Review

Year in review 2008: *Critical Care* - trauma

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Abstract

Eleven papers on trauma published in *Critical Care* during 2008 addressed traumatic brain injury (TBI), burns, diagnostic concerns and immunosuppression. In regard to TBI, preliminary results indicate the utility of either magnetic resonance imaging (MRI) or ultrasound in measuring optic nerve sheath diameter to identify elevated intracranial pressure (ICP) as well as the potential benefit of thiopental for refractory ICP. Another investigation demonstrated that early extubation of TBI patients whose Glasgow Coma Scale score was 8 or less did not result in additional incidence of nosocomial pneumonia. Another study indicated that strict glucose control resulted in worse outcomes during the first week after TBI, but improved outcomes after the second week. Another paper showed the prolonged neuroprotective advantages of progesterone administration in TBI patients. There was also guidance on improved classifications of renal complications in burn patients. Another study found that patients with inhalation injuries and increased interleukin-6 (IL-6) and IL-10 and decreased IL-7 had increased mortality rates. One literature review described the disadvantages of prolonged immobilization or additional use of MRI for ruling out cervical spine injuries in obtunded TBI patients already cleared by computerized tomography scans. Other investigators found that higher N-terminal pro B-type natriuretic peptide (NT-proBNP) levels may be useful markers for post-traumatic cardiac impairment. Finally, an experimental model showed that both splenic apoptosis and lymphocytopenia may occur shortly after severe hemorrhage, thus increasing the threat of immunosuppression in those with severe blood loss.

Introduction

During 2008, *Critical Care* published a number of papers in regard to injured patients. Several of these articles focused on identification and treatment strategies for traumatic brain injury (TBI) and increased intracranial pressure (ICP). Another examined acute renal injury in burn patients, and one described a novel method of assessing serum markers of burn severity. Finally, there were several articles applicable to the multiple-injury patients, including those articles that examined the potential adverse effects of prolonged cervical immobilization or the practice of adding magnetic resonance imaging (MRI) to computerized tomography (CT) scans in ruling out cervical spine injuries. Another article demonstrated the utility of obtaining N-terminal pro B-type natriuretic peptide (NT-proBNP) in identifying multiple organ dysfunction syndrome and decreased cardiac index in multiple-injury patients. The final paper was an experimental investigation that demonstrated two of the potential mechanisms for post-traumatic immunosuppression.

Traumatic brain injury

One of the challenges in treating patients with TBI is the identification of increased ICP. Increased ICP is known to affect outcomes [1] but often requires invasive catheters to determine its presence and monitor its course. One non-invasive modality that has been examined is the use of ultrasound to detect changes in the optic nerve sheath diameter (ONSD). Many of the research studies evaluating the use of ONSD in elevated ICP have used indirect methods to confirm elevated ICP, including CT findings and transcranial Doppler [2-6]. In their 2008 *Critical Care* article in regard to this subject, Soldatos and colleagues [7] used an intraparenchymal catheter to directly measure ICP and found that an ONSD of 5.7 mm was the optimal cutoff value for detecting an ICP of greater than 20 (sensitivity and specificity of 74.1% and 100%, respectively) and that ultrasound measurement of ONSD correlated well with invasive and noninvasive measurements of ICP. These results are similar to those of Geeraerts and colleagues [8] and Kimberley and colleagues [9], suggesting that an ONSD of between 5 and 5.8 can reliably detect elevated ICP, depending on what sensitivity and specificity are desired. While ultrasound is a commonly available and easily performed test, many patients with head injury or other causes of increased ICP may also undergo an MRI. Using MRI, Geeraerts and colleagues [10] performed a study in which they measured ONSD to determine how well it

CT = computerized tomography; GCS = Glasgow Coma Scale; ICP = intracranial pressure; ICU = intensive care unit; IL = interleukin; MODS = Multiple Organ Dysfunction Score; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro B-type natriuretic peptide; ONSD = optic nerve sheath diameter; TBI = traumatic brain injury.

correlates with ICP and found similar results; a diameter of 5.82 mm is the optimal diameter for predicting the presence of elevated ICP.

