HHS Public Access

Author manuscript

Crit Care Clin. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Crit Care Clin. 2017 January ; 33(1): 167–191. doi:10.1016/j.ccc.2016.08.006.

POSTINJURY INFLAMMATION AND ORGAN DYSFUNCTION

ANGELA SAUAIA, MD, PHD,

Professor of Public Health and Surgery, University of Colorado Denver, 655 Broadway #365, Denver, Co 80203

FREDERICK A. MOORE, MD, and

Professor of Surgery, University of Florida, Gainesville, PO BOX 100108, Gainesville, FL 32610

ERNEST E. MOORE, MD

Professor of Surgery, University of Colorado Denver, Denver Health Medical Center, 655 Broadway #365, Denver, CO 80203

ANGELA SAUAIA: Angela.Sauaia@ucdenver.edu; FREDERICK A. MOORE: Frederick.Moore@surgery.ufl.edu; ERNEST E. MOORE: Ernest.Moore@dhha.org

Synopsis

The development of organ dysfunction (OD) is related to the intensity and balance between trauma-induced simultaneous, opposite inflammatory responses. Early proinflammation via innate immune system activation may cause early OD, while anti-inflammation, via inhibition of the adaptive immune system and apoptosis, may induce immunoparalysis, impaired healing, infections, and late OD. Patients discharged with low level OD may develop the persistent inflammation-immunosuppression catabolism syndrome (PICS). Although the incidence of multiple organ failure (MOF) has decreased over time, it remains morbid, lethal and resource-intensive. Single OD, especially acute lung injury, however, remains frequent. At this time, treatment is limited, and prevention remains the mainstay strategy.

Keywords

organ dysfunction; postinjury inflammation; SIRS; CARS; SARS; PICS

Correspondence to: ANGELA SAUAIA, Angela.Sauaia@ucdenver.edu.

Disclosure: Drs. Angela Sauaia and Ernest E. Moore received funding from the National Institute of General Medical Sciences grant P50 GM049222 and National Heart, Lung and Blood Institute grant UM1 HL120877. Dr. Frederick A. Moore received funding from National Institute of General Medical Sciences grant P50 GM111152. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIGMS, NHLBI or National Institutes of Health. The authors have no commercial or financial conflicts of interest.

HISTORICAL PERSPECTIVE: EVOLVING CONCEPTS ON THE PATHOGENESIS OF MULTIPLE ORGAN FAILURE

As advances in prehospital and acute hospital care conquered “the golden hour”, multiple organ failure (MOF) emerged as the leading cause of late trauma death.[1–3] Eiseman et al. coined the term “multiple organ failure” (MOF) in 1977, with a clinical description of 42 patients with progressive organ dysfunction. [4] By the 1990s, Moore et al. proposed that MOF was a bimodal phenomenon. [5] In the “one-event” model, a massive traumatic insult would induce intense systemic inflammation response syndrome (SIRS) and precipitate organ dysfunction (OD). In the “two-event” model, patients initially resuscitated into moderate SIRS became vulnerable to a second activating event (infections, embolism, transfusions, secondary operations, etc.) during the so-called compensatory anti-inflammatory response syndrome (CARS) and could develop late MOF.

Modern hypotheses propose that injury triggers simultaneous, opposite responses: the proinflammation (SIRS) and the anti-inflammation, previously misnamed *compensatory* (CARS) (Figure 1).[6] OD is related to the intensity and the balance between these opposing trauma-induced inflammatory responses. Severe SIRS, a proinflammation via activation of the innate immune system, causes early OD while early anti-inflammation, via inhibition of the adaptive immune system and apoptosis, limits proinflammation and creates a preconditioned state to protect against second hits and hasten healing. When countering unbalanced proinflammation, persistent anti-inflammation leads to severe systemic anti-inflammatory response syndrome (SARS, a more appropriate term than CARS), setting the stage for immunoparalysis, impaired healing, infections, and late OD.[6,7] This was confirmed in a study by the Inflammation and Host Response to Injury Large-Scale Collaborative Research Program (Glue Grant) showing that alterations in the genomic expression of the classical inflammatory and anti-inflammatory responses occurred simultaneously. [8]

As MOF began to recede as a result of aggressive prevention, a new OD phenotype emerged among patients discharged after lengthy ICU stays to long term facilities, where they suffer from a persistent inflammation-immunosuppression catabolism syndrome (PICS). [20] Although the phenotypes and epidemiology of postinjury OD have changed considerably over the past 20 years, it remains morbid, lethal and resource-intensive, as described in the next sections.[21]

DEFINING MOF

The Denver score (Table 1) [9] and the Multiple Organ Dysfunction Score (MODS) [10–12] are among the most common validated definitions in trauma studies. For others, the reader is referred to Baue’s excellent review. [13] The Denver score grades the dysfunction of four systems (pulmonary, renal, hepatic, and cardiovascular), while the MODS grades six organ systems (pulmonary, renal, hepatic, cardiovascular, hematologic and neurologic). Both scores have good predictive performance, but the MODS tends to be more sensitive (high incidence of MOF, low case-fatality rate), while the Denver MOF score tends to be more specific (low incidence, high case-fatality rate).

EPIDEMIOLOGY AND CLINICAL RELEVANCE

US and Australian studies have shown a steady decline in MOF's incidence over the past decade. [14–17] Conversely, a large German study reported an increase in MOF incidence. [18] Most studies agree, however, that MOF associated mortality and morbidity remain high. [14–16,18–23] We recently studied MOF temporal trends in the Glue Grant dataset, a prospective study including adults with severe blunt torso injuries and hemorrhagic shock, enrolled from 2003 to 2010 in several US trauma centers sharing standard operating procedures. [15, 24] MOF, defined by the Denver score, was diagnosed in 223 (13.6%) patients, of whom 36% died. Table 2 details the distribution of admission risk factors, fluids, transfusions, complications, and outcomes over time. After adjustment for risk factors, MOF incidence decreased over time while MOF-related mortality remained persistently high (Figure 2). MOF patients continued to demand lengthy ventilator and critical care support. Applying the MODS definition produced similar results.

The risk factors for developing MOF included: demographic characteristics (advanced age, male sex, obesity), injury severity, and physiologic derangement upon admission (acidosis, number of transfused units of red blood cells [RBC]/12 hours). MOF-related death was positively associated with female sex, injury severity and RBC units transfused in the first 12 hours postinjury. The time interval between MOF onset and death is usually short, with death ensuing in two days in 58% of the cases. Early MOF (<3 days) carried a higher mortality than later MOF (Figure 3).

