Multiple Trauma Part I: Epidemiology, mechanisms and physiological impact

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Multiple Trauma Part I: Epidemiology, mechanisms and physiological impact

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Intended Learning Outcomes

Multiple Trauma Part I: Epidemiology, mechanisms and physiological impact

1. describe the epidemiology of trauma, trauma scoring systems and triage principles
2. describe the mechanism, pathophysiology and presentation of blunt trauma
3. describe the mechanism behind severe trauma induced endotheliopathy, trauma-induced coagulopathy, mitochondrial dysfunction and PICS

eModule Information

Relevant Competencies from CoBaTrICE

Multiple Trauma Part I: Epidemiology, mechanisms and physiological impact

- **1.1** Adopts a structured and timely approach to the recognition, assessment and stabilisation of the acutely ill patient with disordered physiology.
- **1.3** Manages the patient post-resuscitation
- **1.5** Assesses and provides initial management of the trauma patient
- **2.1** Integrates clinical findings with laboratory investigations to form a differential diagnosis
- **3.1** Manages the care of the critically ill patient with specific acute medical conditions
- **3.4** Recognises and manages the patient with, or at risk of, acute kidney injury
- **4.1** Prescribes drugs and therapies safely
- **6.1** Manages the pre- and post-operative care of the high-risk surgical patient
- **6.5** Manages the pre- and post-operative care of the trauma patient under supervision

Abbreviations

ADAMs: a disintegrin and metalloproteinase
ATC: acute traumatic coagulopathy
CARS: compensatory anti-inflammatory response
CRASH: corticosteroid randomisation after significant head injury
DAMPs: damage-associated molecular patterns
DNA: deoxyribonucleic acid
EoT: endotheliopathy of trauma
HMGB1: high-mobility group box 1
HPA: hypothalamic-pituitary axis
ICU: intensive care unit
IMPACT: international mission for prognosis and analysis of critical trials in TBI
ISS: injury severity score
NETs: neutrophil extracellular traps
PAI-1: plasminogen activator inhibitor-1
PICS: persistent inflammation, immunosuppression and catabolism syndrome
RISC: revised injury severity classification
SAMPs: suppressing damage-associated molecular patterns
TBI: traumatic brain injury
TIC: trauma-induced coagulopathy
tPA: tissue plasminogen activator

1. Introduction

Trauma, encompassing injuries from road traffic accidents, falls, violence, and other external causes, is a major global public health concern. It ranks among the leading causes of death and disability worldwide, particularly affecting young and economically productive individuals. According to the World Health Organization (WHO), injuries are responsible for over **5 million deaths each year**, accounting for approximately **9% of global mortality**—a burden greater than that of HIV/AIDS, tuberculosis, and malaria combined. For every death, there are dozens of hospitalizations, hundreds of emergency department visits and individuals left with long-term disabilities.

The global burden of trauma is **unevenly distributed**, disproportionately affecting **low- and middle-income countries (LMICs)**. Over **90% of injury-related deaths** occur in LMICs, where trauma care systems are often underdeveloped or fragmented. Factors such as limited access to emergency services, poor infrastructure, lack of trained personnel, and insufficient funding exacerbate trauma outcomes in these regions. In contrast, high-income countries (HICs) have witnessed significant reductions in trauma-related mortality over recent decades due to organized trauma systems, improved prehospital care, and evidence-based in-hospital interventions.

Road traffic injuries (RTIs) remain the leading cause of death among people aged 5 to 29 years, with more than **1.3 million deaths** annually. The burden of RTIs is growing rapidly in LMICs due to increasing motorization without commensurate improvements in road safety measures. Pedestrians, cyclists, and motorcyclists are particularly vulnerable in urban environments lacking adequate infrastructure.

Other significant contributors to trauma include **falls**, particularly among the elderly, and **interpersonal violence**, which is especially prevalent among young men in certain regions of Latin America and sub-Saharan Africa. **Self-harm and suicide** are also major causes of injury-related deaths globally, particularly in Asia. In conflict-affected regions, trauma from war and violence imposes a unique and often overwhelming strain on already fragile healthcare systems.