Patients with TBI and an elevated ICP that is refractory to all other medical and surgical treatment modalities may very well benefit from high-dose barbiturate therapy, although this practice remains controversial in some centers given its associated high morbidity [11]. However, few data comparing different barbiturate regimens exist. In another 2008 trauma paper in *Critical Care*, Pérez-Bárcena and colleagues [12] randomly assigned 44 patients with TBI and refractory intracranial hypertension to receive high-dose thiopental or high-dose pentobarbital drips. The authors showed better ICP control with thiopental (odds ratio = 5.1, confidence interval = 1.2 to 21.9; $P = 0.027$). Though encouraging, this trial involved a small patient cohort with an unblinded study design. In addition, there were more patients with brain swelling on the initial CT scan in the pentobarbital group, so these preliminary results must be interpreted with caution.

Current practice management guidelines dictate the need for airway protection in patients with TBI and a Glasgow Coma Scale (GCS) score of 8 or less for respiratory protection and prevention of aspiration into the lungs [13]. It has been suggested, however, that prolonged endotracheal intubation leads to increased risk of pneumonia as well as longer intensive care unit (ICU) and overall hospital stays [14]. The 2008 study by Manno and colleagues [15] in *Critical Care* begins to address this issue. They randomly assigned 16 patients to an early extubation arm versus a delayed extubation arm. Although the study was designed to assess study feasibility and to determine the necessary sample size for a higher powered study, it did show that none of the patients in the early extubation arm developed nosocomial pneumonia compared with 37% in the delayed extubation arm. Although the study was underpowered for significant statistical analysis, this very impressive trend was compelling and the concept should be examined further [15].

Prevention of secondary injury is perhaps the most important goal in the critical care of those with TBI. The recent critical care literature has demonstrated significant debate concerning the optimal range and method of glycemic control in many critical illnesses [16-18]. It remains to be seen, however, how strict the glycemic control needs to be in severe TBI. Several recent studies have suggested that hypoglycemic episodes lead to metabolic derangement with lactate production and secondary brain injury [19-23]. A study from Zurich, Switzerland, by Meier and colleagues [24] published in 2008 in *Critical Care* showed that there appears to be a temporal relationship between glucose control and benefit. In their investigation, they compared a strict glucose control regimen maintaining a blood glucose of between 3.5 and 6.5 mmol/L (63 and 117 mg/dL) with a regimen maintaining a blood glucose of between 5 and 8 mmol/L (90 and 144 mg/dL). The lower glucose range was associated with a trend toward increased mortality during the first two weeks. The tight control was also associated with markedly increased insulin and norepinephrine requirements, increased frequencies of hyperglycemic and hypoglycemic episodes, and significantly elevated ICP during the first week after admission. In contrast, during the second week, maintaining patients in the lower glucose range resulted in lower ICP and reduced rates of pneumonia, bacteremia, and urinary tract infections when compared with the group in the higher glucose range. Based on these results, future research efforts should take into account these temporal factors. Lastly, with regard to TBI, progesterone has been shown to have neuroprotective benefits in several different animal models of injury [25-27]. More recently, it was shown to have improved mortality and, in patients with moderate brain injury, better outcomes than those receiving placebo for up to 30 days after injury in humans with TBI [28]. In the first issue of *Critical Care* for 2008, Xiao and colleagues [29] report the results of a related investigation, in which they followed outcomes for up to 6 months to determine whether the benefit was persistent. They found that, at both 3 and 6 months, patients who received progesterone had outcomes that were more favorable as measured by the GCS and the modified functional independence measure. More importantly, progesterone was associated with decreased mortality at 6 months. Along with existing experimental and preliminary clinical data, the results of this article indicate that hormonal intervention in the injured patient may now hold future therapeutic promise.