Lung failure incidence decreased significantly over time, but remained the most common organ failure over the study period, affecting over half of these patients (Table 1). Cardiovascular dysfunction also became significantly less frequent, while renal and liver failures persisted at low, similar levels. The mortality was highest for cardiovascular dysfunction (39%), followed by failure of the kidneys (38%), liver (19%) and lungs (12%). There has been a decrease in the progression from lung dysfunction to MOF over time [25] MOF without lung dysfunction is rare: only 8% of the MOF patients did not have lung involvement.

THE BURDEN OF MOF

In the abovementioned study, Sauaia et al. showed that MOF survivors were responsible for 20% of the total ICU and mechanical ventilation days despite being only 9% of the total population. [15] Based on national estimates of critical care costs [26], the total cost of the critical care delivered to MOF patients in this dataset amounted to $19,990,420, or 22% of the total ICU cost for this population. The estimated median cost per MOF patient was $77,202, compared to the presumed cost of caring for non-MOF patients ($38,442).

PATHOPHYSIOLOGY

Figure 4 shows a framework for the response to trauma. SIRS is the manifestation of the immuno-inflammatory activation in response to ischemia/reperfusion (I/R) injury and factors released from disrupted tissue, mediated by inherent genetic and environmentally determined host characteristics.

The 1994 “danger theory” of the inflammatory response following trauma or infection proposed that the immunological system’s role was to protect the body from danger. [27–32] In this model, immunological responses are triggered by specific types of cell death. If a healthy, undamaged cell dies an apoptotic death, it is scavenged without triggering an immune response. Conversely, cell lysis or apoptosis via trauma or infection releases intracellular contents and signals “danger”, triggering both innate and adaptive responses.[28,30,33]

The injured cell releases endogenous damage-associated molecular patterns (DAMPs), analogous to the microbial pathogen-associated molecular patterns (PAMPs), released in sepsis, both of which activate the innate immunity. [32,34,35] PAMPs are exogenous microbial molecules that alert the organism to pathogens and are recognized by cells of the innate and acquired immunity system, primarily through toll-like receptors (TLRs), and activate several signaling pathways (e.g., NF-κB). [27] DAMPs include HMGB1 (high mobility group box protein-1), heat-shock proteins, uric acid and DNA. HMGB1, a nuclear protein that binds to nucleosomes and promotes DNA bending, has been associated with SIRS and end-organ damage in animals. In humans, it has been shown to be at high levels as early as 1 hour postinjury.[27,36,37] Zhang et al. [34] showed that injury releases mitochondrial DAMPs (MTDs) into the circulation, which create a sepsis-like state and may be the key link between trauma, inflammation, and SIRS.

Most proteins identified in the plasma of blunt trauma victims are intracellular molecules that could function as DAMPS/alarmins and trigger pattern recognition receptors. [38] Our laboratory was the first to describe the proteome of human mesenteric lymph collected from critically ill or injured patients using a label-free semi-quantitative mass spectrometry (MS). [39] A total of 477 proteins were identified, including markers of hemolysis, extracellular matrix components, and general tissue damage in addition to the classical serum proteins. Postinjury hemolysis releases hemoglobin to the extracellular environment, where it becomes a redox-reactive DAMP molecule that can bind to PAMPs, trigger toll-like receptor (TLR)-mediated signal transduction and generate reactive oxygen species (ROS) potentially affecting innate immunity. [40] In the mesenteric lymph, we showed several markers of tissue damage and mitochondrial proteins suggestive of lysed mitochondria. [39] Circulating mitochondrial DNA and formyl peptides may mediate OD through PMN activation. [34]

Our MS analysis of the plasma metabolome of severely injured patients indicated a hypercatabolic state that could provide carbon and nitrogen sources to compensate for trauma-induced energy consumption and negative nitrogen balance. [41] Our MS analysis also confirmed an altered lipidomic profile, a hallmark of metabolic adaptation to injury, with fatty acid mobilization and lipid breakdown, resulting in accumulation of anionic compounds (e.g., ketone bodies) and acidosis. [41] In addition, we noted elevations in proinflammatory arachidonate metabolites (PGE2, LTB4), which supported the immuno-modulatory effect of diets balancing the ratio of omega-3/omega-6 fatty acids. [42]

We also observed significant proteolysis as shown by the accumulation of several aminoacids (alanine, aspartate, cysteine, glutamate, histidine, lysine, and phenylalanine) and

cyclic dipeptide cyclo (glu-glu), which stimulates T-lymphocytes. [41] Glutamate and cysteine buildup could fuel new reduced glutathione synthesis, thereby serving as physiologic protection from the increase in trauma-dependent oxidative stress. There was significant nucleoside breakdown as demonstrated by increased levels of purines and pyrimidine catabolites. [41] Increased nicotinamide, a breakdown product of the purine metabolite NAD, may signal exhaustion of NAD+/NADH reservoirs potentially compromising many energy and redox-related processes dependent on these cofactors. Notably, there was no glutamine accumulation, possibly due to enhanced consumption of this amino acid for cellular energy production or fueling transamination reactions. [41] Glutamine supplementation in critically ill patients has been a long-sought therapeutic approach, yet there are no evidence to date demonstrating its benefit.[43]

Succinate, in particular, has elicited much interest in I/R injury related states. [44–46] This intermediate metabolite, normally produced during cellular respiration, becomes elevated after ischemia due to two potential mechanisms: 1) an interesting activity reversal of the enzyme succinate dehydrogenase (SDH), which, during normal oxygen conditions, breaks down succinate; and 2) macrophage activation by products of tissue ischemia that find to TLRs, leading to glutamine metabolism and succinate production. [46] During reperfusion, succinate is oxidized with the now abundant oxygen, and drives a reversal of the electron transport through complex 1, which produces reactive oxygen species. Succinate has inflammatory signaling capacity, leads to IL-1-beta production and activates immune cells.[46,47] Chouchani et al. showed that preventing succinate elevation protected against I/R injury in mouse models of brain and heart ischemia. [44] Binding of succinate to a specific receptor (SUCNR1) in dendritic cells (antigen-presenting cells with an important role in initiating immune responses) appears to enhance the production of pro-inflammatory factors, suggesting that succinate may have a role in alerting the innate system of “danger”. [46,48]

Specifically in the lungs, succinate has been shown to mediate stabilization of the hypoxia-inducible factor HIF1-alpha, a transcriptor factor that when stabilized by hypoxia (and also by mechanically stretched lung epithelia) mediates a number of protective actions during low oxygen availability. This provides a direct role of succinate in lung protection during acute lung injury. [49–51]

