**REVIEW**

**Pathophysiology of polytrauma**

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**KEYWORDS**
Trauma; Injury; Pathophysiology; Host defence response; Systemic inflammatory response syndrome (SIRS); Compensatory anti-inflammatory response syndrome (CARS); Apoptosis; Necrosis; Multiple organ dysfunction syndrome (MODS); Multiple organ failure (MOF); Damage control; Mortality

**Summary** Immediate and early trauma deaths are determined by primary brain injuries, or significant blood loss (haemorrhagic shock), while late mortality is caused by secondary brain injuries and host defence failure. First hits (hypoxia, hypotension, organ and soft tissue injuries, fractures), as well as second hits (e.g. ischaemia/reperfusion injuries, compartment syndromes, operative interventions, infections), induce a host defence response. This is characterized by local and systemic release of pro-inflammatory cytokines, arachidonic acid metabolites, proteins of the contact phase and coagulation systems, complement factors and acute phase proteins, as well as hormonal mediators: it is defined as systemic inflammatory response syndrome (SIRS), according to clinical parameters. However, in parallel, anti-inflammatory mediators are produced (compensatory anti-inflammatory response syndrome (CARS). An imbalance of these dual immune responses seems to be responsible for organ dysfunction and increased susceptibility to infections.

Endothelial cell damage, accumulation of leukocytes, disseminated intravascular coagulation (DIC) and microcirculatory disturbances lead finally to apoptosis and necrosis of parenchymal cells, with the development of multiple organ dysfunction syndrome (MODS), or multiple organ failure (MOF). Whereas most clinical trials with anti-inflammatory, anti-coagulant, or antioxidant strategies failed, the implementation of pre- and in-hospital trauma protocols and the principle of damage control procedures have reduced post-traumatic complications. However, the development of immunomonitoring will help in the selection of patients at risk of post-traumatic complications and, thereby, the choice of the most appropriate treatment protocols for severely injured patients.

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**Contents**

Introduction ................................................................. 692
Two-hit theory ............................................................... 693
Hyperinflammation—SIRS ................................................ 694

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Introduction

Despite improved traffic and occupational safety, as well as significant advances in pre- and in-hospital management, severe trauma represents the most frequent cause of death in people below the age of 40 years.\(^4,38,60,128,149,168\) Immediate and early trauma deaths are determined by severe primary brain injuries, or significant blood loss (haemorrhagic shock) after blunt, or penetrating, trauma.\(^4,38,60,70,128,149,158,168,173,181\) Late mortality is caused by secondary brain injuries and host defence failure.\(^4,70,158,168,173\) Direct, or indirect, mechanical forces induce organ and soft tissue injuries, or fractures. However, these first hits represent a greater challenge, as local tissue damage, such as contusions or lacerations, hypoxia and hypotension, induce further local and systemic host responses, to preserve the immune integrity and stimulate reparative mechanisms.\(^164\) This systemic inflammation was defined in 1991, through the consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM), as systemic inflammatory response syndrome (SIRS).\(^6\) At least two of the four clinical parameters (Table 1) must be fulfilled for the diagnosis of SIRS.\(^6\) It is characterized by the local and systemic production and release of different mediators, such as pro-inflammatory cytokines, complement factors, proteins of the contact phase and coagulation systems, acute phase proteins, neuroendocrine mediators and an accumulation of immunocompetent cells at the local site of tissue damage (Fig. 1).\(^17,18,40,91,163,169,195\) In addition, this systemic inflammation is augmented by second hits, such as ischaemia/reperfusion injuries, surgical interventions or infections (two-hit theory).\(^163,164\)

However, different clinical trials and animal models have shown that, in parallel with avoid the autodestructive effects of immunocompetent cells (Fig. 1).\(^19,88,91,120,195\) An imbalance between these dual immune responses, with an overwhelm-

<table>
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<th>Table 1 Clinical parameters of systemic inflammatory response syndrome (SIRS)</th>
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<tr>
<td>1. Heart rate &gt; 90/min</td>
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<td>2. Breathing rate &gt; 20/min, respectively, hyperventilation with decrease of the arterial CO(_2) partial pressure (P(_a)CO(_2)) under 32 mmHg</td>
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<tr>
<td>3. Temperature &gt; 38 °C or &lt; 36 °C</td>
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<td>4. Number of leukocytes &gt; 12,000/mm(^3) or &lt; 4000/mm(^3) or ≥ 10% juvenile neutrophil granulocytes</td>
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For the definition of SIRS, two or more parameters must be fulfilled. Sepsis is defined as SIRS with detection of bacteremia or bacterial focus.\(^6\)
failure of clinical trials with immunotherapies in the past two decades and the significance for the development of post-traumatic immunomonitoring.

**Two-hit theory**

The complex cascade of the host defence response is stimulated by primary and secondary insults (two-hit theory). The trauma impact determines primary organ, or soft tissue, injuries and fractures (first hit; trauma load) with local tissue damage as well as an activation of the systemic inflammatory response. In addition, secondary endogenous and exogenous factors play a crucial role in the initiation and severity of post-traumatic complications. Typical endogenous (antigenic load) second hits are respiratory distress with hypoxia, repeated cardiovascular instability, metabolic acidosis, ischaemia/reperfusion injuries, dead tissue, contaminated catheters, or tubes, and infections. Surgical interventions with severe tissue damage, hypothermia or blood loss, inadequate, or delayed, surgical, or intensive care, after neglected or missed injuries, as well as massive transfusions, represent exogenous second hits (interventional load or surgical load).