Burns

Two papers last year in *Critical Care* focused on burn care. Acute renal failure is a relatively uncommon occurrence in burn patients, but it carries a high mortality [30]. It also has been a difficult area to study, due to the variability in nomenclature and definitions used to describe kidney injury in the existing literature. In addition, many of the previous studies have been retrospective, using inconsistent data collection methods and reproducible definitions for variables, outcome measures, and reporting templates. In a 2008 *Critical Care* article, Steinvall and colleagues [31] used a classification system developed by the Acute Dialysis Quality Initiative Group to prospectively describe the incidence and mortality of acute renal injury. Their study involved a cohort of patients with at least 20% total body surface area burns who were admitted to a national burn center. Using the consensus-based approach and its prospective definitions, the authors found that 24% of their cohort developed some significant degree of acute kidney injury, with 5% developing a reproducible criterion for acute renal failure. Overall mortality for patients with the proscribed degree of kidney injury was 14% and, as expected, increased with severity of kidney injury: up to 83% in patients with kidney failure as defined by the classification system. This article adds to the knowledge base of the incidence and associated factors related to kidney disease in burn patients and also provides guidance for future studies.

As in the case of renal failure, inhalational injury is a harbinger of increased mortality in burn patients [32]. Despite the development of a number of potential scoring systems aimed at quantifying the potentiating effect of inhalation injury and dermal injury, none of those approaches has been altogether successful in terms of accurately predicting mortality [33]. However, Finnerty and colleagues [34] have shown that children with burn injury have a marked alteration in inflammatory cytokines when compared with healthy children. Therefore, in a follow-up study published last year in *Critical Care*, the same group, Gauglitz and colleagues [35], showed that patients with elevated interleukin-6 (IL-6) and IL-10 and decreased IL-7 serum levels upon admission had a significantly greater risk for mortality. This finding provides one potential tool for critical care providers to better predict those burn patients who would be at greater risk for mortality earlier in the course of care.

Diagnostic issues

A basic tenet of current trauma care practice is that the cervical spine remains vulnerable to further injury in patients who have received significant blunt force trauma to neck and who may have underlying unstable cervical spine injuries. In an analysis of over 34,000 patients with major trauma, Goldberg and colleagues [36] identified cervical spine injuries in 2.4% of cases. Approximately 70% of those cervical spine injuries were clinically significant insults [36]. This rate of cervical spine injury may be as high as 34% in the subpopulation of patients with severe blunt trauma who require ICU admission [37]. Although there are good data and resulting established criteria for ruling out a significant cervical spine injury in patients with normal mentation [38], there is still some debate with regard to the removal of cervical spine immobilization in those who remain comatose. Many sources recommend a CT scan of the cervical spine [39], but others have recommended that, in patients with a CT that indicates no cervical injury, an MRI may be necessary to detect injuries that may be missed by standard CT [40,41]. At the same time, others question some of the risks associated with getting an MRI or whether prolonged cervical immobilization outweighs the risks of missed injury. In another 2008 *Critical Care* trauma paper, Dunham and colleagues [42] conducted a review to begin the process of answering these questions. The researchers concluded that the risks of secondary brain injury from cervical immobilization or an MRI (largely due to consequences of protracted supine positioning) are much greater than the risk of cervical spine instability [42]. They specifically found that the risk for spinal instability in comatose or obtunded patients with unremarkable bony imaging was 2.5%. This was compared with a 26% increased rate of ICU complications with prolonged cervical collar use and a 27.8% incidence of increasing ICP from less than 15 mm Hg to greater than 20 mm Hg. This complication presumably occurs by virtue of the supine patient positioning (versus some degree of head elevation) that is used to maintain cervical spine precautions. In addition, neurosurgical ICU patients transported to radiology had a greater number of secondary brain injury events compared with those undergoing studies within the unit. The MRI patients, for example, had significant ICP increases during out-of-ICU transportation. With regard to leaving the protective confines of the surgical ICU, 51% of brain-injured patients transported out of the unit developed complications such as hypoxia, hypotension, and increased ICP. With respect to the positioning required for MRI, Dunham and colleagues [42] noted not only that the flat position likely increases ICP but also that the head 'down' position significantly increases the risks of aspiration and ventilator-associated pneumonia. They suggest that, in some comatose or obtunded patients with a negative CT scan and no apparent spinal deficit, early collar removal is a safe and reasonable strategy.