In one of the few clinical studies of ARDS patients, large increases in precursors of uric acid (hypoxanthine, xanthine, guanosine) were observed suggesting that the pathway was activated. (although no uric acid was detected). [52] Uric acid has previously been shown to be a major endogenous danger signal in the lung, activating the NALP3 inflammasome and leading to IL-1β production.[53] Bos et al. suggested that metabolomic analyses targeting lung injury focus on exhaled air, namely “breathomics”. [54,55] Indeed, this group used an electronic nose (sNOSE) to detect patterns in volatile organic compounds (VOC) through gas chromatography and mass spectrometry, which discriminated ICU patients with and without ALI with 92% accuracy. These investigators identified three VOC in ARDS patients within the first 24 hours post ICU admission: acetaldehyde (potentially from neutrophil infiltration in the lungs), octane and 3-methylheptane (the latter two possibly related to lipid peroxidation due to oxidative stress). [55]

The Glue Grant study suggested that severe blunt trauma produced a “genomic storm” in the expression of over 80% of the leukocyte transcriptome across the first 28 days compared to healthy subjects. [8] The overexpressed genes were related to both the innate and adaptive immunity, while genes related to T-cell function and antigen presentation had decreased expression. The genomic response to blunt injury was remarkably similar to the response observed in burns and endotoxemia. Postinjury complications were associated with greater and prolonged overexpression, although there were no major differences in which genes were invoked. Despite providing compelling evidence, the abovementioned investigation had limitations, including a relatively small sample, inclusion of only blunt torso trauma, and focus on circulating leukocytes. [8] It is conceivable that different tissues have specific, localized inflammation expression patterns.

PICS patients have manageable OD with a long, eventful postinjury clinical course with recurrent inflammatory insults and infections, progressive loss of lean body mass (despite good nutritional support), poor wound healing, and decubitus ulcers. [7] Their labs show persistent neutrophilia and lymphopenia. Discharged to acute long-term care facilities, PICS patients die an indolent death or experience sepsis recidivism and ICU readmission. The elderly with baseline comorbidities and sarcopenia is especially prone to this refractory clinical phenotype. Often, the long-term outcome involves impairment of cognitive and functional status from which recovery is uncertain. [7,56] Clinically, PICS is defined as: long ICU stay (>14 days), persistent inflammation (C-reactive protein concentration >150 μg/dl and retinol binding protein concentrations < 10 μg/dl), immunosuppression (total lymphocyte count < 800/mm^3), and a catabolic state (serum albumin < 3.0 mg/dl, creatinine height index < 80%, and weight loss > 10% or BMI<18 kg/m^2 during the current hospitalization). Studies are underway to better define the phenotype, its true significance and novel interventions to prevent it or its progression. As the population ages, PICS is likely to be next challenging horizon in surgical critical care.

Role of the Gut

Initially, the dominant hypothesis linking the gut to MOF was related to bacterial translocation. However, inconsistent results led to experiments demonstrating that the mesenteric lymph acted as a bridge between the gut and the systemic circulation, allowing gut-derived inflammatory mediators to reach the systemic circulation. [57–59] Via the thoracic duct, these mediators reach the lungs before other organs, which is consistent with human studies demonstrating that respiratory dysfunction almost always precedes other ODs.[60]

Role of the PMN and Macrophages

While both MOF patients and non-MOF patients groups develop neutrophilia at 3 hours postinjury, MOF patients show a rapid neutropenia between 6 and 12 hours postinjury suggesting end-organ sequestration.[61] PMNs margination in end organs causes direct local cytotoxic cellular effects via degranulation and release of nitric oxide (NO), reactive oxygen species (ROS), and proinflammatory mediators (IL-6, IL-8, TNF-α).[62]

Following trauma there is an immediate increase in adhesion molecules, including L-selectin and CD18, which allow PMNs to slow and roll along the endothelium and marginate out of

circulation. [63] Antibodies directed against the CD11b/CD18 components of the adhesion receptor complex between leukocytes and endothelium significantly attenuate lung injury and prevent the neutropenia associated with tissue sequestration during experimental sepsis. [63] Circulating monocytes and tissue macrophages also become primed after severe injury and the microvascular endothelium has an important role in priming of the innate inflammatory response.[62]

Role of Platelets

Thrombocytopenia, especially when persistent, is a predictor of postinjury OD. [64,65] Gawaz et al. observed that irreversible degranulation of granule glycoproteins correlated positively with OD severity. [66] Platelet-neutrophil interaction has been shown to be important in models of acute lung injury (ALI) [67] and blocking it reverses ALI in animal models. [68] In a rat model of trauma/hemorrhagic shock, we observed that pretreatment with a platelet P2Y12 receptor antagonist protected from post-injury ALI. [69] Furthermore, isoflurane, an ether that interferes with platelet-granulocyte aggregation, attenuated ALI partially through platelet ADP pathway inhibition.[70]

Pre-injury antiplatelet therapy has been associated with a decreased risk of ALI, MOF and mortality in transfused blunt trauma patients and in patients with adult-respiratory distress syndrome (ARDS). [71, 72] The multicenter trial LIPS-A (NCT01504867) should provide interesting evidence on the therapeutic use of this anti-platelet agent.

Cytokines

Cytokines can be proinflammatory (TNF-α, MIP, GM-CSF, IFN-γ, IL-1, IL-2, IL-6, IL-8, IL-17, etc.) and anti-inflammatory (IL-4, IL-10, IL-13). [63] Jastrow et al. [73] showed that, compared to non-MOF patients, MOF victims had higher levels of IL-1 receptor antagonist (IL-1Ra), IL-8, eotaxin, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, inducible protein 10, monocyte chemotactic protein-1, and macrophage inflammatory protein-1. Adams et al.[74] demonstrated that IL-8 can activate PMNs via two different receptors, and differential early expression of these receptors explained higher MOF risk.

Although inflammatory mediators' levels vary greatly according to injury and individual characteristics, most studies agree that the changes start very early postinjury. [75] Indeed, a 2009 German study found that IL-6, IL-8, and IL-10 levels predicted MOF within 90 minutes of injury. [75]

Toll-Like Receptors (TLR)

TLRs are transmembranal proteins present in most body cell types, which form the major pattern recognition receptors that transduce signals in response to DAMPs after I/R.[76] Innate immune system responses are then initiated, including NF-kappa-B activation and proinflammatory cytokine production. Inhibition of TLR2 or TLR4 seems to be protective for I/R injury in liver, kidneys, brain, and heart, but not in the gut. Because the gut mucosa is continuously exposed to local bacterial endotoxins, local TLRs may be uniquely regulated to prevent inflammation.

