stabilization of the cervical spine has been shown to be safe and effective in patients with potentially unstable necks. Cricoid pressure assists the intubator by displacing the larynx posteriorly, and may help to prevent both gastric insufflation during bag-valve-mask ventilation and passive reflux of gastric contents during laryngoscopy. However, both cervical spine injury and aspiration during intubation are relatively low-risk events when compared to the potential risks of hypoxia, and in-line stabilization and cricoid pressure should be relaxed or abandoned if they are interfering with successful intubation.¹⁰

Succinylcholine (1.5 mg/kg) provides the best and fastest muscle relaxation to facilitate intubation, and is the preferred agent in any patient without a specific contraindication to its use (history of malignant hyperthermia, demyelinating neurologic disease prior to injury). Lethal hyperkalemia following succinylcholine administration is a risk in patients with neurologic deficits from spinal cord injury, but not until 24-48 hours following injury.¹¹ High doses of vecuronium (0.2 mg/kg) or rocuronium (1.5 mg/kg) can also be used for rapid sequence intubation with only a slight delay in achieving complete relaxation, although the longer duration of paralysis will necessitate ongoing sedation, and will make subsequent neurologic assessment more difficult.

Anesthetic induction for rapid sequence intubation can be achieved with a number of different agents, but care should be taken when selecting an initial dose. Any induction agent—including otherwise cardiac friendly agents

such as etomidate or ketamine—will cause a dramatic decrease in blood pressure in the hemorrhaging, hypovolemic patient. This is due to inhibition of high circulating catechol levels and to increased sensitivity of the brain to these agents during shock.¹² Our practice is to use one-tenth to one-half of the normal induction dose of sodium thiopental or propofol for most cases, while reserving the more expensive use of etomidate for patients with limited cardiac reserve on the basis of age or underlying disease.

In patients who cannot be preoxygenated or in those at risk for desaturation it is appropriate to provide positive pressure bag-valve-mask ventilation throughout induction. An increased oxygen reservoir in the lung will benefit the patient more than the (theoretical) increased risk of aspiration caused by ventilating through cricoid pressure. Successful endotracheal tube placement is immediately confirmed by capnometry. If unsuccessful, a second direct laryngoscopy should be attempted, incorporating some change in technique (operator, laryngoscope blade, patient position) or—our preference—an intubating stylet. This simple and inexpensive device is of enormous benefit in trauma patients because it is readily available and specifically designed to facilitate blind or limited view intubation in the non-sniffing position during in-line stabilization. If intubation is again unsuccessful the next step should be an airway adjunct to support oxygenation. The esophageal combitube was the first available in the US and is predominantly used in the pre-hospital environment.¹³ The laryngeal mask airway (and assorted variations) is more familiar to anesthesiologists and is thus the rescue device of choice in the ED or OR.¹⁴

Whenever rapid sequence intubation is undertaken the need for an emergent surgical airway is always a possibility, and any anesthesiologist caring for trauma patients should be familiar with how to place one. A recent comprehensive review (in press) demonstrated a first-pass intubation rate of about 90%, a second-pass rate (largely using an intubating stylet) of 90% of the remainder, successful LMA salvage of 90% of the remaining 1%, and the need for a surgical airway in only about 1 in 1,000 patients intubated within 24 hours of admission. This success rate was attributed to institutional preparation, an organized and consistent approach, and experienced providers.