The severity of organ injuries, varying from contusions to complete lacerations, and the remaining organ perfusion influence the post-traumatic systemic inflammatory response. The highest incidence for the development of SIRS can be observed after isolated or combined severe head injuries. Although the central nervous system has been defined historically as an "immunologically privileged organ", due to its separation from the peripheral circulation by the blood–brain barrier (BBB), different studies have shown that the brain acts as a target and as an effector organ. Glial cells, astrocytes and neurons are potent producers of pro- and anti-inflammatory mediators and their receptors, leading to local tissue damage and a systemic response. In addition, systemic mediators released by peripheral immune, endothelial, or parenchymal cells influence the integrity of the BBB, leading to a bi-directional communication of the inflammatory mediators. Primary epidural hematoma, or cerebral oedema, as well as post-traumatic secondary oedema, induced by local and
systemic inflammatory processes, are responsible for the development of a cerebral compartment syndrome, which is lethal without intervention.\textsuperscript{173}

Thoracic injuries, with multiple rib fractures, lung contusions, or lacerations, are often complicated by local and systemic inflammation, with or without manifestation of pneumonia, acute lung injury (ALI), or acute respiratory distress syndrome (ARDS).\textsuperscript{9,120,137} Injuries of intra-abdominal organs cause haemorrhagic shock (liver, spleen, vascular injuries) and aseptic, or septic, peritonitis (pancreatic or hollow organ injuries).\textsuperscript{11} Severe intra-abdominal or retroperitoneal haemorrhage, after vascular, renal, or pelvic injuries, as well as systemic inflammatory processes in septic patients, can lead to an abdominal compartment syndrome with systemic complications.\textsuperscript{59,125}

Soft tissue injuries of the extremities, especially in patients with haemorrhagic shock, are often complicated by decreased perfusion (low-flow hypoxia), with a high risk for ischaemia/reperfusion injuries and secondary infections. Furthermore, severe muscle crushing injuries predispose to a compartment syndrome with muscle necrosis, rhabdomyolysis and finally acute renal failure (crush kidney).\textsuperscript{159} Fractures of the femur, multiple long bone fractures and unstable pelvic ring fractures are characterized by a high blood loss and contribute to the inflammatory activity.\textsuperscript{22,49,53} Additionally, fat embolism syndrome is an infrequent clinical consequence with the typical triad of pulmonary distress, mental changes and petechial rash, 24–48 h after pelvic or long-bone fractures.\textsuperscript{148}

The incidence of septic complications has increased during the last decade.\textsuperscript{122} Closed wounds with large soft tissue damage and open wounds, or fractures, as well as neglected soft tissue injuries, represent portal of entry for microorganisms.\textsuperscript{205,210} Central venous catheters, intracheal tubes, chest tubes and bladder catheters are often contaminated and raise the infection risk in severely injured patients.\textsuperscript{32} The most common reasons for sepsis after trauma are hospital acquired pneumonia, catheter infections, intra-abdominal and wound infections.\textsuperscript{9,140,179} Furthermore, ischaemic lesions of the gastrointestinal tract after haemorrhagic shock seem to be responsible for bacterial translocation into the circulation (gut hypothesis).\textsuperscript{103,130}

\section*{Hyperinflammation—SIRS}

Tissue damage induces in commensurate with the severity of trauma (trauma load), genetic factors (gene polymorphism), the general condition of the host and the type of antigens (antigenic load), both local and systemic release of pro-inflammatory cytokines and phospholipids.\textsuperscript{40,88,143,171,190} Polymorphonuclear leukocytes (PMNL), monocytes, tissue macrophages (e.g. alveolar macrophages), lymphocytes, natural killer cells, and parenchymal cells are involved in a complex network of this host defence response.\textsuperscript{195} An overwhelming pro-inflammatory response (hyperinflammation) leads to the clinical manifestation of SIRS and finally to host defence failure (MODS, MOF).\textsuperscript{55,71,135,195}

Cytokines are polypeptides and act in a para- or autocrine manner.\textsuperscript{40} They are capable of exerting many effects on an array of cell types (pleiotropy).\textsuperscript{40} Besides hyperacute pro-inflammatory cytokines, such as tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), or interleukin-1\(\beta\) (IL-1\(\beta\)), with an effect after 1–2 h, there exist subacute (secondary) cytokines such as IL-6, IL-8 (neutrophil activating peptide (NAF)), macrophage migratory factor (MMF), high motility group protein -1 (HMG-1), as well as IL-12 and IL-18, interferon-\(\gamma\) (IFN-\(\gamma\)) and tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) or IL-8 serum levels are observed in patients with systemic inflammation, as well as in bronchoalveolar lavage fluids of patients with thoracic trauma, or acute respiratory distress syndrome.\textsuperscript{42,43,100,121,187} In addition, IL-6 serum levels correlate with the ISS, the incidence of MODS, ARDS, or sepsis and with outcome.\textsuperscript{15,121,166}

Through the influence of antigens, T-helper lymphocytes (T\(_4\) cells, CD4\(^+\) cells) differentiate into two phenotypes, the T\(_{41}\) and T\(_{42}\) lymphocytes.\textsuperscript{146} T\(_{41}\) cells support the pro-inflammatory cascade through secretion of IL-2, interferon-\(\gamma\) and TNF-\(\beta\), whereas T\(_{42}\) cells are important producers of anti-inflammatory mediators. Monocytes/macrophages are involved in the differentiation of T\(_{41}\) cells, via the secretion of IL-12. Depressed IL-12 production after trauma correlated with a shift of the T\(_{41}/T_{42}\) ratio towards the T\(_{42}\)-type pattern, with an adverse clinical outcome.\textsuperscript{146}