The **epidemiology of trauma is influenced by demographic, economic, and cultural factors**, which shape both the patterns of injury and the systems in place to respond to them. For example, urbanization, industrialization, aging populations, and changing social dynamics all influence the incidence and outcomes of trauma.

Efforts to address the global burden of trauma require a **multifaceted approach**. These include the development of trauma surveillance systems, implementation of national injury prevention programs, establishment of trauma systems with designated trauma centers, and investment in education and training of emergency personnel. Global health organizations have increasingly recognized trauma as a **neglected epidemic**, calling for greater attention and resource allocation to improve injury prevention and trauma care, particularly in resource-limited settings.

In sum, trauma remains a significant and growing cause of global morbidity and

mortality. Addressing this challenge necessitates coordinated action across health systems, governments, and international partners to reduce disparities, improve outcomes, and ultimately save lives.

2. Definitions and mortality distribution

Severe trauma refers to an injury — or set of injuries — that threatens a patient's **life or functional prognosis**. This may be due to the **severity of a specific injury** (e.g. severe traumatic brain or spinal cord injury), the **cumulative impact** of multiple injuries (e.g. hemorrhagic shock), or **patient-specific factors**. For instance, a femur fracture will have **different consequences in a young adult, an elderly patient, or an immunocompromised individual**. This overall effect is described as **trauma burden**.
Polytrauma is a subgroup within severe trauma; the term "polytrauma" is now discouraged in favor of **"severe trauma."**

The **leading cause of death** in severe trauma is **traumatic brain injury**, followed by **hemorrhage** (20–30%) . In the 1980s, Trunkey described trauma mortality as **trimodal** (immediate, early, late). Today, mortality is generally **yet in recent years several studies observed a shift towards**:

- ~50% of deaths within the **first 2 hours**
- 25–30% within **6 hours**
- The remainder in the **days following trauma**.

Late mortality occurs in the **ICU**, often due to **multiple organ failure** including **ARDS**, **pneumonia**, or **pulmonary embolism** .
Hemorrhage is the **leading preventable cause of death**, typically due to delays in diagnosis or management. **Respiratory causes** account for around **10% of preventable deaths**.

3. Trauma scores and systems

3. 1. Trauma scores

3. 1. 1. Trauma Scoring Systems: Focus on the Injury Severity Score (ISS)

Trauma scoring systems are essential tools in trauma care and research. They provide a standardized method to assess injury severity, predict outcomes, guide triage, allocate resources, and evaluate quality of care. These systems can be broadly categorized into physiologic, anatomic, and combined scores, each offering unique insights into a trauma patient's condition.

One of the most widely used anatomical trauma scoring systems is the Injury Severity Score (ISS). Developed in 1974, the ISS provides a single numerical value to represent the overall severity of injury in a polytrauma patient and remains a cornerstone of trauma research and system evaluation worldwide.

3. 1. 2. Understanding the ISS

The ISS is derived from the Abbreviated Injury Scale (AIS), which assigns a severity code (ranging from 1 to 6) to individual injuries in 6 specific body regions:

1. Head and neck
2. Face
3. Chest
4. Abdomen and pelvic contents
5. Extremities and pelvic girdle
6. External (skin and soft tissues)

The AIS codes are based on the threat to life associated with the injury:

- 1 = Minor
- 2 = Moderate
- 3 = Serious
- 4 = Severe
- 5 = Critical
- 6 = Maximal (virtually unsurvivable)

To calculate the ISS, the highest AIS scores in the three most severely injured body regions are identified, each score is squared, and the results are summed:

$ISS=(AIS1)^2+(AIS2)^2+(AIS3)^2$

The ISS ranges from 1 to 75. If any injury is assigned an AIS of 6, the ISS is automatically set to 75, indicating unsurvivable trauma. An ISS >15 is generally considered to indicate major trauma. Yet, ISS is often not accurately known at the time of triage decisions or trauma team activation. This threshold of 16 or more of ISS is usually applied retrospectively to separate severe and less severe trauma as benchmark to estimate under or overtriage).
The ISS has been extensively validated and correlates with mortality, morbidity, hospital length of stay, and resource use. It is commonly used in trauma registries, benchmarking between institutions, trauma research, and policy development. The strengths of ISS lie in its simplicity and global acceptance, making it useful for comparing injury severity across populations and time periods. It is especially valuable for evaluating multi-system trauma, as it captures the cumulative burden of injuries.

However, the ISS has several limitations:

- It does not account for multiple injuries within the same body region.
- It lacks physiologic data (e.g., blood pressure, consciousness), which can be critical for early outcome prediction or triggering trauma team activation
- It is retrospective and requires accurate injury coding using AIS, limiting its utility in the prehospital or emergency department settings.

To address these shortcomings, alternative or complementary scoring systems have been developed, including:

- Revised Trauma Score (RTS) – a physiologic score using GCS, systolic blood pressure, and respiratory rate.
- Trauma and Injury Severity Score (TRISS) – a combined score using RTS, ISS, and age to predict survival.
- New ISS (NISS) – a modified version that uses the three highest AIS scores regardless of body region, improving predictive accuracy for some outcomes.

Despite newer alternatives, the ISS remains a benchmark tool in trauma care and continues to play a vital role in trauma systems worldwide.

3. 1. 3. Other scoring systems

More complex scores have been proposed to predict outcome and allow for benchmarking of hospitals by taking into account the case mix. RISC I and more recently RISC II score, established from data collected in the Trauma Register DGU (Deutsche für Unfallchiururgie), showed robust discrimination and precision to assess prognosis on admission in trauma patients.
In patients with TBI (GCS of 14 or less), the CRASH (corticosteroid randomisation after significant head injury) trial collaborators developed and validated the CRASH score prognostic models for death at 14 days and death/disability at 6 months. The IMPACT (International mission for prognosis and analysis of clinical trials in TBI) score

investigators developed prognostic models for predicting 6 months outcome in adult patients with moderate to severe head injury (GCS of 12 or less). It includes clinical, lab and CT-scan variables on admission.

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3. 2. Trauma systems

Effective trauma care does not rely solely on emergency medical services or advanced surgical techniques—it depends on the integration of these elements into a comprehensive trauma system. Trauma systems are organized, multidisciplinary networks designed to optimize the care of injured patients from the point of injury through rehabilitation. These systems play a critical role in reducing preventable deaths and improving functional outcomes.

Core Components of a Trauma System
A trauma system encompasses all phases of care:

- Injury prevention
- Prehospital care
- Hospital-based acute care
- Rehabilitation
- Performance improvement
- Education and training
- Research and system governance

Key elements include:

- Designated trauma centers (levels I–IV or equivalent)
- Prehospital triage and transport protocols
- Data collection and trauma registries
- Quality assurance programs
- Public health integration

The ultimate goal is to ensure that patients receive the right care, at the right time, in the right place.

3. 2. 1. Trauma System Models in Different Countries

1. United States
The U.S. has one of the most mature trauma system, organized at the state level but coordinated nationally. Trauma centers are designated by the American College of Surgeons (ACS) or state authorities into:

- Level I (comprehensive trauma care and academic research),
- Level II (similar capabilities without research requirements),
- Level III (initial stabilization and transfer),
- Level IV/V (basic emergency care and transfer capabilities).

The U.S. model emphasizes regionalization, rapid prehospital triage, standardized trauma team activation, and continuous quality improvement, supported by trauma registries like the National Trauma Data Bank (NTDB).

2. United Kingdom

The UK adopted the Major Trauma Centre (MTC) model more recently. Since 2012, the UK has implemented regional trauma networks linking MTCs with trauma units and ambulance services. MTCs are responsible for managing complex injuries, while trauma units handle minor injuries and transfers. The NHS England coordinates trauma systems with a strong emphasis on standard protocols, rehabilitation planning, and outcome measurement through the Trauma Audit and Research Network (TARN).