Fluid Resuscitation

Surgical care of trauma patients in the past decade has focused on the concept of “damage control,” defined as limiting initial surgery to that required to stop ongoing hemorrhage, while deferring reconstructive procedures until after the completion of resuscitation.¹⁵ At the core of this approach is the awareness that early and definitive cessation of bleeding is critical to good outcomes. Preservation of normothermia and coagulation function are facilitated by abbreviated surgical procedures, while the fewer blood products the patient receives, the better long term outcomes are likely to be.¹⁶ The typical damage control laparotomy is performed in a hemodynamically unstable patient with a FAST exam positive for free intraperitoneal fluid. The patient is intubated and transported to the OR. A midline abdominal incision is made from the xiphoid to the pubis. Intraperitoneal blood is evacuated and all four quadrants of the abdomen are packed with gauze. Each quadrant is then examined, and any required hemostasis achieved. Injured solid organs are fully or partially resected. Injured bowel is stapled off and removed, without reanastomosis. Injured vessels are ligated if possible. Diffuse hemorrhage is addressed by packing with gauze and the liberal use of topical fibrin sealants, and will be further facilitated in the near future by the use of pro-coagulant dressings now under investigation. The abdomen is covered with a sterile dressing, but not definitively closed, and the patient is transported to angiography (if indicated) or to the intensive care unit. Assuming that subsequent resuscitation is successful the patient will be returned to the OR in 1-2 days for removal of packing, reanastomosis of the bowel, and careful exploration and debridement of all injured tissue. Abdominal closure is typically staged over a series of operations.

Part of the damage control model is the evolving concept of “hemostatic resuscitation.” This consists of the restoration of normal fluid volume and tissue perfusion over the course of care, but with an emphasis on the preservation and support of the coagulation system. Coagulopathy from hemorrhagic shock is caused by a number of different mechanisms (Figure) and is strongly associated with poor outcomes.¹⁷ Components of hemostatic resuscitation include the following:

Permissive hypotension is standard practice in hemorrhaging patients without traumatic brain injury. Numerous animal models of uncontrolled hemorrhagic shock have demonstrated improved outcomes when a lower than normal blood pressure (mean arterial pressure [MAP] of 60-70 mm Hg) is taken as the target for fluid administration during active hemorrhage.¹⁸ Hypotension facilitates *in vivo* coagulation, while the avoidance of bolus doses of crystalloid fluid both preserves normothermia and prevents excessive dilution of red blood cells (RBCs) and clotting factors. Two large human trials of this technique have been conducted, demonstrating the safety of this approach relative to

the conventional target (> 100 mmHg), and suggesting various other benefits including shorter duration of hemorrhage and reduced mortality.^{19,20}

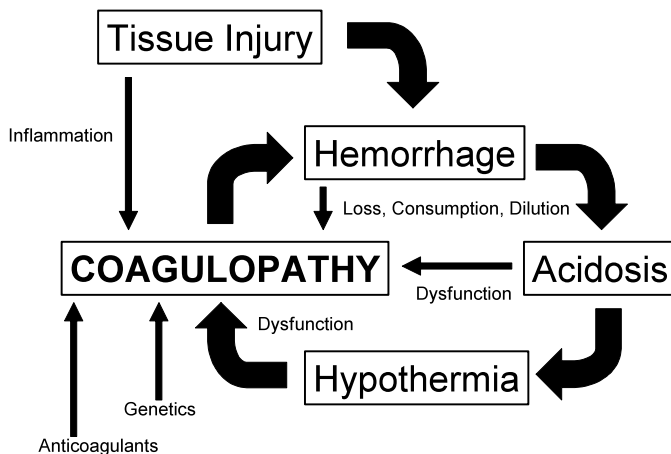


Figure 1. Causes of coagulopathy in trauma patients.

Early transfusion is of critical importance to the actively hemorrhaging patient. Oxygen delivery depends on having adequate quantities of RBCs, and the patient in shock is especially susceptible to tissue ischemia when allowed to become anemic. Busy trauma centers maintain a ready supply of type-O “universal donor” RBC units for immediate transfusion in patients with life-threatening hemorrhage. This practice has been found safe and effective in large numbers of cases.²¹

Early use of plasma and platelets is critical to maintaining clotting capability in the actively bleeding patient. Data recently gathered by the US Army in Iraq supports the anecdotal

experience of busy civilian trauma centers that an early ratio of plasma units to RBC units of 1:1 is optimal for patients requiring massive transfusion.²² Earlier and more aggressive use of plasma was associated with a significant reduction in mortality. Type AB “universal donor” plasma can be kept pre-thawed and immediately available to facilitate this practice, without significant additional expense to the Blood Bank (abstract in press).