Complement

The complement system is a major component of the innate immunity response, enhances the adaptive response and links the immune system with the coagulation system. [29, 77, 78] Complement system activation occurs immediately after trauma, with production of proinflammatory activation products C3a, C3b, and C5a and generation of the terminal C5b–C9 complex (the complement membrane-attack complex) that leads to lysis of the target cells. [29,35] Complement activation also results in the production of oxygen free radicals, arachidonic acid metabolites, and cytokines. However, excessive intravascular C5a may lead to neutrophil function "paralysis", rendering them incapable to respond to C5a or other chemo-attractants. [79] Complement activation, especially serum C3 and C3a levels as well as C5a, seems to reflect severity and treatment of injury and OD. [80–83]

Complement regulatory proteins (CD55, CD46, CD55, CD59), the C5a receptor (CD88) inhibitors of complement, such as C4b-binding protein (C4BP) and factor I, modulate the complement cascade and protect against complement-mediated tissue destruction. Several studies in polytrauma patients indicate that these regulatory factors are significantly altered post-injury suggesting "a trauma-induced complementopathy." [83–85]

Oxidative Stress

Excessive reactive oxygen intermediates (ROIs) cause direct oxidative injury to cellular proteins and nucleic acids, and disrupt cell membranes by inducing lipid peroxidation.[76,86] I/R leads to significant disturbances in ROI production. [35,76] ROI secreted from PMNs after I/R injury induces cytokines, chemokines (IL-8), HSP, and adhesion molecules (P-selectin, ICAM-1) leading to cell and tissue damage.[35]

Under normal conditions, NO production greatly exceeds O_2^- production in the endothelial cell.[87] However, with reperfusion, the balance between NO and O_2^- shifts in favor of O_2, leaving little NO available to reduce arteriolar tone, prevent platelet aggregation, and minimize PMN adhesion to endotellium. [88] In addition, NO seems to upregulate the production of proinflammatory cytokines.[87] Thus, altering the cell's redox state may contribute to the ongoing inflammatory cytokine production and progression to MOF. ROIs also play a role as second messengers in the intracellular signaling pathways of inflammatory cells, in particular activation of NF-κB and activator protein 1 (AP-1), which can be activated by both oxidants and antioxidants depending on the cell type and on intracellular conditions.[86]

Endogenous antioxidant defenses, including enzymatic (superoxide dismutase, catalase, glutathione peroxidase) and nonenzymatic (vitamins E and C, provitamin A, glutathione, bilirubin, urate) groups, were the focus of interventions to modulate the inflammatory response. However, the REDOX [89–91] and METAPLUS [92] trials demonstrated harm in systemic administration of anti-oxidants. [43] For both glutamine and antioxidants, the greatest potential for harm was renal dysfunction in patients with MOF. [91]

Later Risk Factors

Several conditions can serve as secondary stimulus that precipitate OD. Abdominal compartment syndrome (ACS), now in frank decline, leads to high ventilator pressures, decreased cardiac output, and impaired renal function. [93] While ACS physiologic effects usually reverse on decompression, the immunomodulatory effects may persist and trigger MOF.[94]

Although judicious blood transfusions have contributed to lower MOF incidence, early transfusion remains one of the most powerful independent risk factors for postinjury MOF. [19, 15] Blood products are immunoactive, contain proinflammatory cytokines and lipids, and have an early immunosuppressive effect predisposing to SARS, infection, and late MOF.[95] Transfusing stored RBC older than three weeks early postinjury is associated with a higher MOF rates compared to units with shorter storage. [96] Leukodepletion does not remove the potential for blood to act as a second hit, as red blood cells contain proinflammatory mediators. Biologically active lipids, capable of PMN priming, accumulate in stored blood and “passenger leukocytes” have been implicated as pivotal components. Proposed mechanisms include induction of T-cell anergy in the recipient, decreased natural killer cell function, altered ratio of T-helper to T-suppressor cells, and soluble proinflammatory cytokines produced by leukocytes during storage. [95]

Other blood-derived products (platelets, plasma, and coagulation factors) are also immunoactive.[97] Proteomic analyses of platelet supernatants of healthy donors suggested a storage and sex-dependent impairment of blood coagulation mediators, pro-inflammatory complement components and cytokines, energy and redox metabolic enzymes as well as platelet activation. [98,99]

Infections remain important predictors of late MOF. In the late 1970s, intra-abdominal abscess (IAA) was a frequent inciting event [100], but currently nosocomial pneumonia is the principal infection associated with MOF.[101] While SARS limits potentially auto-destructive inflammation, it is associated with immunosuppression predisposing the host to infections. [102]

The secondary operations can be considered controlled traumatic events.[63] While early definitive fracture fixation decreases postinjury morbidity and improves recovery [103], it is not without consequences when performed within the priming window. A 2003 randomized controlled trial (RCT) demonstrated that early external fixation followed by delayed conversion to intramedullary instrumentation was associated with a decreased inflammatory response to the operative fixation.[104] The same group compared damage control orthopedics (DC, femoral fracture stabilized with an external fixator) and primary intramedullary nailing (IMN) and showed that, despite more severe injuries, DC patients had less postoperative SIRS compared to IMN. [105]

Our group showed that DC was a safer initial approach, significantly decreasing the initial operative exposure and blood loss compared to early total care with IMN for multiple injury patients with femoral shaft fractures. [106] We observed similar beneficial effects regarding

pulmonary complications, infections, mechanical ventilation and ICU stay in spine fractures. [107]

INTERVENTIONS

Preventing the onset of MOF through therapies directed at modulating the balance of SIRS and SARS offers more practical benefit than efforts to treat MOF once established, when the treatment is largely supportive.[15]

Protective Resuscitation Techniques

Certain resuscitative strategies protect against distant OD after periods of gut I/R. [57] Resuscitation with isotonic crystalloids in the late 1960s decreased mortality and renal failure, but contributed to the emergence of ARDS. There is still controversy about the use of isotonic crystalloids compared with colloids. The 2004 multicenter, randomized SAFE trial [108] and a 2012 large RCT [109] found similar outcomes, which was confirmed in a 2013 Cochrane systematic review. [110]

A 2007 systematic review comparing hypertonic with isotonic crystalloid solutions for trauma/burns resuscitation did not provide enough data to determine a difference in outcomes.[111] Hypertonic resuscitation was compared with lactated Ringer's solution in adult, blunt trauma patients in a 2011 RCT [112], which was stopped at an interim analysis for potential safety concern (increased mortality in the subgroup of non-transfused patients receiving hypertonic saline) and futility. It demonstrated no significant difference in ARDS-free survival (hazard ratio, 1.01; 95% CI: 0.6–1.6). A subsequent analysis of patients in severe shock suggested that hypertonic saline was associated with hyperfibrinolysis. [113]

Hypertonicity has an effect on multiple immune response functions, which may translate into improved outcomes when administered locally (as opposed to systemically) or using alternative modes of administration.[114] To test this hypothesis, we are conducting a Phase I trial of nebulized hypertonic saline in moderately injured patients (NCT01667666).