3. Germany

Germany's trauma system is based on the "white paper" on trauma care developed by the German Society for Trauma Surgery. It established Trauma Networks (TraumaNetzwerk DGU®), which consist of regional hospital networks categorized into local, regional, and supra-regional trauma centers. Emphasis is placed on structured training, standardized care algorithms, and telemedicine consultations, especially in rural areas.

4. France

France utilizes a pre-hospital physician-led model, with SAMU (Service d'Aide Médicale Urgente) providing advanced care at the scene. Trauma centers are categorized into CHUs (University Hospitals) and CHRs (Regional Hospitals). The trauma pathway emphasizes rapid coordination between emergency services, mobile ICU teams, and designated centers (most regional trauma systems are now getting organised with trauma centres of level I to III designated by regional health agencies) capabilities. The national registry is the Traumabase.

5. Australia and New Zealand

These countries have trauma systems tailored to their geography. In Australia, each state (e.g., New South Wales, Victoria) runs its own trauma network with centralized major trauma centers and retrieval services such as HEMS (Helicopter Emergency Medical Services). New Zealand has two major trauma centers and a National Trauma Network established to improve system coordination and standardization.

6. Low- and Middle-Income Countries (LMICs)

In many LMICs, trauma systems are either rudimentary or non-existent. Barriers include:

- Limited prehospital care infrastructure
- Lack of trauma training
- Inconsistent hospital capabilities
- Poor access to rehabilitation

However, efforts are underway to implement essential trauma care frameworks as recommended by the World Health Organization (WHO), including basic trauma registries, first responder training, and protocol-driven emergency care.

3. 2. 2. Impact of trauma systems on patient outcomes and future challenges

The introduction of trauma systems has repeatedly been associated with:

- Reduced mortality and morbidity
- Shorter hospital stays
- Improved functional outcomes
- Better resource allocation

For instance, the U.S. National Study on the Costs and Outcomes of Trauma (NSCOT) demonstrated a 25% reduction in mortality when patients were treated in trauma centers compared to non-trauma hospitals. Similarly, the UK's implementation of regional trauma networks led to a significant reduction in 30-day mortality, particularly for severely injured patients.

Other positive outcomes include:

- Faster time to definitive care
- Greater access to specialized interventions (e.g., neurosurgery, interventional radiology)
- Improved rehabilitation planning
- Enhanced disaster preparedness and mass casualty response

Moreover, trauma registries facilitate benchmarking, help identify gaps in care, and guide policymaking.

Despite clear benefits, trauma systems face ongoing

Challenges

- Disparities in access in rural or underserved areas
- Integration of rehabilitation services
- Sustainable funding and resource allocation
- Standardization across regions or countries
- Addressing non-communicable trauma (e.g., geriatric falls, self-harm)
- Lack of sufficient funding for research, prevention and system consolidation despite high societal burden

Future trauma systems are evolving towards:

- Data-driven decision-making using AI and real-time dashboards
- Inclusive systems that involve all hospitals in trauma care
- Public health integration focusing on injury prevention
- Cross-border coordination in areas with high population mobility
- Telemedicine and digital trauma platforms to support rural care

Global initiatives like the WHO Essential Trauma Care Project and collaborations like the Pan-European Trauma Network aim to bridge disparities by promoting training, standardization, and system development, especially in resource-limited settings.

Trauma systems are critical infrastructures that determine how quickly and effectively injured patients receive life-saving care. While their structures vary globally—tailored to healthcare systems, geography, and resources—their core mission remains the same: to reduce preventable death and disability through coordinated, timely, and evidence-based care.

The maturation of trauma systems has demonstrably improved patient outcomes, but gaps remain, particularly in LMICs and rural areas. Moving forward, investment in inclusive, efficient, and adaptive trauma systems is essential to meeting the global burden of trauma and ensuring equitable care for all.