Pro-inflammatory cytokines activate the recruitment and phagocytosis activity of PMNL (priming), the immune cells of the first hours (the first defence line), and stimulate PMNL to release proteases and free oxygen radicals (respiratory burst, oxidative stress) (Fig. 1).\textsuperscript{21} Furthermore, PMNL are influenced by colony-stimulating factors, such as granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF).\textsuperscript{20,31,51,188} They enhance monocyte- or granulocytopenia, on the one hand and reduce the spontaneous programmed cell death (apoptosis) of PMNL during SIRS or sepsis, on the other hand.\textsuperscript{20,31,51} Other pro-inflammatory mediators contribute addi-
tionally to the reduction of neutrophil apoptosis, with an accumulation of PMNL at the site of local tissue damage.16,47,54,78,97,102,109,124

Mechanical and hypoxic cellular damage leads further to an increase of intracellular Ca\(^{++}\) levels with an activation of phospholipase A\(_2\) (PLA\(_2\)) and phospholipase C (PLC).163 These enzymes catalyse the release of arachidonic acids from membrane phospholipids. Through the activation of cyclooxygenase and 5-lipoxygenase prostaglandine E\(_2\) (PGE\(_2\)) leucotriene B\(_4\) (LTB\(_4\)) and thromboxane A\(_2\) (TXA\(_2\)), respectively, are produced (Fig. 1).163 These metabolites are involved in the recruitment of inflammatory cells, regulation of vascular permeability and motility, as well as the aggregation of thrombocytes.163 Additionally, PLA\(_2\) induces the release of the platelet activating factor (PAF).212 It supports the activation of macrophages, their interaction with endothelial cells and the activation and aggregation of thrombocytes.212

### Hypoinflammation—CARS

Depending on the severity of injury and the post-traumatic course, anti-inflammatory mediators are also produced. T\(_H\)2-cells and monocytes/macrophages release IL-4, IL-10, IL-13, or transforming growth factor-\(\beta\) (TGF-\(\beta\)) (Fig. 1).35,33,57 In addition, different cytokines (e.g. IL-6) have shown a dual effect with pro- and anti-inflammatory activities. The serum levels of IL-10 correlate with ISS and post-traumatic complications, such as MODS, ARDS, or sepsis.88,138 In addition, natural inhibitors of receptors, such as soluble TNF-receptors (TNF-RI (55 kD) and TNF-RII (75 kD)), or IL-1 receptor antagonist (IL-1ra) are detectable in the sera of injured patients, correlating also with the ISS and the incidence of post-traumatic complications.52,88,99

Furthermore, the readiness of blood monocytes from injured patients to release pro-inflammatory cytokines was decreased in in vitro studies after stimulation with Gram-negative (endotoxin, lipopolysaccharide (LPS)), or Gram-positive (e.g. peptidoglycan, lipoteichonic acid), bacterial products and correlated with the post-traumatic course.23,56,84,85,101,203 The mechanisms of this “endotoxin tolerance” are still incompletely understood.203 It seems that anti-inflammatory mediators, like IL-10, depress the activity of intracellular transcription factors, such as nuclear factor-kappa B (NF-\(\kappa\)B), which are essential for the synthesis of pro-inflammatory cytokines.

The expression of the LPS-receptor CD14 on monocytes is decreased after trauma, combined with an increase of the soluble CD14 (sCD14), through shedding of the membrane-bound CD14.203 However, the decreased expression of CD14, as well as expression alterations of the pattern-recognition receptors for bacterial products, the toll-like receptors, seem not to be responsible for “endotoxin tolerance”.83 By contrast, the expressions of the toll-like receptors for Gram-positive (TLR2) and Gram-negative (TLR4) bacterial products are increased on monocytes, or PMNL, during systemic inflammation.80 Furthermore, antigen-presenting cells (APC), such as monocytes/macrophages, showed a depressed expression of the MHC (major histocompatibility complex) class II molecule HLA-DR (human leukocyte antigen) that correlated with post-traumatic infections.71

During the early phase of the post-traumatic course, a lymphocytopenia has been observed.22,92,111,195 This lymphocyte depletion was associated with morbidity and outcome after trauma.195 It may be related to increased apoptosis, triggered by stress hormones (steroids) and cell death proteins.39,111,117,145,153 Apoptosis is characterized morphologically by cell shrinking, with cytoplasmic condensation (apoptotic bodies), nuclear condensation (pycnosis) and DNA-fragmentation (DNA laddering).134,153 The cell membranes stay primarily intact and no surrounding inflammatory signs can be observed, in contrast to necrosis.153

Typical cell death proteins are TNF-\(\alpha\) or Fas ligand (CD95 ligand)5,134 They induce cell death after binding with their receptors, respectively, TNF-R1 and Fas antigen (CD95 antigen) and activation of complex intracellular cascades and effector enzymes, such as intracellular proteases (e.g. calpains, caspases).5,39,75,111,134,156 The cellular expressions of TNF-R1 and Fas antigen, or their soluble molecules, were elevated in serum from injured patients, postoperatively or during sepsis.37,145

An overwhelming anti-inflammatory response (hypoinflammation) seems to be responsible for post-traumatic immunosuppression, with a high susceptibility to infections and septic complications.19,171,195 This immunological status is called compensatory anti-inflammatory response syndrome.19 However, it does not look like a compensatory mechanism in a biphasic model; as only a few hours after trauma anti-inflammatory mediators (e.g. IL-10) were detectable in the serum of injured patients.138 It seems that the host defence response tries to strike a fine balance between SIRS and CARS, to induce reparative mechanisms and limit entry or overload of microorganisms, on the one hand, and to avoid autoaggressive inflammation, with secondary tissue damage and susceptibility to infections, on the other hand. These mixed inflammatory
mechanisms are called mixed antagonistic response syndrome (MARS).19