Early post-traumatic mortality is determined by the initial traumatic impact and early resuscitation, whereas late mortality is usually associated with the development of septic inflammatory response syndrome and progresses to multiple organ dysfunction syndrome and death. This pathophysiological pathway is thought to be responsible for up to 80% of trauma deaths in the ICU [43]. Cardiac function has been described as having particular relevance to multiple organ failure, but the traditional methods of assessment, such as pulmonary artery catheterization or echocardiography, either are invasive or may not be readily available in an ICU. Therefore, Kirchhoff and colleagues [44] performed a cohort study in which they compared serum NT-proBNP levels in patients with minor signs of organ dysfunction, specifically those with a Marshall Multiple Organ Dysfunction Score (MODS) of 4 or less, with those with major signs of organ dysfunction, namely a MODS of greater than 4. The researchers found that, at admission, both groups had slightly elevated NT-proBNP but that, at 24, 48, and 72 hours after admission, the patients with the higher MODS had significantly higher levels than those with the lower MODS. They also showed that NT-proBNP levels correlated with decreased cardiac index, thus suggesting that NT-proBNP measurement may serve as a useful marker for post-traumatic cardiac impairment.

Post-traumatic immunocompromise

Hemorrhagic shock states are known to produce a variety of immunosuppressive effects that can lead to increased susceptibility to infections and post-traumatic complications like multiple organ dysfunction syndrome, multiple organ failure, or adult respiratory distress syndrome [45-48]. While the exact mechanisms of post-traumatic immunocompromise still are not well understood, several studies have suggested that functional and immunological alterations in the spleen may play a major role [49-51]. In an experimental design developed by Hostmann and colleagues [52], a murine model of resuscitated hemorrhagic shock was used to detect apoptosis in the spleen as a marker of cellular injury and

reduced immune functions. The authors showed a distinct lymphocytopenia immediately after severe hemorrhage that did return to baseline within the subsequent 72 hours. They also showed a rapid activation of splenic apoptosis in a biphasic onset, both immediately after the hemorrhage and 72 hours after the bleeding was induced. This article thus demonstrated two of the potential mechanisms for post-traumatic immunosuppression and provides us with important hypothesis-generating clues for future interventions.

Conclusions

The 2008 volume of *Critical Care* contained several articles related to the care of injured patients. Proper care of patients with TBI is necessary to prevent secondary brain injury. New therapeutic interventions may be on the horizon. Consistent approaches to the identification of renal injury and inhalational trauma in patients with thermal injury may improve future research and care. Reports from that volume also suggest that the CT scan is an adequate method of identifying unstable cervical spine injuries in comatose or obtunded trauma patients and that prolonged immobilization or MRI studies may actually cause adverse outcomes. It was also shown that NT-proBNP may be helpful in identifying post-traumatic cardiac impairment and that the response of the splenic and lymphocytic systems to massive hemorrhage may provide clues to the pathophysiology (and future interventions) in post-traumatic immunocompromise.

Competing interests

The authors declare that they have no competing interests.

