

Title: “Polytrauma - new horizons for management.”

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Abstract:

The management of polytrauma has evolved considerably in the last century. Advances have been made in all disciplines involved in trauma care from the pre-hospital care and resuscitation protocols to diagnostics, surgical techniques, administration of novel pharmacological agents and late reconstruction procedures. The ongoing better understanding of the altered physiology and the induced response at the molecular level is offering potentials for novel management strategies and prevention of post-traumatic complications. Extensive research must continue in all related fields so that advances will continue to evolve in the years to come.

Key words: new horizons, polytrauma, management.

“Polytrauma - new horizons for management.”

Polytrauma can be defined as an injury to at least two organ systems leading potentially to a life threatening condition (Edwards *et al.*, 2007); but, in general, a prospectively validated or consensus definition is lacking within the international trauma community (Butcher and Balogh, 2009).

The management of polytrauma has evolved considerably in the last century, even though its rational involving a number of steps based on priorities, prompt decisions and actions remains unaltered. The recent developments made in all disciplines involved in trauma care have helped to improve the management of these patients, with remarkable advances being achieved in pre-hospital care, diagnostics, interventional radiology, surgical and fracture fixation techniques, ventilation strategies, as well as rehabilitation and late reconstruction procedures (Giannoudis, 2009). Additionally, the understanding of the altered physiology and the induced immune-inflammatory response at the molecular level that occur after major trauma is continuously increasing offering potentials for novel pharmacological interventions, minimising thus the risk of development of post-traumatic complications (Giannoudis, 2009).

The management of multiple injured patients is initiated at the scene of the accident, as immediate support of vital organ functions is of fundamental importance. Prompt and safe transfer of these patients with the availability of regional ambulances, helicopters within a well organized trauma care system is essential with on-going treatment of haemorrhagic shock and hypoxia (Kauvar *et al.*, 2006). Even though standard resuscitation protocols are imperative, the ideal early resuscitation strategy for polytrauma remains a topic of vivid discussion. The concept of

“permissive hypotension” for bleeding trauma patients and particularly for blunt trauma and patients with associated head injuries contributes further to the existing controversy in the field (Stahel *et al.*, 2009). New resuscitation strategies have been developed, mainly acquired from the experience during military conflicts such as in Iraq and Afghanistan, from where the concept of damage control resuscitation has been derived and evolved. This resuscitation strategy combines the concepts of permissive hypotension and haemostatic resuscitation in association with damage control surgery (Duchesne and Holcomb, 2009). Intravenous fluid administration at the scene of the accident is restricted to a volume that the radial pulse is maintained and haemostatic resuscitation includes the prompt administration of blood products as primary resuscitation fluids in order to treat intrinsic acute traumatic coagulopathy and to prevent dilutional coagulopathy. Increasing evidence has shown that acute early coagulopathy can be triggered by the injury itself and the subsequent release of trauma-associated mediators occurring even prior to emergency room (ER) admission (Duchesne and Holcomb, 2009). A retrospective analysis of 8,724 patients from the German Trauma Registry revealed that coagulopathy upon ER admission was present in 34.2% of all patients, with the incidence being increased to >70% when >4000 ml of i.v. fluids were administered during early resuscitation and the preclinical phase of care (Maegle *et al.*, 2007).

Regarding the administration of artificial blood substitutes as alternative to red blood cells in order to ensure oxygen transport to the tissues, it is believed that they could be used during fluid resuscitation especially in pre-hospital trauma care, military trauma care, prolonged transport times or in the developing world where there are high rates of HIV carriage and blood donation is not widely taken up (Goosen *et al.*, 2003; Shirley, 2008). Advocates supporting their usage believe that

they can overcome the disadvantages of blood transfusion such as the safety issues relating to transmission of infections, the induction of immunological reactions, the limited donated blood quantity and the need of screening.

In addition, the administration of novel systemic haemostatic agents such as tranexamic acid (CRASH-2 trial collaborators, 2010) and recombinant factor VIIa (Felfernig, 2007) have also been shown to reduce the risk of death in bleeding trauma patients. Although proven efficacious to the military trauma care (Felfernig, 2007), the use of such agents has not been adapted to the everyday trauma care in the civilian practice. Administration of other agents can also be beneficial in the initial management of polytrauma patients. For example, the tris-(hydroxymethyl) aminomethane (THAM), an alkalizing agent, has been shown to be an effective alternative to sodium bicarbonate for treating acidosis and to improve significantly arterial pH and base deficit during acute lung injury (Kallet *et al.*, 2000) and renal acidosis ((Nahas *et al.*, 1998). Moreover, it can also be a potent cerebroprotective agent in cases of brain injury (Nahas *et al.*, 1998; Okauchi *et al.*, 2002). However, their potential application in the clinical setting as adjuncts to the polytrauma management requires further investigation.