**Activation of plasmatic cascade system**

Pro-inflammatory mediators (cytokines, arachidonic acid metabolites) and toxins activate the plasmatic cascade system, consisting of the complement cascade, the kallikrein–kinin system and the coagulation cascade (Fig. 2). The classical pathway of complement activation is induced by antigen–antibody complexes (immunoglobulins M or G (IgM, IgG)), or activated coagulation factor XII (FXIIa), whereas bacterial products (e.g. LPS) activate the alternative pathway (Fig. 2).66,129,182 Cleavages of C3, by C3 convertase, and C5, by C5 convertase, lead to the formation of opsonins, anaphylatoxins and, finally, the membrane attack complex (MAC).66,129,182 The opsonins C3b and C4b are involved in the phagocytosis of cell detritus, and especially bacteria, by covalent binding of pathogen surfaces (opsonization).56,129 The anaphylatoxins C3a and C5a support different inflammatory mechanisms, the recruitment (chemotaxis) and activation of phagocytic cells (PMNL, monocytes, macrophages), the enhancement of the hepatic acute phase response, the degranulation of mast cells and basophils, with release of vasoactive mediators, such as histamine, as well as the adhesion of leukocytes to endothelial cells, leading to increased vascular permeability with oedema.129,169

In addition, apoptosis and cell lysis (necrosis) of parenchymal cells, or bacteria, are induced by C5a, through the C5a receptor (C5aR) and the MAC (C5b-9).129,169,182 In clinical studies, elevated serum levels of different complement components, or their expression in injured tissue, were observed after trauma, or during sepsis.42,86,165,169,182,211 Similarly to some cytokines, C3a and C5a showed dual effects with activation of reparative mechanisms too.129 Furthermore, during systemic inflammation, serum levels of the C1-inhibitor, produced by hepatocytes, endothelial cells, monocytes and macrophages, were decreased through a degradation by PMNL-elastases. C1-inhibitor regulates the classical complement pathway through inactivation of the active subunits C1s and C1r.129

The plasma proteins FXII, prekallikrein, kininogen and the factor XI (FXI) represent the contact phase system (Fig. 2).185 They are characterized by the fact, that they can be activated by negatively-charged cellular surfaces (contact activation).185 FXII and prekallikrein activate mutually and form FXIIa and kallikrein. FXIIa stimulates the classical cascade along the classical pathway.185 Kallikrein induces the fibrinolysis through conversion of plasminogen to plasmin, or activation of
the urokinase-like plasminogen activator (u-PA) (Fig. 2). The tissue-plasminogen activator (t-PA) works as a cofactor, whereas natural inhibitors of the fibrinolytic system are α2-antiplasmin (α2AP), α2-macroglobulin (α2MG) and the plasminogen-activator-inhibitor 1 (PAI-1). In addition, kallikrein stimulates the formation of bradykinin from kininogen. Kinins are vasodilators, increase the vascular permeability and inhibit the functions of thrombocytes.1,185

The intrinsic coagulation system is linked to the contact activation system through the formation of FIIXa by FXIa (Fig. 2). During the host defence response, a consumption of FXII, prekallikrein and FXI has been observed, whereas plasma levels of enzyme—inhibitor complexes, such as FXIIa—C1-inhibitor or kallikrein—C1-inhibitor, were increased.1 C1-inhibitor and α1-protease-inhibitor (α1PI) represent the inhibitors of the intrinsic coagulation system (Fig. 2).1,94

However, the coagulation system is initially activated over the extrinsic pathway with an increased expression of the tissue factor (TF) on endothelial cells and monocytes, induced by bacterial cell wall fragments and pro-inflammatory cytokines (TNF-α, IL-1β) (Fig. 2).61,68,94 The FVII—TF complex stimulates the coagulation cascade, with the formation of FXa and finally thrombin (FIIa), from prothrombin (FII). Thrombin activates FV, FVIII and FXI, leading to enhanced formation of thrombin. After cleavage of fibrinogen by thrombin, fibrin monomers polymerize to form stable fibrin clots, via support of FXIIIa.1,94

To control the consumption of coagulation factors, antithrombin (ATIII) produced by hepatocytes inhibits thrombin and FXa, through the formation of a thrombin—antithrombin complex.1 This effect can be enhanced by heparin. Furthermore, ATIII inhibits the factors IXa, Xla and XIIa. Further inhibitors are the tissue factor pathway inhibitor (TFPI) and the activated protein C, in combination with the free protein S.160 However, the plasma level of free protein S is decreased during systemic inflammation, through binding to the C4b binding protein (C4bBP).1,160

Disseminated intravascular coagulation can occur after trauma (Fig. 2).1,68,94,113 After the initial phase, with increased thrombin formation and reduced fibrinolytic cascade, intra- and extravascular (e.g. intra-alveolar in ARDS) fibrin clots (hypercoagulability) and increased interaction between endothelial cells and leukocytes was observed.1,61,94,113 The consumption of coagulation factors (hypercoagulability) and dysfunction of thrombocytes are responsible for diffuse bleeding (haemorrhagic diathesis).1,68 The intravascular fibrin clots lead finally to microcirculatory disturbances with hypoxia-induced cellular damage.1,94 The consumption of coagulation factors is further enhanced through the proteolysis of fibrin clots to fibrin fragments by the protease plasmin (fibrinolysis).94,115

Acute phase reaction

The local (Kupffer-cells) and systemic release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) induce the acute phase reaction in the liver, to enhance tissue protective and antimicrobial mechanisms.204 The synthesis of positive acute phase proteins (APP) in hepatocytes, such as C-reactive proteins (CRP), α1-antitrypsin, α2-macroglobulin, caeruloplasmin, lipopolysaccharide (LPS)-binding protein (LBP), fibrinogen, prothrombin or C4BP, is increased, whereas the production of negative APP, such as albumin, high-density lipoproteins (HDL), protein C, protein S and ATIII, is reduced.45,204

CRP increases the expression of TF on PMNL and monocytes/macrophages, and thereby enhances the activation of the extrinsic coagulation cascade.45 Clinical studies have shown that the level of CRP is relatively non-specific and not predictive of post-traumatic complications, such as infections.74,127,165 Serial measurements appear to be helpful however, especially in the first 2 weeks, as, whilst the levels of CRP reduce with time in cases of systemic inflammation, in the presence of infection an upward trend is seen consistently.