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(MacKenzie et al. 2006; NHS 2020; German Trauma Society) 2022; TARN 2023; WHO 2012; Gauss et al. 2024)

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4. Mechanisms of injury

Trauma results from the transfer of energy to the body. Mechanisms include:

- **Blunt trauma** (e.g. motor vehicle crashes, falls): Most common globally; leads to widespread internal damage from deceleration forces, compression, or shear.
- **Penetrating trauma** (e.g. gunshot, stab wounds): Focal injuries along the projectile's path.
- **Blast injuries**: Complex injuries from explosions (primary, secondary, tertiary, quaternary effects).
- **Thermal trauma**: Burns due to heat, chemicals, electricity.

Understanding the mechanism helps predict internal injuries and guide initial imaging and intervention. High-energy mechanisms warrant full trauma imaging even in asymptomatic patients.

4. 1. Blunt trauma

Blunt trauma occurs when external force is applied without skin penetration. It's most often seen in road traffic accidents (RTAs), falls, and assaults.
Common injuries:

- **Thoracic**: Rib fractures, pulmonary contusions, hemothorax, pneumothorax.
- **Abdominal**: Liver and spleen lacerations, hollow viscus injury.
- **Cranial**: Concussion, intracranial hemorrhage.
- **Spinal or orthopedic**: Vertebral fractures, pelvic disruption, spinal cord injury

Initial evaluation includes **primary survey (ABCDE)** and **eFAST ultrasound**. If stable, **CT imaging** is the gold standard for detecting internal injuries.

Management is driven by injury severity and location: airway protection, hemorrhage control, optimise cerebral perfusion, analgesia, and surgical intervention if necessary. Mortality increases with multiple rib fractures or combined head and abdominal trauma.

4. 2. Penetrating trauma and comparison

Penetrating trauma involves an object piercing the skin and damaging internal structures. Mechanisms include gunshot wounds (GSWs), stabbings, and impalements.

Key characteristics:

- Injury follows a linear trajectory (unlike blunt trauma)
- Damage depends on kinetic energy (e.g. high-velocity bullets cause cavitation)
- Higher infection risk

Table 1: Blunt vs. Penetrating Trauma

Aspect	Blunt Trauma	Penetrating Trauma
Mechanism	Compression, shear	Direct tissue disruption
Organs affected	Widespread	Localized
Imaging	CT scan often needed	May go directly to surgery

Management prioritizes **bleeding control** and rapid assessment for surgical indications. For hemodynamically unstable patients, **damage control surgery** may be lifesaving.

4. 3. Blast injuries

Blast trauma is classified into **four types**:

1. **Primary**: Shockwave injuries (barotrauma to lungs, intestines, eardrums)
2. **Secondary**: Injuries from projectiles (e.g., shrapnel)
3. **Tertiary:** Body displacement (blunt trauma)
4. **Quaternary**: Burns, inhalation, radiation, crush injuries

Blast trauma causes polytrauma even without visible injury. Pulmonary barotrauma is common and life-threatening. Tension pneumothorax, air embolism, and gastrointestinal rupture may occur.

Diagnosis:

- FAST and chest X-ray immediately
- CT for chest, abdomen, head once stabilized

Management:

- Oxygen and early intubation for blast lung

- Chest decompression for pneumothorax
- Surgical debridement of penetrating injuries
- Fluid resuscitation and damage control surgery if needed

Civilian blast injuries are increasing in both conflict zones and from accidental industrial explosions.

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5. Physiological response to trauma

With improvement of trauma systems worldwide, early deaths associated with major haemorrhage have decreased and 20% of trauma patients now die from late complications while in the ICU. The likelihood of patients surviving the initial impact of a major trauma is increasing and so the likelihood to develop shock-induced multiple organ failure and post-intensive care syndrome. Thus, more patients are now surviving to reach the hospital, they are older, more severely injured have undergone greater injury loads, have had more profound shock and ischemia-reperfusion injury.