Finally, the ALM™ (adenosine, lidocaine, magnesium) resuscitation has shown protective effects in animal models of sepsis and injury as well as in a few clinical trials in cardiac surgery patients. [115,116] Specifically, the combination of these three agents seems to confer cardiovascular protection, improvement of coagulation (presumably by inducing a shift in thrombin substrate specificity from the pro-fibrinolytic protein C pathway to the anti-fibrinolytic TAFI [thrombin-activatable-fibrinolysis-inhibitor] pathway at the endothelial thrombomodulin-thrombin complex level), reduction of proinflammatory factors (e.g., TNF-a) and increase of anti-inflammatory cytokines (e.g., IL-10). However, the mechanisms through which ALM™ exerts the abovementioned beneficial effects remain elusive.

Judicious Use of Blood Transfusions

A 12-year analysis of our Denver trauma dataset suggests that reduction in blood use contributed to the decreased incidence of MOF.[19] Current transfusion guidelines support the safety of restrictive transfusion practices in trauma patients.[117,118] Other techniques to reduce the deleterious effects of PRBCs are washed PRBCs and prestorage

leukoreduction. [95] Washed PRBCs have benefits but it is an unrealistic practice in most settings. Prestorage leukoreduction trials have shown modest improvements in outcomes, except for cardiac surgery patients, among whom mortality was halved. [119,120]

Blood substitutes have offered promising results in trauma. Two hemoglobin substitutes have been studied extensively in injured patients: the diaspirin cross-linked hemoglobin (Hemassist ™, Baxter Corporation) and the polymerized, pyridoxylated human hemoglobin (PolyHeme™ Northfield Laboratories).[95,121,122]

Our experience in the trauma setting with PolyHeme™ suggests it provides an immunologic advantage relative to blood in the injured patient by diminishing PMN priming and decreasing IL-6 and IL-8.[123] Although PolyHeme has been associated with outcomes comparable to standard of care and with more adverse events, the benefit-to-risk ratio of PolyHeme was favorable when blood was needed but not available.[124] As of 2015, the Food and Drug Administration (FDA) has not approved any blood substitutes, but Hemopure was approved in South Africa for use in acute anemia in 2001 and in Russia for use in the treatment of acute anemia in adults in 2010. [121]

Protective Lung Ventilation

Positive pressure ventilation can result in lung injury that is functionally and histologically identical to that seen in ARDS. Areas of low compliance (pulmonary contusion, edema, or infection) force tidal volumes to areas of high compliance resulting in increased alveolar pressures, overdistension, and injury to uninvolved lung tissue. Mechanical injuries to the lung (barotrauma, atelectrauma, volutrauma) initiate a local inflammatory reaction and biotrauma with release of inflammatory mediators from damaged cells and recruitment of PMNs. Mechanical stresses on the living cell are translated into intracellular inflammatory signal transduction and the combination of mechanical damage from positive pressure ventilation and the inflammation increases pulmonary dysfunction.[125]

The effects of ventilator-induced lung injury extend beyond the lung. Impaired oxygen delivery amplifies post-traumatic I/R injury. Inflammatory cytokines generated in the lung spill over into the systemic circulation and have the capacity to increase the inflammatory state and promote remote OD via direct cell signaling.

The ARDS Network lung-protective ventilation (LPV) trials [126] and a 2013 systematic review convincingly showed that LPV reduced mortality. [127]

Adrenal Insufficiency and Cortisol Replacement Therapy

Adrenal insufficiency (AI) occurs frequently in trauma and is associated with mortality.[128,129] International guidelines recommend that AI should be suspected in hypotensive patients responding poorly to fluids and vasopressor agents, with laboratorial signs of compromised adrenal function. [130] For patients with vasopressor-dependent septic shock and patients with early severe ARD, the decision to treat should be based mainly on clinical criteria. The corticosteroid dose should be sufficient to downregulate the proinflammatory response without causing immunodeficiency and impaired wound healing.

The use of extended course, stress-dose corticosteroids (200–350 mg/dL of hydrocortisone) in critically ill patients has been associated with improved outcomes.

Insulin and Glycemic Control

While glycemic control (≤180 mg/dL) is important, tighter glucose control (81–108 mg/dL) in critical care patients has had conflicting results.[131–133] Our Denver MOF showed that, after exclusion of diabetes patients, older patients benefitted more from tight glucose control levels than their younger counterparts. [134] In addition to glucose control and induction of anabolic processes, insulin can attenuate SIRS and modulate the proliferation, apoptosis, differentiation, and functions of monocytes/macrophages, neutrophils, and T cells associated with severe trauma, burn injury, or sepsis.[135]

Immunonutrition

Two aspects are relevant in immunonutrition: the delivery route (enteral vs. parenteral) and the diet composition. [6] Although controversy exists concerning the safety of feeding the hypoperfused small bowel, evidence supports that early enteral nutrition (EEN) is not only feasible but also associated with decreased incidence of nosocomial infection. EEN effects go far beyond mere nourishment; rather EEN induces a complex immunologic response.[135] EEN supports the function of the mucosal-associated lymphoid tissue (MALT) that produces 70% of the body's secretory IgA.[136] Naïve T and B cells target and enter the gut-associated lymphoid tissue (GALT) where they are sensitized and stimulated by antigens sampled from the gut lumen and thereby become more responsive to potential pathogens in the external environment. These stimulated T and B cells then migrate via mesenteric lymph nodes and the thoracic duct and into the vascular tree for distribution to GALT and extraintestinal sites of MALT. Lack of enteral stimulation (i.e., use of TPN) causes a rapid and progressive decrease in T and B cells within GALT and simultaneous decreases in intestinal and respiratory IgA levels. Previously resistant TPN-fed lab animals, when challenged with pathogens via respiratory tree inoculation, succumb to overwhelming infections. These immunologic defects and susceptibility to infection are reversed within 3–5 days after initiating EN.[136] Indeed, feeding the gut in critically ill patients has been shown to reverse shock-induced mucosal hypoperfusion and impaired intestinal transit as well as attenuate gut permeability defects and lessen the severity of CARS.[6]

Regarding content, to be effective, immunonutritional therapies must ameliorate cellular defense, oxidative stress, and mitochondrial function without increasing SIRS. As mentioned in previous sections, rigorous studies on immunomodulating diets, so far, have been disappointing. [43,89,91]