α1-antitrypsin inactivates the proteases secreted by PMNL or macrophages, whereas α2-macroglobulin and caeruloplasmin neutralize free oxygen radicals and pro-inflammatory cytokines.204 LBP suppresses the effects of LPS in high concentrations, whereas in small quantities an enhancement of the LPS-effects can be observed.213 Serum levels of LBP are significantly increased during the early post-traumatic course and seem to be predictive of septic complications.213 Furthermore, the elevated ratio of positive APP to negative APP accelerates the development of DIC after trauma.204

For the past decade, procalcitonin (PCT) has been more and more of interest as a diagnostic marker. PCT is a precursor of calcitonin, which is normally produced in the C-cells of the thyroid. Different studies have shown that hepatocytes, as well as immune cells, are also capable of secreting PCT.71 The biological function of this acute phase protein is still unclear. However, it seems that PCT may be a useful marker for monitoring the post-traumatic course, predicting severe SIRS, MODS and septic complications.71,110,127,201
Leukocyte recruitment

The infiltration and accumulation of PMNL represent a crucial event for the development of secondary organ and tissue damage (theory of neutrophil-mediated tissue injury). Pro-inflammatory mediators and toxins induce a leukocyte/endothelial cell interaction (adherence) through upregulation of adhesion molecules on these cells. During the initial phase of adherence, selectins on leukocytes (L-selectin, leukocyte adhesion molecule (LAM-1)) and endothelial cells (E-selectin, endothelial leukocyte adhesion molecule (ELAM-1) and P-selectin (platelet)) are responsible for the “rolling” of PMNL. In the second step, upregulation of integrins on PMNL such as CD11a/CD18 (leukocyte function associated molecule-1 or LFA-1), CD11b/CD18 (macrophage antigen-1 or Mac-1), CD11c/CD18 and intercellular adhesion molecules (ICAM-1), or vascular cell adhesion molecules (VCAM-1) on endothelial cells can be observed after trauma. The interaction of these adhesion molecules leads to a stable cell-to-cell contact with a stable cell-to-cell interaction (adherence) through upregulation of adhesion molecules on these cells.112,144,172

Proteases, oxidative stress and capillary leakage

Infiltrated PMNL and tissue macrophages are responsible for the phagocytosis of microorganisms and cellular detritus. However, activated PMNL have a Janus face (Janus, the mythological gate-keeper has two faces, looking in opposite directions). They are also able to induce secondary tissue and organ damage by degranulation of extracellular proteases (elastase, metalloproteinase) and formation of reactive oxygen species (ROS, oxygen radicals), the so-called respiratory burst, or oxidative stress (Fig. 3). Elastases have the capacity to degrade most proteins in the extracellular matrix and important plasma proteins. Their proteolytic activity is regulated by endogenous protease inhibitors (PI), such as α1-antitrypsin, α2-macroglobulin, or α1-protease-inhibitor. In addition, neutrophil elastase induces the release of pro-inflammatory cytokines. Elevated levels of elastase, or elastase—a1-protease-inhibitor complex (Eα1PI), were detectable in multiply injured patients depending on the injury severity and the post-traumatic course. In the same manner, metalloproteinases seem to be involved in the degradation of important structural proteins after trauma.23,115,133,152,199

Oxidative cell injury involves the modification of cellular macromolecules by ROS, often leading to cell death. Superoxide anions (O2•−) are generated by membrane-associated nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, which is activated by pro-inflammatory cytokines, arachidonic acid metabolites, complement factors and bacterial products. Thereafter, superoxide anions are reduced in the Haber-Weiss reaction to hydrogen peroxide (H2O2) by superoxide dismutase in cytosol (SOD 1), mitochondrion (SOD 2), or cell membrane (SOD 3). H2O2 is the substrate for the myeloperoxidase that forms the highly toxic and bactericidal hypochloric acid (HOCL). In addition, accumulated H2O2 is transformed to hydroxyl ions (OH•) in the Fenton reaction. The free ROS induce lipid peroxidation, cell membrane disintegration and DNA-damage of endothelial and parenchymal cells. Furthermore, oxygen radicals and HOCL activate PMNL to release proteases and collagenase and to inactivate protease-inhibitors (PI). In addition, the capacity of non-enzymatic antioxidants, such as vitamins E or C (scavenger), or enzymatic antioxidants, such as SOD, catalase, or glutathione peroxidase, is reduced during systemic inflammation.