5. 1. Time frame of physiological responses to trauma

Severe trauma triggers many simultaneous interrelated processes which end up in endotheliopathy of trauma (EoT), trauma-induced coagulopathy (TIC), mitochondrial injury, persistent inflammation, immunosuppression, and catabolism syndrome (PICS).
The first steps appear within the first minutes after trauma. Indeed, large tissue attrition (muscular, skeletal), blood brain barrier breakdown and organ hypoperfusion release a large number of intracellular compounds and extracellular matrix commonly referred as damage-associated molecular patterns (DAMPs). For instance, cell free haemoglobin is released shortly after traumatic injury because of endogenous haemolysis. It is partially scavenged by haptoglobin and, as it captures nitric oxide, cell free haemoglobin may promote oxidative damage and endothelial dysfunction. Cell-free DNA (either from nuclear or mitochondrial origin) results from necrosis of injured cells, apoptosis and active release by netosis (the cellular phenomenon resulting in cell extrusion of neutrophil extracellular traps, NETs). It is associated with endotheliopathy, increased length of stay in the ICU and increased mortality.
Simultaneously, the hypothalamic-pituitary axis (HPA) and sympathetic system are massively recruited and end up in a sympathetic stress response which impede cardiovascular coupling and promote widespread endothelial dysfunction.

Although these events are interrelated and merely simultaneous, we will approach them separately for the sake of understanding.

5. 2. Clinical features of physiological responses to trauma

A schematic visualisation of the physiological response to multiple trauma and TBI is provided in the Figure 1 below.

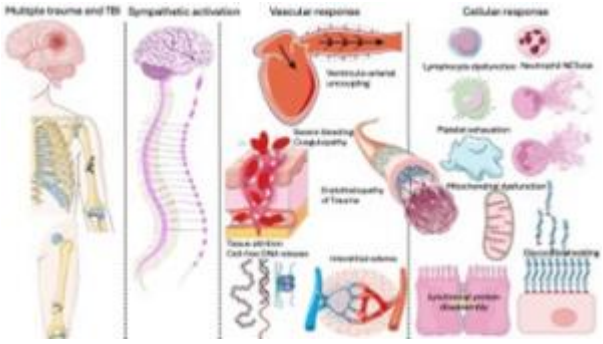

Figure 1: A schematic visualisation of the physiological response to multiple trauma and TBI

5. 2. 1. Central Nervous System surge, sympathetic hyperactivity and cardiovascular coupling

The brain is among the first organs being affected by severe trauma. Indeed, pain signals and alarmins from injured sites all converge to the brain especially if the brain/blood barrier is impaired by concomitant traumatic brain injury. The HPA and nucleus tractus solitarius then multiply sympathetic outflow. The sympathetic surge undermines physiological ventriculo-arterial coupling and may trigger splanchnic hypoperfusion, gut wall ischemia, microbiome alteration and bacterial translocation. The sympathetic overdrive also sows the seeds of endothelial dysfunction. Indeed, shock-induced sympatho-adrenal hyperactivation damages the endothelium within the microcirculation7.

5. 2. 2. Endothelial dysfunction

The endothelial surface is lined with glycocalyx which expands endothelial surface area from 3000 to 46 000 m. It also contains up to 1.7L of non-circulating plasma. This negatively charged surface coated with sulphated proteoglycans traps positively charged soluble components (proteins and growth factors) and prevents interactions of endothelial cells with platelets and leukocytes by steric hindrance.