References

1. Marmarou A, Anderson RL, Ward J, Choi DW: **Impact of ICP instability and hypotension on outcome in patients with severe head trauma.** *J Neurosurg* 1991, **75:**S59-S66.
2. Blaivas M, Theodoro D, Sierzenski PR: **Elevated intracranial pressure detected by bedside emergency ultrasonography of the optic nerve sheath.** *Acad Emerg Med* 2003, **10:**376-381.
3. Girisgin AS, Kalkan E, Kocak S, Cander B, Gul M, Semiz M: **The role of optic nerve ultrasonography in the diagnosis of elevated intracranial pressure.** *Emerg Med J* 2007, **24:**251-254.
4. Tayal VS NM, Norton HJ, Foster T, Saunders T, Blaivas M: **Emergency department sonographic measurement of optic nerve sheath diameter to detect findings of increased intracranial pressure in adult head injury patients.** *Ann Emerg Med* 2007, **49:**508-514.
5. Karakitsos D, Soldatos T, Gouliamos A, Armaganidis A, Poularas J, Kalogeromitros A, Boletis J, Kostakis A, Karabinis A: **Transorbital sonographic monitoring of optic nerve diameter in patients with severe brain injury.** *Transplant Proc* 2006, **38:** 3700-3706.
6. Goel RS, Goyal NK, Dharap SB, Kumar M, Gore MA: **Utility of optic nerve ultrasonography in head injury.** *Injury* 2008, **39:** 519-524.
7. Soldatos T KD, Chatzimichail K, Papathanasiou M: **Optic nerve sonography in the diagnostic evaluation of adult brain.** *Crit Care* 2008, **12:**R67.
8. Geeraerts T, Launey Y, Martin L, Pottecher J, Vigue B, Duranteau J, Benhamou D: **Ultrasonography of the optic nerve sheath may be useful for detecting raised intracranial pressure after severe brain injury.** *Intensive Care Med* 2007, **33:**1704-1711.
9. Kimberly HH, Shah S, Marill K, Noble V: **Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure.** *Acad Emerg Med* 2008, **15:**201-204.
10. Geeraerts T, Newcombe V, Coles J, Abate M, Perkes I, Hutchinson P, Outtrim J, Chatfield D, Menon D: **Use of T2-weighted magnetic resonance imaging of the optic nerve sheath to detect raised intracranial pressure.** *Crit Care* 2008, **12:**R114.
11. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW: **Guidelines for the management of severe traumatic brain injury. XI. Anesthetics, analgesics, and sedatives.** *J Neurotrauma* 2007, **24 Suppl 1:**S71-76.
12. Pérez-Bárcena J, Llompart-Pou J, Homar J, Abadal J, Raurich J, Frontera G, Brell M, Ibáñez J, Ibáñez J: **Pentobarbital versus thiopental in the treatment of refractory intracranial hypertension in patients with traumatic brain injury: a randomized controlled trial.** *Crit Care* 2008, **12:**R112.
13. Marik PE, Varon J, Trask T: **Management of head trauma.** *Chest* 2002, **122:**699-711.
14. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD: **Implications of extubation delay in brain-injured patients meeting standard weaning criteria.** *Am J Respir Crit Care Med* 2000, **161:**1530-1536.