The advances made in diagnostics have been extremely beneficial since they allowed early recognition of life-threatening injuries and prompt, efficacious management. Lately, the most recent evolution of the multi-slice CT allows accurate diagnosis to be made within 2-4 minutes when integrated into the early diagnostic protocol, which is of enormous benefit for early initiation of the appropriate treatment strategy (Berne *et al.*, 1999; Hilbert *et al.*, 2007). Although the exposure of these patients to radiation remains a concern, future research should assess the actual risk of carcinogenesis. A recent study on the impact on trauma patient management after

installing a CT scanner in the emergency department reported that more trauma patients had diagnostic CT scanning before definitive care with a decreased time required for CT without significant increase in the number of unnecessary scans (Lee *et al.*, 2009).

Advanced or novel therapeutic methods applied either simultaneously or in a priority oriented way with the multidisciplinary cooperation of different specialists, have also contributed in the improved quality of the provided polytrauma care. In addition to the standard life saving surgery such as laparotomy, thoracotomy or application of a pelvic C-clamp and concomitant pelvic packing (Probst *et al.*, 2009), advances made in interventional radiology helped to manage patients with solid organ trauma or pelvic ring injuries where the source of bleeding has been identified and successfully treated with angio-embolisation without the need for immediate surgical intervention or as adjunct to damage-control surgery in complex injury patterns (Durai and Ng, 2010; Shaftan, 2008). However, such interventions are not without risks and, although less invasive, patients should be followed up with caution (Durai and Ng, 2010).

With regard to the strategy of fracture fixation, the realisation that early total care may not be beneficial to different groups of patient (“second hit” insult) (Giannoudis *et al.*, 1999; Pape *et al.*, 2000) resulted in a shift towards the “damage control” approach (Giannoudis, 2003). A recent study has shown that definitive intramedullary fixation of femoral shaft fractures in the setting of hypo-perfusion defined by serum bicarbonate is predictive of pulmonary organ dysfunction and increases morbidity among multi-system trauma patients (Morshed *et al.*, 2010). Advanced minimal invasive surgical techniques and the development of appropriate surgical instrumentation for systems with distinct biomechanical advantages (Egol *et*

al., 2004; Perren, 2002) could have an impact in terms of reducing the ‘second hit’ (surgeon induced trauma) on the overall physiological state of these patients. Also, novel systems that simultaneously ream, irrigate, and aspirate, and reduce the elevated intramedullary pressures, generated heat and systemic and inflammatory effects of reaming, like the Reamer/Irrigator/Aspirator (RIA) system [Synthes, Inc., West Chester, PA] (Giannoudis *et al.*, 2009; Higgins *et al.*, 2007), could be beneficial in polytrauma patients with long bone fractures and concomitant lung injury (Giannoudis *et al.*, 1999; Pape *et al.*, 2005).

Furthermore, with the better understanding of the biology of fracture healing and the novel methods of biological stimulation for bone regeneration, early intervention in cases where fracture delayed union or non-union is foreseen (open fractures, critical sized bone defects) by means of administration of pharmacological agents (BMPs, other growth factors and hormones) (Nauth *et al.*, 2010) could accelerate the normal bone healing process to hasten the rehabilitation period.

In cases of polytrauma with concomitant spinal cord and non-cord injuries, early surgical stabilisation may be beneficial as a recent review on the timing of spinal stabilisation and the impact in morbidity and mortality in such patients reported that early surgical stabilisation consistently seems to lead to shorter hospital stays, shorter intensive care unit stays, less days on mechanical ventilation, and lower pulmonary complications. This was more evident in patients with more severe injuries, without increased complication rates compared to late surgery (Dimar *et al.*, 2010).

The key advances that opened new horizons in the management of polytrauma patients involve mainly the improvement of our understanding of the events regulating the immediate physiological reaction and subsequent events following trauma. At the molecular level, a number of molecules (mediators), such as pro-

inflammatory and anti-inflammatory cytokines and damage-associated molecular patterns (DAMPs) as well as cells, termed as antigen-presenting cells (lymphocytes, neutrophils, monocytes, macrophages and natural killer cells) interact whilst the patient enters a state of physiological crisis with the up-regulation of various complex mechanisms (Giannoudis and Pape, 2007; Tsukamoto *et al.*, 2010). An immuno-inflammatory response is initiated not only by the injury itself, but also by the additional stress induced from the events that may be encountered during the management of multiple injured patients, like surgical procedures or subsequent complications. This state of hyper-inflammation represents the early phase of the immunological dysfunction by trauma-induced danger signals in an effort for the body to maintain homeostasis, and is followed by a phase of immunosuppression with increased susceptibility to infection, sepsis and multiple organ failure (Stahel *et al.*, 2007). In addition to the immune response, a variety of endocrinological and haematological phenomena evolve concurrently and proportionally to the severity of trauma sustained until normalisation of all the physiological processes take place (Giannoudis and Pape, 2007; Giannoudis *et al.*, 2007).