Once injured, the glycocalyx sheds and releases large amount of glycoproteins and proteoglycans in the systemic circulation. The exact mechanism by which glycocalyx is disrupted remains to be established but it may involve enzymes named sheddases (matrix metalloproteases, a disintegrin and metalloproteinase (ADAMs), heparanases and hyaluronidases). One of the most assayed molecules is syndecan-1, the backbone of endothelial glycocalyx. Shedding of glycocalyx results in exposure of heparan sulfate from endothelial cells, promotes auto-heparinization and facilitates non-specific adhesion of platelets and leukocytes to the endothelium. EoT also includes increased transendothelial and inter-endothelial permeability which is associated with the degree of shock (correlated with base excess) and implies an increased activation of Rhoa GTPases. Endothelial permeability may also be due to a calcium-triggered contraction of the actin cytoskeleton and junctional proteins disassembly. Indeed, severe traumatic load and shock induce a large endothelial cell calcium influx, mediated by transient receptor potential vanilloid 4 activation which may also account for the hypocalcaemia frequently encountered in severe trauma patients. As endothelial permeability increases at the brain level, the brain/blood barrier becomes disrupted, and the brain

loses its immune privilege over the rest of the body.
The healthy endothelium exerts many critical regulatory functions over the coagulation cascade which may be lost in case of coagulopathy. Indeed, the endothelium physiologically binds anti-thrombin III, expresses thrombomodulin and endothelial protein C receptor and releases tissue factor pathway inhibitor. Shock-induced endotheliopathy (SHINE) in trauma is a heterogeneous syndrome across patients with at least 4 different identified phenotypes which are merely independent of syndecan-1 levels.

It is hypothesized that plasma-induced replenishment of fibrinogen and endothelial healing may account for some of plasma beneficial effects. Potential vasculoprotective agents in plasma are albumin, fibrinogen, adiponectin and sphingosine-1 phosphate. As endotheliopathy of trauma develops within minutes of injury, plasma should be administered early for the timely correction of both endotheliopathy and coagulopathy. Similarly, early fibrinogen supplementation may both correct trauma-induced coagulopathy and endothelial dysfunction. Indeed, fibrinogen interacts with syndecan-1 and stabilizes the endothelium, reducing its inter-cell permeability. By binding syndecan-1, fibrinogen also modulates sheddases by regulating their gene expression and shields syndecan-1 cleavage site. In the clinical arena, prehospital plasma may benefit some patients (blunt trauma, traumatic brain injury (TBI), large traumatic load with injury severity score (ISS) >30) but their early accurate identification, based on biomarkers and computational methods, remains a challenge. Recent randomized trials such as PAMPER, RePHILL and SWIFT could not establish an effect on mortality.

5. 2. 3. Acute traumatic coagulopathy (ATC) and Trauma-Induced Coagulopathy (TIC)

Trauma-induced coagulopathy could be an evolutionary conserved compensatory mechanism by which the body blunts the shock-induced prothrombotic endothelium within the microcirculation to maintain tissue perfusion and oxygenation.
The dominant phenotype is usually fibrinolytic on presentation to the trauma bay and progressively becomes prothrombotic while the patient is admitted to the ICU.
Endothelial release of tissue factor, platelet activating factor and von Willebrand Factor activates platelets beyond their primary haemostasis role and results in “platelet exhaustion”. This functional platelet failure may weaken the clot and jeopardizes haemostasis.
Ischemia/reperfusion injury decreases plasma fibrinogen concentrations and fibrinolysis becomes dysregulated owing to the overwhelming release of tissue plasminogen activator (tPA) from Weibel-Palade bodies which activates plasminogen into plasmin. Injured cerebral tissue also releases large amounts of tPA. Many simultaneous phenomena are encountered at the early phase of trauma, which promote bleeding:

- increased fibrinolysis from endothelial release of large amounts of tPA and protein C binding to plasminogen activator inhibitor-1 (PAI-1)
- decreased coagulation enzyme activity

- decreased platelet function (defective calcium mobilization and glycoprotein VI function) and consumption
- hypofibrinogenemia and fibrinogen breakdown by histones
- delayed thrombin generation
- reduced clot strength

After some hours or days, a prothrombotic phenotype takes over. It is then characterized by a fibrinolytic shutdown due to reduced plasminogen activity (as a result of PAI-1 release, degradation by NETs-bound elastases and byproducts of cell injury). Thus, the risk of venous thromboembolism is highly increased in those severely injured patients who furthermore often develop resistance to low molecular wight heparins due to progressive antithrombin deficiency.
The treatment of TIC lies beyond the scope of this chapter, it will be dealt with on chapter 11.3 Coagulation and managing thromboembolic risk and supplemental clues can be found in recent extensive recommendations.