In addition, reactive nitrogen species (RNS) are involved in the pathogenesis of trauma-induced tissue damage. Nitric oxide (NO) is generated from the amino acid L-arginine by inducible nitric oxide synthase (iNOS) in PMNL, or vascular muscle cells, and by endothelial nitric oxide synthase (eNOS) in endothelial cells (Fig. 3). NO induces vasodilatation, through increase of guanosine 3′,5′-cyclic monophosphate (cGMP) by activation of the guanylate cyclase. The activity of iNOS is stimulated by cytokines and toxins, whereas eNOS is stimulated...
by mechanical shearing forces, or by acetylcholine. Additional metabolites emerging from the interaction of superoxide anions and NO, such as peroxynitrite (ONOO⁻) have been shown to mediate cellular cytotoxicity. The results of the vascular dysfunction caused by ROS and RNS are a generalized oedema, clinically manifest as capillary leakage syndrome, with a disturbance of nutritional and metabolic exchange, cell swelling and cellular dysfunctions.

Microcirculatory disturbances

The microcirculation as functional unity, consisting of terminal arterioles, capillaries and venules, regulates nutritional and metabolic exchange in organs and tissues. Microcirculatory disturbances during haemorrhagic shock and systemic inflammation are primary mediated through the sympathetic-adrenal reaction leading to a vasoconstriction of arterioles and venules. However, through decreased catecholamine effect on arterioles, a reduced capillary flow with an increased hydrostatic pressure can be observed. This microcirculatory alteration, in combination with the cytokine and NO mediated capillary leakage, are responsible for a secondary hypovolaemia and haemoconcentration, with agglutination of erythrocytes (red sludge) and thrombocytes (white sludge). The sludge phenomenon leads to an obstruction of the microcirculation with a failure of the transcapillary exchange. The cellular oxygen deficiency and the accumulation of metabolites (hidden acidosis) are finally responsible for tissue and cell damage. In addition, NO (vasodilatation) and endothelin (vasoconstriction) induce a shock-specific microcirculatory change with a shunting of some organ or tissue areas, enhancing their damage.

Ischaemia/reperfusion injury

Systemic hypoxaemia and hypotension during the resuscitative period after trauma, as well as local hypoperfusion through contusions, lacerations, vascular injuries, or compartment syndromes lead to an oxygen deficit in endothelial, parenchymal, or immune competent cells, which is partially compensated for by the intracellular degradation of the energy-store adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and adenosine monophosphate (AMP). As a result of the ATP-consumption, disturbances of membrane permeability and energy-dependent Na⁺/K⁺-ATPase-pump arise, with an intracellular Na⁺ increase and cellular swelling. Finally, the generation of hypoxanthine leads to a deficit of the cellular second messenger cyclic AMP (cAMP). The ATP-deficit is further responsible...
for an increase of cytosolic Ca²⁺ with metabolic disturbances of glucose, proteins, release of neurotransmitters, or hormones, and an activation of phospholipases, proteases and endonucleases, with membrane disintegration and DNA-damage (Fig. 4). However, irreversible tissue damage through apoptosis, or necrosis of parenchymal cells, caused by energy deficit, are only observed after prolonged severe haemorrhagic shock, or missed vascular injuries.

Of more importance for secondary tissue damage and organ dysfunction is the reperfusion phase (Fig. 4). During this post-ischaemic phase, hypoxanthine is degraded to xanthine and finally to uric acid by xanthine oxidase, with the generation of superoxide anions (O₂⁻) from available oxygen. Superoxide anions are further reduced to hydrogen peroxide (H₂O₂) and hydroxyl ions (OH⁻) by superoxide dismutase. These free oxygen radicals enhance disturbances of the intracellular Ca²⁺ homeostasis and induce lipid peroxidation, membrane disintegration and DNA-damage, with apoptosis and necrosis of endothelial, parenchymal and immune cells.

**Neuroendocrine reaction and metabolic alterations**

The post-traumatic host response is also influenced by neuroendocrine and metabolic disorders. Stress, fear, pain and inflammatory mediators produced in the intracranial compartment, or flowing across the damaged blood–brain barrier after severe head injury, act as afferent signals to the hypothalamus. Primary (bleeding) and secondary (capillary leakage) hypovolaemia trigger, via aortic or carotic baroreceptors, a sympathetic-adrenal response and, via juxta-glomerular baroreceptors, an activation of the renin–angiotensin system to support the perfusion of vital organs. Angiotensin is an effective vasoconstrictor, induces a renal retention of sodium and fluids, and stimulates the adrenal release of aldosterone. In addition, osmotic receptors in the hypothalamus are responsible for the secretion of antidiuretic hormone (ADH) by the posterior lobe of the pituitary (neurohypophysis). In addition, chemoreceptors in the central nervous system for the registration of acidosis, hypercapnia, hypoxaemia or hypoglycaemia, as well as thermoreceptors, are involved in this neuroendocrine reaction.

The sympathetic nervous system and the adrenal gland represent the efferent regulators of cardiovascular, respiratory and metabolic responses. Signals in the sympathetic area of the hypothalamic evoke a release of catecholamines from the adrenal medulla. In addition, post-ganglionic sympathetic nerve ends influence organs and vessels directly. Adrenaline stimulates the cardiac output by increasing heart contractility, the heart rate and the preload (Frank–Starling mechanism). In addition the blood pressure is elevated by the increased peripheral vascular inflow.
resistance (vasoconstriction of arterioles) and a centralization of the blood in favour of vital organs, such as heart and brain, established through a decrease of the perfusion of splanchic area, kidneys and muscles.\textsuperscript{159}