TLR-Directed Interventions

Because TLR activation leads to an intense and immediate inflammatory reaction in response to I/R injury, targeting TLRs may be a promising intervention strategy to reduce MOF. Yet, because TLR activation occurs through a variety of mechanisms, generating full antagonists is technically difficult. The development of eritoran, a potent and full antagonist of LPS at TLR4, is a significant advance and offers hope that other TLR-selective antagonists may become available in future years.[137]

Immunomodulation

In the immunodepression stage of the inflammatory response to injury, it may be useful to enhance immune function to prevent infections that can act as second insults. An analysis of leukocyte gene expression associated with post-trauma Gram-negative bacteremia in the Glue Grant dataset showed that both innate and adaptive immunity appeared to be suppressed by 96 hours postinjury. [138] These findings suggested that immunostimulants, such as interferon-gamma, in patients with decreased immune gene expression, may be a promising therapeutic approach. GM-CSF was tested in small trauma populations and shown to counteract trauma-induced monocyte function depression while IFN-γ had the capacity to enhance HLA-DR on B and T lymphocytes.[139,140]

Mesenchymal stem or stromal cells (MSC) have been shown to exert protective effects through the release of promitotic, antiapoptotic, antiinflammatory, and immunomodulatory soluble factors.[141] Initially, MSC cells were believed to regenerate dysfunctional, damage organs, however, later it became clear that their beneficial effects were mediated by secretion of factors. MSCs tend to migrate toward sites where there is inflammation or injury, thus dysfunctional organs are potential targets. Since most approaches targeting a single pathway or mechanism have not been promising, MSCs are attractive because they tackle several pathways modulating multiple immune cells and the oxidative process, in addition to their antibacterial properties. A few Phase 1 trials have been completed showing an acceptable safety profile. [142,143] At the time of this writing, no Phase 2 trial results are available.

In the 2015 Shock Society Thirty-Eighth Annual Conference on Shock, Sordi and colleagues from Europe presented promising results using artesunate (a medication commonly used to treat falciparum malaria) in a rat model of hemorrhage-induced organ dysfunction. [144] Artesunate treatment was associated with lower levels of creatinine and lung myeloperoxidase activity as well as increased activation of Akt and eNOS, reduced activation of GSK-3 beta and NF-kappa B activation, and attenuated increase in serum TNF-alpha associated with the hemorrhagic shock. These findings suggest that artesunate attenuated organ dysfunction (lungs and kidneys) likely via activation of the Akt-eNOS survival pathway, and/or by reducing inflammation via inhibition of GSK-3 beta and NF-Kappa B. Based on these experiments, the group received funding from the Wellcome Trust for a Phase IIa, single-center, placebo-controlled, randomized, phase II clinical trial of Artesunate for Trauma Organ Protection (TOP-ART) (ISRCTN15731357, available at www.isrctn.com and www.c4ts.qmul.ac.uk/organ-failure--protection/top-art, accessed December 18, 2015).

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Key Points

1. The development of organ dysfunction (OD) is related to the intensity and balance between trauma-induced simultaneous, opposite inflammatory responses.
2. Early proinflammation via innate immune system activation may cause early OD while early anti-inflammation, via inhibition of the adaptive immune system and apoptosis, may induce immunoparalysis, impaired healing, infections, and late OD.
3. Patients discharged with low level OD may develop the persistent inflammation-immunosuppression catabolism syndrome (PICS), which may cause an indolent death.
4. The incidence of multiple organ failure (MOF) has decreased over time, yet MOF remains morbid, lethal and resource-intensive. Single OD, especially acute lung injury, remains frequent.
5. At this time, treatment of organ dysfunction is limited, and prevention via adequate resuscitation, ventilation and nutritional support remains the mainstay strategy.

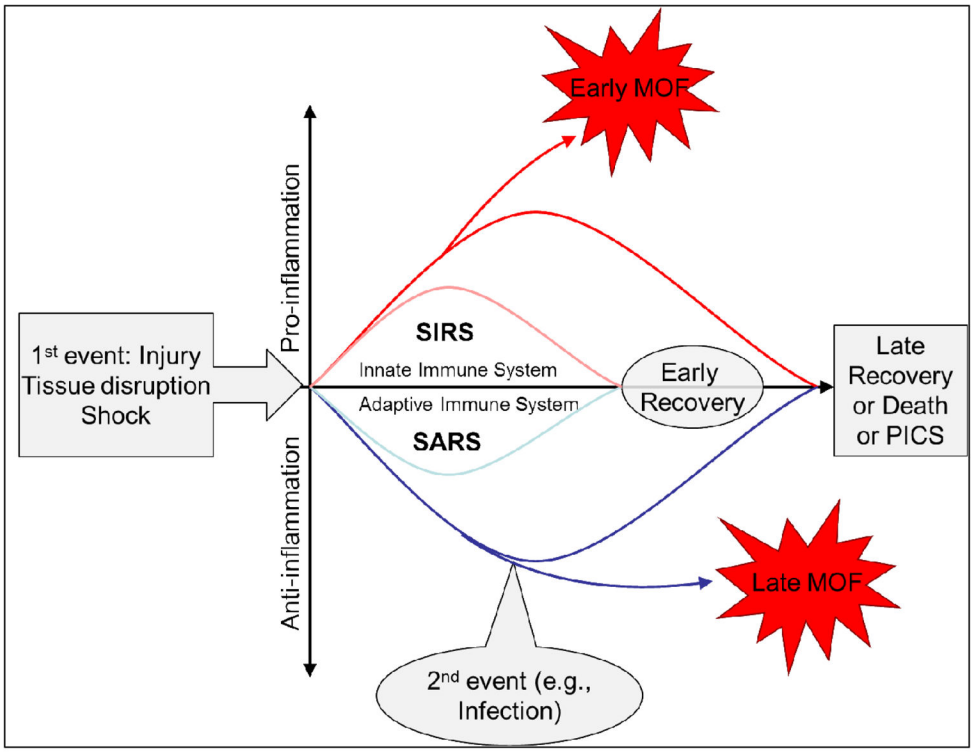

Figure 1.