Research is ongoing in an effort to identify mediators with the best specificity and sensitivity for both diagnostic and prognostic purposes. At present, the knowledge acquired from the developing field of clinical genomics and proteomics has not been applied extensively in trauma management (Alpantaki *et al.*, 2007). The elucidation of cellular and molecular events occurring in trauma patients, in terms of gene expression and protein synthesis may allow the screening of candidate genes and assist clinicians in accurate diagnosis and selection of appropriate and “accordingly modified” treatment options for each patient. Endothelial injury markers could be used to quantify the magnitude of the immuno-inflammatory response and detect

early the potential development of posttraumatic complications such as adult respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) (Giannoudis *et al.*, 2007). Further elucidation of the pathophysiology of injury at the molecular level would allow to select the appropriate management strategy and also at the appropriate time to augment or at the least not “interfere” with the normal homeostatic processes. Therapeutic strategies in the terms of biological response modifiers to temper or modulate the post-traumatic innate and adaptive immune response would be of benefit, but their translation from "bench to bedside" is difficult and still under extensive research, with various pharmacological strategies including anti-inflammatory (steroids) and immune-stimulatory (interferon) agents and other unconventional immune-modulatory approaches, such as immuno-nutrition being investigated aiming to restore immune homeostasis after traumatic injuries and to prevent the development of lethal complications (Stahel *et al.*, 2007).

All this extensive research and monitoring of the immune response is of great interest for all disciplines involved in the management of polytrauma, but particularly for the intensive care physicians, who often deal with an uncontrollable immunoinflammatory response, immunoparalysis and sepsis when treating trauma patients in the intensive care unit (ICU). With the improved resuscitation protocols, the rapid transfer of polytrauma patients, the early diagnosis and treatment in combination with the damage control strategy, the survival of multiple injured patients has been increased, making the role of ICU pivotal in the interval between emergency and further required surgery, during which a high quality evidence-based intensive care treatment, but also tailored to the current individual injuries, must be provided (Mann *et al.*, 2010). Management should be performed in dedicated trauma ICUs, whilst in close cooperation with physicians of all surgical disciplines involved,

with up-to-date diagnostic, monitoring and treatment tools, such as extracorporeal membrane oxygenation (Campione *et al.*, 2007) and thorough monitoring of the immunological status of the patient with Interleukin-6 (IL-6) and procalcitonine measurements, additionally to the “traditional” inflammatory markers (WBC and CRP) (Giannoudis *et al.*, 2008) in an effort to initially stabilise and then optimise patients’ condition for further interventions and ultimately rehabilitation.

Undoubtedly, the management of patients with multiple injuries continues to be a challenging process. However, prevention with increased and efficacious safety measures remains to be the key to reduce the incidence of trauma in general, as it remains one of the main causes of death and disability worldwide, affecting mostly young adults as well as the elderly population (Aldrian *et al.*, 2007; Giannoudis *et al.*, 2009; WHO, 2006). Besides prevention, well organised health systems should provide all the components of an efficient and high quality overall management of polytrauma patients. Ongoing improvements on this field are anticipated with the continuous clinical effort of all physicians involved in trauma care to further reduce mortality, improve functional outcome and quality of life for these patients, and reduce the economic implications in health care and society.

So, are there new horizons for polytrauma management? The answer is yes, and it includes advances in all aspects and disciplines involved in trauma care, aiming to provide the most prompt and efficient care. Even faster rescue and transfer times are aimed; while providing optimal resuscitation strategies by administration of novel agents to lessen the induced immune response and supplement the homeostatic processes or artificial blood products to overcome the limitations and risks of blood transfusion. Moreover, rapid accurate diagnosis by the provision of multi-slice CT scanners across all trauma centre levels, if possible, would allow prompt treatment

with ideally more minimal invasive surgical techniques to minimise further trauma, and early supportive care in the ICU with better monitoring methods and pharmacological support. Further elucidation of how genetic variations among patients could influence physiological processes, such as the magnitude of immune response after trauma, the response to sepsis or to the administration of various pharmacological agents, and the normal healing responses including fracture healing, may offer novel treatment strategies and genetic tests to allow 'modified' treatments to be provided or to early identify patients at risk for potential complications. Advanced therapies in terms of injectable formulations of growth factors or systemic administration of biological response modifiers could also be of benefit in trauma patients; as well as the establishment of early and efficacious rehabilitation based on the individual demands of each patient and the planning of late reconstructive procedures when required.

For all these new horizons for the management of polytrauma patients to be expanded and eventually novel strategies to be added and improve the trauma care practise in the years to come, extensive research should continue in all related fields.

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