Specific pro-coagulant therapy is an emerging option in trauma resuscitation. Fibrin sealant bandages and chitosan and zeolite based agents have been approved for topical use on external hemorrhage, and are under investigation for use during open procedures. Recombinant human clotting factor VIIa (FVIIa) will reverse many forms of acquired coagulopathy and has been used successfully in traumatic hemorrhage on numerous occasions in the past six years.²³ Trials are also underway to establish the role of prothrombin complex concentrates (PCCs) in coagulopathic hemorrhage. Both FVIIa and PCCs share a risk of thrombotic complications (myocardial infarction, stroke, pulmonary embolus) that may limit their use in non-emergent settings.

Hemostatic resuscitation ends when active hemorrhage is definitively controlled. Goals for completion of resuscitation thereafter include normal vital signs and mental status, acceptable laboratory values, and normothermia. Compensatory vasoconstriction, especially in young patients, may allow for normal vital signs despite inadequate fluid volume replacement. This phenomenon, known as the occult hypoperfusion syndrome, is associated with increased organ system failure.²⁴ It is important to look beyond heart rate and blood pressure as endpoints of resuscitation, to more accurate indicators of tissue perfusion such as arterial base deficit, pH, and lactate level. Massively transfused trauma patients that achieve a normal lactate rapidly after initial resuscitation have substantially better outcomes than patients who remain hypoperfused.²⁵

Traumatic Brain Injury

Traumatic brain injury (TBI) is the leading cause of death from trauma.²⁶ Death may occur pre-hospital, due to apnea and loss of airway reflexes, or after resuscitation, due to progressive cerebral edema causing loss of blood flow. Preventive measures such as airbags and motorcycle helmets are effective at reducing the incidence of TBI; once a brain injury has occurred, however, the only available care is supportive. Evacuation of mass-occupying epidural, subdural, or intraparenchymal hematoma is a critical first step, followed by careful medical management to minimize secondary brain injury from intracranial edema and inflammation. Retrospective study has established a strong association between episodes of hypotension and/or hypoxia occurring during resuscitation and worsened outcomes from TBI.²⁷ For this reason the timing of indicated non-cranial surgery is controversial: early repair of a closed femur fracture, for example, may improve pulmonary outcomes but simultaneously expose the patient to a greater risk of hypotension or hypoxia and thus a worse outcome from TBI.²⁸

TBI is stratified by the Glasgow Coma Scale (GCS) score at the time of hospital admission. Mild TBI is a GCS of 14-15; moderate TBI is GCS 9-13; severe TBI is GCS 3-9. Patients with isolated mild TBI are often discharged within 24 hours of admission, although up to 50% will have significant post-concussive symptoms (e.g. headache,

drowsiness, memory loss, emotional lability, visual disturbances). Patients with moderate TBI require close observation in the hospital, as deterioration is a possibility. Patients with severe TBI will require intubation and respiratory support as well as precise and aggressive therapy to minimize the risk of secondary injury.

Following the exclusion (or evacuation) of intracranial hematoma, further care is directed by assessment of intracranial pressure (ICP).²⁹ ICP is measured by placement of an intraventricular catheter or parenchymal pressure monitor. The goal thereafter is to optimize cerebral perfusion (MAP minus ICP). Therapies to lower ICP are applied in a “stairstep” fashion, and include the following:

- *Elevation of the patient’s head.* This simple step allows greater drainage of cerebrospinal fluid (CSF) out of the brain and into the spinal cistern.
- *Sedation and analgesia.* Control of pain and agitation will reduce circulating catechol levels and cerebral metabolism. Muscle relaxation is not indicated outside of specific procedural requirements, because prolonged chemical paralysis may lead to permanent polyneuropathy syndromes.
- *Normothermia.* While therapeutic hypothermia has been proposed as a treatment for severe TBI, the most recent multicenter trial of this therapy did not show a benefit.³⁰ Hyperthermia is clearly detrimental, and should be aggressively treated.
- *Normocapnia.* Hyperventilation dramatically reduces ICP, which is beneficial in the short term when trying to prevent herniation. Unfortunately, the therapy works by reducing cerebral blood flow, meaning that it may actually exacerbate regional ischemia.
- *Normotension.* Maintenance of adequate MAP is critical, especially in the face of other therapies to lower ICP. It is not unusual for patients with severe TBI to require central pressure monitoring and the aggressive use of inotropes and vasopressors to maintain adequate perfusion. There is some thought, as yet unvalidated, that a supranormal blood pressure (i.e. the “MAP push” to 90 mmHg) may improve outcomes in severe TBI.³¹
- *Osmotic diuresis.* Intermittent bolus therapy with mannitol or hypertonic saline (titrated to a serum osmolality of about 320) will reduce ICP and may improve outcomes from TBI. It is unclear if the benefit is due to reduction of edema volume directly or to scavenging of free radicals and other inflammatory mediators.
- *Drainage of CSF.* This therapy requires placement of an intraventricular catheter, which may be problematic if swelling is severe. A closed system is used which allows for continuous drainage of CSF at a set pressure.
- *Induced coma.* Barbiturates or propofol may be administered to achieve a deep level of brain anesthesia (burst suppression on EEG). This reduces the cerebral metabolic rate and thus the demand for oxygen in ischemic tissue. Hemodynamic consequences may be severe. Continuous propofol infusion in this setting has been associated with fatal rhabdomyolysis in young TBI patients.³²
- *Decompressive craniotomy.* Once out of favor, resection of the skull to allow for brain swelling is now thought to be beneficial in selected patients.³³ Improved intensive care has made this possible, although further research will be necessary to establish optimal patient selection and timing of surgery.

Therapies not beneficial in TBI include steroids and any number of “silver bullet” anti-inflammatory pharmaceuticals (although the search goes on). While secondary brain injury is an inflammatory disease, the ideal balance of factors in a given patient is impossible to determine. New monitoring systems for TBI which incorporate tissue oxygen tension with microdialysis assay of lactate and other factors may eventually guide anti-inflammatory therapy. Management of the severe TBI patient in the OR should be a continuation of management in the ICU. Head elevation and continuous assessment of ICP should be continued throughout the case, with special emphasis on avoidance of hypotension or hypoxia. It is appropriate to clamp off CSF drainage during patient transport and surgical positioning, but this therapy should be re-established once the patient is settled in the OR.

Spinal Cord Injury

Few injuries are as devastating to the patient as a complete spinal cord injury, largely because there are very few therapies available. Hemodynamic and respiratory support should be provided as needed, and surgical fixation should be expedited for any patient with an unstable spinal column. High dose steroid therapy is thought to provide a marginal benefit (with substantial long-term complications).³⁴ Very few patients presenting to the trauma center with a complete level will recover function. Despite recent anecdotes, deliberate hypothermia to treat SCI is still an investigational therapy only, and is complicated by shivering, coagulopathy, and increased risk for infection.

Patients with complete or near-complete deficits at the cervical level will suffer significant respiratory impairment.³⁵ Even young athletes will become hypoxic over time due to loss of accessory muscle function, prolonged supine positioning, and the inability to cough. Early intubation under semi-elective conditions is recommended, allowing

an awake technique using a fiberoptic bronchoscope and minimal motion of the spine. Failure to perform this procedure electively will necessitate an emergent procedure a few hours later, with greater risk to the patient. A plan for early intubation is especially important if the patient will require magnetic resonance imaging (MRI) for diagnostic purposes.

Conclusion

Trauma anesthesiology is a uniquely exciting specialty, offering great variety in patient pathology, presentation, and surgical requirements. Accumulating scientific evidence is changing many traditional practices, including the risk/benefit assessment of rapid sequence intubation, the value of aggressive fluid therapy for patients in hemorrhagic shock, and the role of hyperventilation in TBI. In the coming years we will see a growing role for noninvasive diagnostic technologies, increased control over blood composition and function, and patient-specific application of anti-inflammatory therapies. Specialty knowledge of trauma anesthesiology is important for practitioners now, and will remain so for years to come.