Theoretical framework for postinjury multiple organ failure: The synchronous immunoinflammatory model

A: MOF incidence

B: Mortality in MOF patients

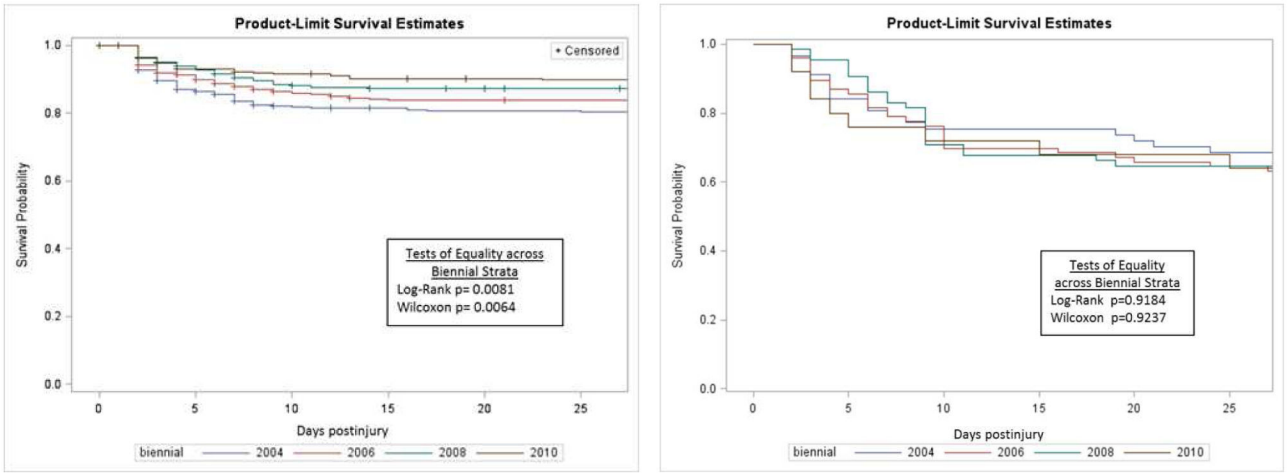

Figure 2. Kaplan-Meyer curves for MOF incidence and outcomes across biennial periods from 2003–2010 in 1643 adult, blunt trauma patients admitted to four US trauma centers (Glue Grant Dataset)

*stratum 2004=2003–2004; stratum 2006=2005–2006; stratum 2008=2007–2008; stratum=2009–2010

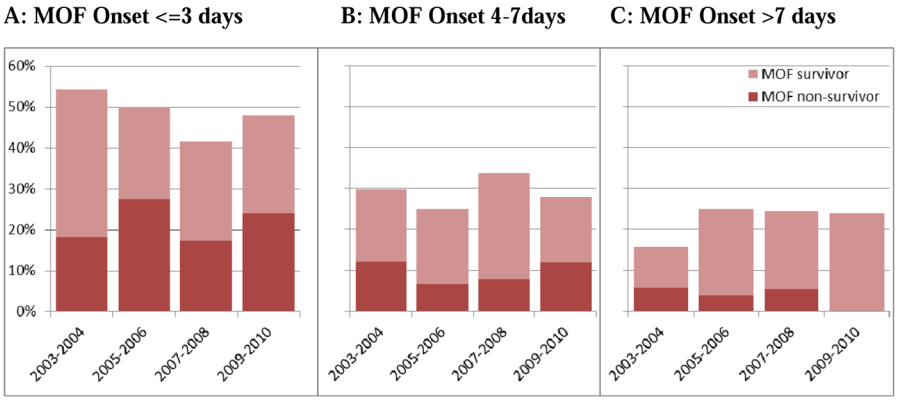

Figure 3.
MOF onset and respective case-fatality rates

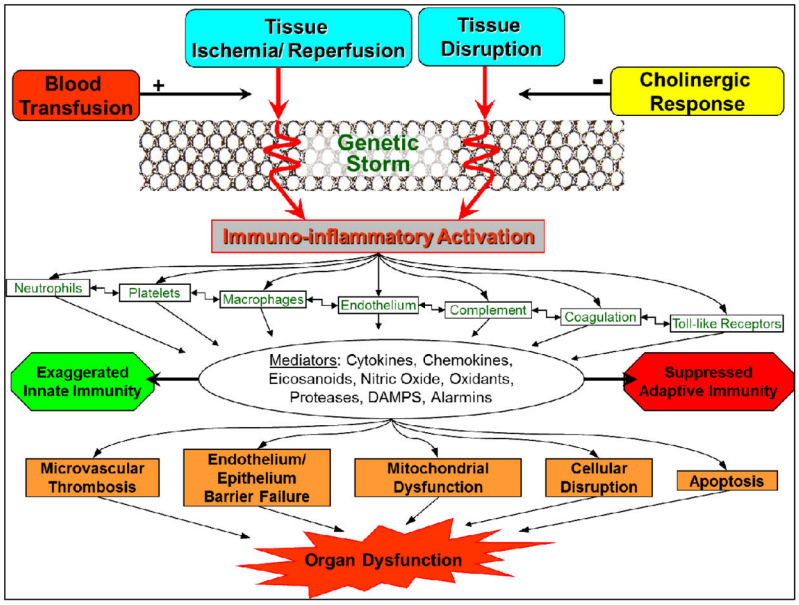

Figure 4.

Response to trauma: hemostatic, inflammatory, endocrine and neurological systems interaction

TABLE 1

Denver Postinjury Multiple Organ Failure Score

Organ System	Grade 0	Grade 1	Grade 2	Grade 3
Pulmonary				
PaO_2/FiO_2 ratio	>250	250–200	200–100	≤100
Renal				
Creatinine (mg/dL)	≤1.8	1.9–2.5	2.51–5.0	>5.0
Creatinine (μmol/L)	<159	160–221	222–442	>442
Hepatic				
Bilirubin (mg/dL)	≤2.0	2.0–4.0	4.1–8.0	>8.0
Bilirubin (μmol/L)	<34	34–68	69–137	>137
Cardiac	No inotropes	Only one inotrope at a small dose[a]	Any inotrope at moderate dose or >1 agent, all at small doses[a]	Any inotrope at large dose or >2 agents at moderate doses[a]

	Small	Moderate	Large
Milrinone	<0.3	0.4–0.7	>0.7
Vasopressin	<0.03	0.03–0.07	>0.07
Dopamine	<6	6–10	>10
Dobutamine	<6	6–10	>10
Epinephrine	<0.06	0.06–0.15	>0.15
Norepinephrine	<0.11	0.11–0.5	>0.5
Phenylephrine	<0.6	0.6–3	>3

[a]Inotrope doses (in μg/(kg min)):

[a]Need for inotropes more than dopamine .× μg/(kg min).

[b]PAR: pressure-adjusted heart rate. PAR = heart rate × central venous pressure/mean arterial blood pressure.