5. 2. 4. Mitochondrial dysfunction

For some authors, severe trauma is an “acute acquired mitochondrial disease”. Trauma-induced inflammation and hypoperfusion result in mitochondrial damage with dysfunctional mitochondrial respiratory chain, energy failure, increased production of reactive oxygen species, loss of mitochondrial DNA repair functions, release of cytochrome c and mitochondrial DNA in the systemic circulation. This is all the more important as mitochondrial DNA lacks repair mechanism and histone protection. Potential tracks to cure post-traumatic mitochondrial dysfunction may include intercellular mitochondrial transfer from mesenchymal stem cells as a carrier.

DAMPs from mitochondrial origin (mitochondrial DNA, formyl peptide) then exacerbate remote injuries in the lung and central nervous system. Mitochondrial dysfunction in white blood cells is thought to contribute to trauma-induced immunosuppression.

Scavenging mitochondrial DAMPs on the site of sterile injury with microfiber meshes or scavenging them with polymers has been proposed by some authors but these strategies lack a prospective clinical validation.

5. 2. 5. Immunosuppression and Persistent Inflammation Immunosuppression and Catabolism Syndrome (PICS)

PICS may now replace multi-organ failure as the predominant phenotype of chronic critical illness after severe trauma. Indeed, as ICU techniques improve, multi-organ failure is less and less lethal and patients experience the burden of compensatory anti-inflammatory response (CARS). Thus, suppressing/inhibiting DAMPs (SAMPs) like prostaglandin E2 or annexin A1 are now recognised as fuelling this anti-inflammatory response and their level was found inversely correlated with HLA-DR expression on monocytes. Some nuclear DAMPs like high-mobility group box 1 (HMGB1) can either

promote or inhibit immune cell function depending on their redox state. Formyl peptides (mitochondrial DAMPs) attract neutrophils towards distal injury sites, away from regions of bacterial challenge.

Immune suppression following trauma relies on many redundant mechanisms often designed as the “storm”. Interestingly, what differentiates surviving from dying patients is not the magnitude of the biologic storm, but the time taken to resolve it.

(Wei et al. 2018) established a strong association between endotheliopathy of trauma (increased plasma syndecan-1 above 40ng/mL) and risk of developing subsequent sepsis (OR: 2.94; 95% CI (1.53-5.66)). Release of large quantities of DAMPs and ischemia/reperfusion end up in immune dysfunction whose cellular manifestations are reduced neutrophil and monocyte chemotaxis capacities, reduced antimicrobial functions and lymphocyte dysfunction.

These mechanisms are exacerbated in traumatic brain injury patients. Indeed, TBI triggers intense and prolonged activation of the sympathetic nervous system which, mediated by ß-adrenoreceptors, upregulates death signals on CD4+ and CD8+ T cells.
New technologies like whole blood transcriptome allow for precise prediction of multi-organ failure following trauma. However, they require extensive analysis and large machine learning algorithms which make them currently inoperative in the clinical arena but may provide useful tools in the near future to enhance clinical decision making and enrich clinical prospective data focusing on immunomodulation.
Lymphocyte mitochondrial exhaustion also manifests in trauma patients and may facilitate the development of secondary sepsis. Gouel-Cheron et al. have investigated the monocyte HLA-DR (mHLA-DR) expression in 80 trauma patients and observed a 29% sepsis incidence, most of septic episodes being pneumonias. A ratio of mHLA-DR expression between day 3 and day 1 < 1.2 was the only factor associated with onset of sepsis (Odds ratio: 5; 95%CI(1.6 - 19);p = 0.008; 88% sensitivity).

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