Furthermore, catecholamines influence the post-traumatic metabolism with an increase in the energy expenditure, hepatic glycogenolysis and gluconeogenesis (glucose-lactate (Cori-cycle) and glucose-alanin cycles), as well as release of free fatty acids.\textsuperscript{90,150,209} Early hyperglycaemia (glucose $\geq 200$ mg/dL) after trauma was associated with significantly higher infection and mortality rates.\textsuperscript{106} The natural post-traumatic insulin secretion is too low to cope with this post-traumatic hyperglycaemia. In addition, insulin secretion is partially suppressed by catecholamines, mediated by $\alpha$-receptors, whereas glucagon release is elevated by $\beta$-receptor stimulation, contributing to hepatic glycogenolysis and gluconeogenesis.\textsuperscript{90} A peripheral insulin resistance has also been observed.\textsuperscript{177} Different cytokines (TNF-$\alpha$, IL-1$\beta$) increase the expression of glucose transport systems (insulin-like activity). The increased intracellular glucose is oxidized to pyruvate and finally reduced to lactate (stress lactate acidosis), which contributes to the elevated lactate levels caused primarily by the metabolic lactic acidosis (cellular hypoxia).\textsuperscript{150} Different studies have shown that early increased serum levels of lactate, or base deficit, are reliable markers for a poor outcome in severely injured patients.\textsuperscript{3,36}

Pain, stress and fear cause the hypothalamus to release corticotropin-releasing hormone (CRH), leading to a secretion of adrenocorticotropic hormone (corticotropin, ACTH) from the anterior lobe of pituitary (adenohypophysis).\textsuperscript{62,177} ACTH stimulates the adrenal cortex to release glucocorticoids (cortisol), or mineralocorticoids (aldosterone). Within minutes after trauma, increased serum levels of steroids are detectable.\textsuperscript{52,177} Glucocorticoids have different effects on the metabolism, such as hepatic gluconeogenesis, glycogenesis, inhibition of protein synthesis, increase of protein degradation in muscles and mobilization of free fatty acids by lipolysis.\textsuperscript{90,177} In addition they limit inflammatory processes of mononuclear cells and suppress the production of antibodies.\textsuperscript{90} In contrast, the spontaneous apoptosis of PMNL is reduced by cortisol.\textsuperscript{34} Aldosterone increases the renal resorption of sodium-associated by fluid retention.

The metabolic disorders after trauma are initially characterized by a reduced metabolism for about 24 h (acute, shock or ebb phase).\textsuperscript{90,150,177} This is followed by a flow phase with a catabolic metabolism for some days to 2 weeks and a final reparative phase with a turnover from a catabolic to an anabolic metabolism.\textsuperscript{90,150,177} In the second phase, all energy stores, such as glucose, fat acids and proteins, are made available for the host defence response. The increase of the energy expenditure reaches a maximum after 5–10 days.\textsuperscript{82,90,150,177} The increased levels of amino acids are needed for the synthesis of acute phase proteins in the liver and inflammatory mediators in mononuclear cells. In addition, glutamate represents a neurotransmitter and is the most important substrate for the metabolic processes of enterocytes and immune cells, conserving the immune integrity of the intestinal wall to avoid bacterial translocation during the systemic inflammation.\textsuperscript{90}

**Multiple organ dysfunctions or failure**

The evolution of the physiological and reversible systemic inflammation after trauma (host defence response) to a host defence failure, which is associated with irreversible organ defects and high mortality, can be described as an overload of primary and secondary hits and an imbalance of pro- and anti-inflammatory mechanisms.\textsuperscript{18,19,118,159,177,188} In addition, natural protective factors such as antioxidants or protease inhibitors are consumed.\textsuperscript{1}

Endothelial cell damage, dysfunction of vascular permeability with capillary leakage, microcirculatory disturbances with cellular hypoxia and finally apoptosis of parenchymal cells by cell-associated, or free, cell death proteins and/or necrosis of parenchymal cells, are involved in the multiple organ dysfunctions syndrome or multiple organ failure.\textsuperscript{18,27,58,79,92,117,153,159,200} Depending on the responsible insults (primary or secondary) MODS can be classified in primary, or early, MODS and secondary, or late, MODS.\textsuperscript{18,27,50,98,157,159,202} Examples of early organ dysfunction are the primary cerebral oedema after head injury, or the primary ARDS after thoracic injury.\textsuperscript{15,18,95,120,137} The clinical manifestation of secondary MODS varies in affected organs and dysfunction severities. Therefore, different scores, such as the MOF score (Goris score), MODS score (Marshall score), or sequential organ failure assessment (SOFA) score are available to describe dysfunctions of seven systems: respiratory, cardiovascular, renal, hepatic, gastrointestinal, haematological and central nervous systems.\textsuperscript{8,63,73,119} For the diagnosis of acute lung injury (ALI), or acute respiratory distress syndrome, bilateral lung infiltrations on thoracic X-ray and a decrease of the Horowitz ratio must be observed ($P_{a}O_{2}/F_{i}O_{2}$ ratio $< 300$ corresponds to an ALI, $< 200$ to an ARDS).\textsuperscript{137} Renal and gastrointestinal systems are very sensitive to microcirculatory disorders,
leading to a necrosis of renal tubules with increase of serum creatinine concentrations and oliguria (< 0.5 ml/kg KG/h) or anuria, and to necrosis of intestinal villi.\textsuperscript{103,159} The alteration of the intestinal mucosa seems to be responsible for a bacterial translocation and explains the high rate of bacteraemia in the absence of a detectable infective focus in lethal septic complications after trauma (gut hypothesis).\textsuperscript{103,130,159} The gastrointestinal tract often represents the source for the development of secondary multiple organ failure after trauma, whereas the liver represents the engine, with an acute phase and cytokine response, and decreased function of hepatocytes (increase of serum bilirubin concentration).\textsuperscript{130,157,162} Repeated scoring is helpful for identifying categories of injured patients at major risk of death, or complications, after surgical interventions.\textsuperscript{8}