Table 2

Population characteristics, admission risk factors, resuscitation fluids and blood transfusions, outcome and complications of 1643 adult, blunt trauma patients admitted to four US trauma centers (Glue Grant Dataset). Data are expressed in Median and Lower Quartile (LQ) and Upper Quartile (UQ) or percentages

	2003–2004			2005–2006			2007–2008			2009–2010			p-value *
	N=335			N=506			N=546			N=256			
Variable	**Median or %**	**LQ**	**UQ**	**Median or %**	**LQ**	**UQ**	**Median or %**	**LQ**	**UQ**	**Median or %**	**LQ**	**UQ**	
DEMOGRAPHIC													
Age (years)	40	26	54	41	26	54	43	28	57	45.5	25.5	58	0.0246
Body Mass Index (kg/m^2)	25.7	23.1	29.9	26.7	23.7	31.4	27.1	23.8	31.3	27.3	24.1	32.0	0.0017
Male sex (%)	64.5			66.6			67.2			67.6			0.3940
Comorbidity Index >=2 (%)	8.4			12.9			8.4			10.2			0.8276
Anti-platelet therapy (%) **	6.6			7.1			10.1			8.2			0.1414
INJURY													
Moderate TBI (%) ***	30.2			18.0			21.6			18.0			0.0037
Injury severity score	29	22	41	32	22	41	34	24	41	34	22	43	0.0622
Pre-hospital GCS	13	4	15	14	10	15	14	9	15	14	9	15	<.0001
Pre-hospital SBP (lowest)	89.0	72.5	104.5	86.0	71.0	102.0	88.0	73.0	108.0	85.0	74.0	100.0	0.8425
Pre-hospital HR (highest)	116	95	131	118	100	130	115	97	130	118	102	132	0.4810
Admission GCS	6	3	15	10	3	15	11	3	15	3	3	15	0.1534
Admission SBP (mmHg)	110	93	135	111	90	132	110	90	131	109.5	89	128	0.0429
Admission SBP<=90mmHg	22.1			25.9			26.7			29.9			0.0350
Admission HR (beats/min)	108	86	127	110	90	126	109	91	127	110	92	127.5	0.2080
FLUIDS/BLOOD													
RBC units/12 hours	5	3	11	6	3	12	5	2	9	5	2	9	0.0739
FFP units/12 hours	3	0	8	3	0	8	2	0	6	3	0	7	0.0798
0–6hrs RBC:FFP ratio	0.6	0	1.5	0.5	0	1.6	0	0	1.5	0.6	0	1.4	0.1224
Platelet units/12 hours	0	0	1	0	0	1	0	0	1	0	0	1	0.4160
Pre-hospital crystalloids(ml)	1.6	0.6	3.0	1.8	0.7	3.3	1.4	0.5	2.9	1.8	0.7	3.1	0.3504

	2003–2004			2005–2006			2007–2008			2009–2010			p-value *
	N=335			N=506			N=546			N=256			
Variable	**Median or %**	**LQ**	**UQ**	**Median or %**	**LQ**	**UQ**	**Median or %**	**LQ**	**UQ**	**Median or %**	**LQ**	**UQ**	
Crystalloids (ml)/12 hours	10.3	7.2	15.7	10.0	7.6	13.6	8.7	5.9	12.3	9.0	6.3	12.0	<.0001
LABORATORIAL TESTS													
ED Base Excess (mEq/L)	−8.9	−11.4	−6	−8.4	−11.2	−6	−7.6	−0.8	−5	−8	−11.1	−5.35	0.0012
ED Lactate (mg/dL)	4.3	3	5.9	3.9	2.7	5.6	3.6	2.4	5.2	4	2.4	6	0.0016
Day 1 Platelet 1,000/mcL	100	79	129	95	76	123	107	87	133	101	84	128.5	0.0028
PaO2/FiO2 ratio/12 hours	119	66	213	161	86.5	256	158	89	269	163	79	285	0.0003
ED Hemoglobin g/dL	10.9	9.33	13	11.3	9.5	13.1	11.9	10	13.3	11.5	9.6	12.9	0.0217
ED INR	1.2	1.1	1.5	1.3	1.1	1.5	1.21	1.1	1.5	1.3	1.1	1.5	0.3152
COMPLICATIONS													
Non-septic complication (%)	44.5			47.2			44.1			40.4			0.2365
Surgical site infection (%)	13.1			16.4			14.8			8.2			0.1180
VAP (%)	26.6			26.5			24.4			23.1			0.2335
OUTCOMES													
Multiple organ failure (%)	17.0			15.0			11.9			9.8			0.0033
Lung failure (%)	57.6			56.5			55.3			50.8			0.1073
Cardiac failure (%)	20.9			17.6			16.1			12.5			0.0064
Liver failure (%)	15.2			16.2			13.4			14.1			0.3762
Renal failure (%)	10.1			10.7			11.9			12.5			0.2804
ICU days	8	4	19	9	4	17	10	5	18	9	5	17	0.1070
ICU free days	11	0	21	15	4	23	15	3	22	17	8	22	0.0002
Ventilator days	6	2	14	5	2	13	7	2	13	6	2	12	0.8414
Ventilator free days	16	0	24	19	7	25	20	8	25	21	12	25	<.0001
Mortality (%)	23.9			15.4			12.3			10.5			<.0001
MOF RELATED OUTCOMES													
Case-fatality (%)	33.3			38.2			36.9			36.0			0.7800
ICU days	22	9	34	17	8.5	8.0	15	9	27	19	10	24	0.1889
ICU free days	0	0	4	0	0	8	0	0	10	4	0	7	0.2289

	2003–2004			2005–2006			2007–2008			2009–2010			p-value *
	N=335			N=506			N=546			N=256			
Variable	**Median or %**	**LQ**	**UQ**	**Median or %**	**LQ**	**UQ**	**Median or %**	**LQ**	**UQ**	**Median or %**	**LQ**	**UQ**	
Ventilator days	20	9	26	15	6.5	27	12	7	21	13	6	19	0.0642
Ventilator free days	0	0	8	0	0	11.5	0	0	14	4	0	14	0.1969
MOF RELATED COMPLICATIONS													
Non-septic complication (%)	77.2			75.0			83.1			80.0			0.4481
Surgical site infection (%)	22.8			27.6			16.9			20.0			0.4042
VAP (%)	47.3			43.4			50.8			44.0			0.8946

*Cochran-Armitage Trend Test for trend was used for categorical variables and the non-parametric Spearman correlation coefficient and test for continuous variables; negative correlation coefficients indicate values decreased over time, while positive coefficients indicate values increased over time ; significance set at p<0.01 to account for large number of comparisons;

**: antiplatelet medication previous to injury;

***Moderate Traumatic Brain Injury (TBI) : Head Abbreviated Injury Scale(AIS)>3 with Glasgow Coma Scale (GCS) motor component>3; SBP: systolic blood pressure; HR: heart rate; RBC: packed red blood cells; FFP: fresh frozen plasma; INR: international normalized ratio, VAP: ventilator-associated pneumonia; ICU: intensive care unit