15. Manno EM, Rabinstein AA, Wijdicks EF, Brown AW, Freeman WD, Lee VH, Weigand SD, Keegan MT, Brown DR, Whalen FX, Roy TK, Hubmayr RD: **A prospective trial of elective extubation in brain injured patients meeting extubation criteria for ventilatory support: a feasibility study.** *Crit Care* 2008, **12:**R138.
16. Van Beek JG, Mushkudiani NA, Steyerberg EW, Butcher I, McHugh GS, Lu J, Marmarou A, Murray GD, Maas AI: **Prognostic value of admission laboratory parameters in traumatic brain injury: results from the IMPACT study.** *J Neurotrauma* 2007, **24:**315-328.
17. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A: **The impact of hyperglycemia on patients with severe brain injury.** *J Trauma* 2005, **58:**47-50.
18. Gale SC, Sicoutris C, Reilly PM, Schwab CW, Gracias VH: **Poor glycemic control is associated with increased mortality in critically ill trauma patients.** *Am Surg* 2007, **73:**454-460.
19. Vespa PM, McArthur D, O'Phelan K, Glenn T, Etchepare M, Kelly D, Bergsneider M, Martin NA, Hovda DA: **Persistently low extracellular glucose correlates with poor outcome 6 months after human traumatic brain injury despite a lack of increased lactate: a microdialysis study.** *J Cereb Blood Flow Metab* 2003, **23:**865-877.
20. Strong AJ, Smith SE, Whittington DJ, Meldrum BS, Parsons AA, Krupinski J, Hunter AJ, Patel S, Robertson C: **Factors influencing the frequency of fluorescence transients as markers of peri-infarct depolarizations in focal cerebral ischemia.** *Stroke* 2000, **31:**214-222.
21. Hopwood SE, Parkin MC, Bezzina EL, Boutelle MG, Strong AJ: **Transient changes in cortical glucose and lactate levels associated with peri-infarct depolarisations, studied with rapid-sampling microdialysis.** *J Cereb Blood Flow Metab* 2005, **25:** 391-401.
22. Strong AJ, Hartings JA, Dreier JP: **Cortical spreading depression: an adverse but treatable factor in intensive care?** *Curr Opin Crit Care* 2007, **13:**126-133.
23. McMullin J, Brozek J, McDonald E, Clarke F, Jaeschke R, Heels-Ansdell D, Leppert R, Foss A, Cook D: **Lowering of glucose in critical care: a randomized pilot trial.** *J Crit Care* 2007, **22:**112-118; discussion 118-119.
24. Meier R, Béchir M, Ludwig S, Sommerfeld J, Keel M, Steiger P, Stocker R, Stover J: **Differential temporal profile of lowered blood glucose levels (3.5 to 6.5 mmol/l versus 5 to 8 mmol/l) in patients with severe traumatic brain injury.** *Crit Care* 2008, **12:**R98.
25. Djebaili M, Guo Q, Pettus EH, Hoffman SW, Stein DG: **The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis, and functional deficits after traumatic brain injury in rats.** *J Neurotrauma* 2005, **22:**106-118.
26. Roof RL, Duvdevani R, Stein DG: **Gender influences outcome of brain injury: progesterone plays a protective role.** *Brain Res* 1993, **607:**333-336.
27. Roof RL, Hall ED: **Gender differences in acute CNS trauma and stroke: neuroprotective effects of estrogen and progesterone.** *J Neurotrauma* 2000, **17:**367-388.