References

1. Resources for optimal care of the injured patient: 1998. American College of Surgeons, 1998
2. Advanced Trauma Life Support Program for Doctors. American College of Surgeons, 1997
3. Rozycki GS: Abdominal ultrasonography in trauma. *Surg Clin North Am* 75: 175-91, 1995
4. Scalea TM, Henry SM: Problems in Anesthesia 13:271-278, 2001
5. Scalea TM, Burgess AR: in *Trauma*, 4th ed. New York: McGraw-Hill, 2000, 817-8
6. Bednar DA: *J Orthop Trauma* 7:532, 1993
7. Dunham CM, Bosse MJ, Clancy TV, et al: *J Trauma* 50: 958-967, 2001
8. Wilson WC et al. "Definitive airway management" in *Trauma*, vol 1. Informa Healthcare 2007: pp 155-196
9. Talucci RC, Shaikh KA, Schwab CW: *Am-Surg* 54:185-187, 1988
10. Dutton RP, McCunn M: "Anesthesia for trauma" in *Miller's Anesthesia* (6th edition) 2005: 2451-2495
11. Gronert GA, Theye RA: *Anesthesiology* 43: 89, 1975
12. Johnson KB, Egan TD, Kern SE, McJames SW, Cluff ML, Pace NL. *Anesthesiology*. 101:647-59, 2004
13. Frass M: in: *Airway Management: Principles and Practice*. St. Louis: Mosby; 1996: 444-451
14. Ferson D: in *Refresher Courses in Anesthesiology*. American Society of Anesthesiologists, 2000: 47-56
15. Rotondo MF, Schwab CW, McGonigal MD, et al.: *J Trauma* 35:375-382, 1993
16. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. *J Trauma*. 54:898-905, 2003
17. Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. *J Trauma* 42:857-61, 1997
18. Shoemaker WC, Peitzman AB, Bellamy R, et al: *Crit Care Med* 24: S12-S23, 1996
19. Bickell WH, Wall MJ, Pepe PE, et al: *N Engl J Med* 331: 1105-1109, 1994
20. Dutton RP, Mackenzie CF, Scalea TM. *J Trauma* 52: 1141-1146, 2002
21. Dutton RP, Shih D, Edelman BB, Hess JR, Scalea TM. *J Trauma* 59: 1445-1449, 2005
22. Tieu BH, Holcomb JB, Schreiber MA. *World J Surg* 31:1055-65, 2007
23. Dutton RP, Stein DM. *Injury, Int. J Care Injured* 37:1172-1177, 2006
24. Blow O, Magliore L, Claridge JA et al: *J Trauma* 47: 964-9, 1999
25. Abramson D, Scalea TM, Hitchcock et al: *J Trauma* 35:584-8, 1993
26. Thurman D, Alverson C, Dunn K et al: *J Head Trauma Rehabil* 14: 602-615, 1999
27. Chestnut RM, Marshall LF, Klauber MR, et al: *J Trauma* 134: 216 -222, 1993
28. Kalb DC, Ney AL, Rodriguez JL, et al: *Surgery* 124: 739-744, 1998
29. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 17: 451- 627, 2000
30. Clifton GL, Emmy RM, Choi SC, et al: *N Engl J Med* 344: 556 - 563, 2001
31. Malhotra AK, Schweitzer JB, Fox JL, Fabian TC, Proctor KG. *Neurotrauma* 20:827-39, 2003
32. Cremer OL, Moons KG, Bouman EA, Kruijswijk JE, de Smet AM, Kalkman CJ. *Lancet* 357:117-8, 2001
33. Soukiasian HJ, Hui T, Avital I, Eby J, et al: *Surg* 68: 1066-71, 2002
34. Short DJ, El Masry WS, Jones PW: *Spinal Cord* 38: 173-286, 2000
35. Como JJ, Sutton ERH, McCunn M, Dutton RP, et al. *J Trauma* 59: 912-916, 2005