28. Wright DW, Kellermann AL, Hertzberg VS, Clark PL, Frankel M, Goldstein FC, Salomone JP, Dent LL, Harris OA, Ander DS, Lowery DW, Patel MM, Denson DD, Gordon AB, Wald MM, Gupta S, Hoffman SW, Stein DG: **ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury.** *Ann Emerg Med* 2007, **49:**391-402, 402.e1-2.
29. Xiao G, Wei J, Yan W, Wang W, Lu Z: **Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial.** *Crit Care* 2008, **12:**R61.
30. Mustonen KM, Vuola J: **Acute renal failure in intensive care burn patients (ARF in burn patients).** *J Burn Care Res* 2008, **29:**227-237.
31. Steinvall I, Bak Z, Sjoberg F: **Acute kidney injury is common, parallels organ dysfunction or failure, and carries appreciable mortality in patients with major burns: a prospective exploratory cohort study.** *Crit Care* 2008, **12:**R124.
32. Miller SF, Bessey P, Lentz CW, Jeng JC, Schurr M, Browning S, Committee AN: **National burn repository 2007 report: a synopsis of the 2007 call for data.** *J Burn Care Res* 2008, **29:**862-870; discussion 871.
33. Smith DL, Cairns BA, Ramadan F, Dalston JS, Fakhry SM, Rutledge R, Meyer AA, Peterson HD: **Effect of inhalation injury, burn size, and age on mortality: a study of 1447 consecutive burn patients.** *J Trauma* 1994, **37:**655-659.
34. Finnerty CC, Herndon DN, Przkora R, Pereira CT, Oliveira HM, Queiroz DM, Rocha AM, Jeschke MG: **Cytokine expression profile over time in severely burned pediatric patients.** *Shock* 2006, **26:**13-19.
35. Gauglitz G, Finnerty C, Herndon D, Mlcak R, Jeschke M: **Are serum cytokines early predictors for the outcome of burn patients with inhalation injuries who do not survive?** *Crit Care* 2008, **12:**R81.
36. Goldberg W, Mueller C, Panacek E, Tigges S, Hoffman JR, Mower WR, Group N: **Distribution and patterns of blunt traumatic cervical spine injury.** *Ann Emerg Med* 2001, **38:**17-21.
37. Berne JD, Velmahos GC, El-Tawil Q, Demetriades D, Asensio JA, Murray JA, Cornwell EE, Belzberg H, Berne TV: **Value of complete cervical helical computed tomographic scanning in identifying cervical spine injury in the unevaluable blunt trauma patient with multiple injuries: a prospective study.** *J Trauma* 1999, **47:**896-902; discussion 902-893.
38. Hoffman JR, Mower WR, Wolfson AB, Todd KH, Zucker MI: **Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. National Emergency X-Radiography Utilization Study Group.** *N Engl J Med* 2000, **343:**94-99.
39. Brohi K, Healy M, Fotheringham T, Chan O, Aylwin C, Whitley S, Walsh M: **Helical computed tomographic scanning for the evaluation of the cervical spine in the unconscious, intubated trauma patient.** *J Trauma* 2005, **58:**897-901.
40. Muchow RD, Resnick DK, Abdel MP, Munoz A, Anderson PA: **Magnetic resonance imaging (MRI) in the clearance of the cervical spine in blunt trauma: a meta-analysis.** *J Trauma* 2008, **64:**179-189.
41. Sliker CW, Mirvis SE, Shanmuganathan K: **Assessing cervical spine stability in obtunded blunt trauma patients: review of medical literature.** *Radiology* 2005, **234:**733-739.
42. Dunham CM, Brocker B, Collier BD, Gemmel D: **Risks associated with magnetic resonance imaging and cervical collar in comatose, blunt trauma patients with negative comprehensive cervical spine computed tomography and no apparent spinal deficit.** *Crit Care* 2008, **12:**R89.
43. Maier B, Lefering R, Lehnert M, Laurer HL, Steudel WI, Neugebauer EA, Marzi I: **Early versus late onset of multiple organ failure is associated with differing patterns of plasma cytokine biomarker expression and outcome after severe trauma.** *Shock* 2007, **28:**668-674.
44. Kirchhoff C, Leidel B, Kirchhoff S, Braunstein V, Bogner V, Kreimeier U, Mutschler W, Biberthaler P: **Analysis of N-terminal pro-B-type natriuretic peptide and cardiac index in multiple injured patients: a prospective cohort study.** *Crit Care* 2008, **12:**R118.
45. Chaudry IH, Ayala A: **Mechanism of increased susceptibility to infection following hemorrhage.** *Am J Surg* 1993, **165(2A Suppl):** 59S-67S.
46. Stephan RN, Kupper TS, Geha AS, Baue AE, Chaudry IH: **Hemorrhage without tissue trauma produces immunosuppression and enhances susceptibility to sepsis.** *Arch Surg* 1987, **122:** 62-68.
47. Livingston DH, Malangoni MA: **An experimental study of susceptibility to infection after hemorrhagic shock.** *Surg Gynecol Obstet* 1989, **168:**138-142.
48. Carrico CJ, Meakins JL, Marshall JC, Fry D, Maier RV: **Multiple-organ-failure syndrome.** *Arch Surg* 1986, **121:**196-208.
49. Kawasaki T, Fujimi S, Lederer JA, Hubbard WJ, Choudhry MA, Schwacha MG, Bland KI, Chaudry IH: **Trauma-hemorrhage induces depressed splenic dendritic cell functions in mice.** *J Immunol* 2006, **177:**4514-4520.
50. Kawasaki T, Choudhry MA, Schwacha MG, Bland KI, Chaudry IH: **Lidocaine depresses splenocyte immune functions following trauma-hemorrhage in mice.** *Am J Physiol Cell Physiol* 2006, **291:**C1049-1055.
51. Meldrum DR, Ayala A, Perrin MM, Ertel W, Chaudry IH: **Diltiazem restores IL-2, IL-3, IL-6, and IFN-gamma synthesis and decreases host susceptibility to sepsis following hemorrhage.** *J Surg Res* 1991, **51:**158-164.
52. Hostmann A, Jasse K, Schulze-Tanzil G, Robinson Y, Oberholzer A, Ertel W, Tschoeke S: **Biphasic onset of splenic apoptosis following hemorrhagic shock: critical implications for Bax, Bcl-2, and Mcl-1 proteins.** *Crit Care* 2008, **12:**R8.