**Therapeutic strategies for multiply injured patients**

Hypoxia and severe haemorrhagic shock correlate with high mortality rates, as well as with an high incidence of SIRS, sepsis and organ dysfunction.\textsuperscript{95} To reduce these high mortality and morbidity rates in the post-traumatic course, early “preventive” interventions are necessary. According to the guidelines of advanced trauma life support (ATLS\textsuperscript{5}), early oxygenation therapy by intubation and controlled assisted ventilation and an adequate volume therapy with crystalloids, colloids and/or blood products are essential.\textsuperscript{29} However, the large-volume loading scheme is the subject of controversial debate in severe haemorrhagic shock.\textsuperscript{131,174} Patients with blood loss > 2 l should not be overwhelmed by crystalloids or colloids until surgical management of bleeding is undertaken, whereas in septic shock early, goal-directed, high volume therapy is successful.\textsuperscript{161} In contrast, small volume resuscitation in severe traumatic shock seems to avoid a reduced \( O_2 \) transport capacity, coagulopathy, and infusion-induced hypothermia.\textsuperscript{131,174}

After the primary survey, with basic imaging, multiply injured patients are graded as non-responders, “borderlines” and responders, according to the initial response to volume therapy, or pharmaceutical resuscitation.\textsuperscript{29} Life saving surgical procedures, such as decompressing pneumothorax, cardiac tamponade or acute epidural haematoma, and surgical control of massive haemorrhage in the thoracic or abdominal cavities and from pelvic fractures, or traumatic amputations are carried out without delay.\textsuperscript{29,53,60,154} These early interventions seem to limit the systemic inflammation and decrease the early and late mortality.\textsuperscript{13} Patients with a borderline state after primary survey, or patients with a high trauma impact, or at risk of adverse outcome, such as head injury, bilateral lung contusions, multiple long bone fractures, coagulopathy, hypothermia or a presumed operation time > 6 h, should be supplied with a staged sequential surgical management as damage control, after the further work up in the secondary survey, to avoid or limit the influence of second hits (interventional or antigenic loads).\textsuperscript{147,202} Damage control includes haemorrhage control through tamponade, vascular repair or vessel ligation, and organ resections.\textsuperscript{99} In addition, a reduction of contamination after hollow organ injuries, or open fractures, as well as decompression of compartment syndromes of the extremities by fasciotomy, or of the abdomen by decompressive laparotomy, should contribute to the limitation of secondary inflammatory processes.\textsuperscript{11,49,89,154} Furthermore, the temporary stabilization of pelvic and long bone fractures, or dislocations of large joints, by rapidly assembled and applied external fixators seem to be beneficial.\textsuperscript{99,53,89,141,147,154} This concept decreases the systemic release of pro- and anti-inflammatory mediators, in comparison with definitive interventions, such as reamed nailing (early total care).\textsuperscript{147} Débridement of open wounds and fractures, with resection of non-viable tissues, temporary closure by vacuum assisted closure therapy and second look interventions, contribute to a limited antigenic load, with a decrease in septic complications.\textsuperscript{89,186} However, the early stabilization of major skeletal injuries (early total care) represents still the concept for patients with isolated fractures and in the absence of high traumatic impact and the risk factors mentioned above.\textsuperscript{147}

With regard to strategies for post-traumatic intensive care, only supportive therapies are established to avoid secondary organ damage and hits.\textsuperscript{95} Secondary brain injuries, with elevated intracranial pressure (ICP) due to cerebral oedema, or ischaemia/reperfusion injuries, can be limited by applying different neuroprotective strategies, such as controlled hyperventilation, moderate hypothermia, and release of cerebrospinal fluid (CSF).\textsuperscript{167,183} Whenever these therapeutic regimens fail to reduce ICP, intravenous administration of barbiturate may become necessary.\textsuperscript{183} The beneficial effect of barbiturates, in terms of lowering elevated ICP, is thought to be due to decreased cerebral metabolism and blood flow.\textsuperscript{41} Other supportive therapies include mechanical ventilation, inotropes and haemofiltration for renal failure.\textsuperscript{159,177} Furthermore, a single shot of an antibiotic (cephalosporin) after trauma reduces the post-traumatic wound infection rate.\textsuperscript{196}
Further antibiotics should only be given according to an antibiogram of an infectious focus.196 Early enteral nutrition, via gastric or duodenal tubes, reduces the accumulation of pathogenic bacteria in the intestinal tract and avoids atrophy of intestinal mucosa.177,184 Additional arginine, glutamine, nucleotides, or unsaturated omega-3-fatty acids (“immune-enhanced enteral nutrition” (IEEN)) reduce post-traumatic hypermetabolism and improve immune competence.26

Despite thorough insights into the pathophysiological mechanisms of post-traumatic systemic inflammation and hopeful results of animal studies, multiple prospective clinical trials performed in the past decades, especially in patients with sepsis, have failed to provide a benefit of anti-inflammatory, anti-coagulant, or antioxidant strategies with regard to the mortality, whereas the incidence of post-traumatic complications, such as infections, or multiple organ dysfunctions, has partially decreased.2,13,64,65,72,91,113,136,151 However, the magic bullet is still not found. Reasons for these equivocal results may include individual injury patterns, inappropriate timing of drug administration, or suboptimal drug levels at the target site.35,65 In addition, the study protocols have focused on single mechanisms only, whereas the immune network is more complex and individual (gene polymorphism, sexual dimorphism), as described above.13,64,65,93,151 Nevertheless, some successful clinical studies are available, especially for septic patients, although the underlying mechanisms have not been clearly defined.91 Trauma patients receiving high doses of intravenous immunoglobulins exhibit a reduction in septic complications and an improvement in serum bactericidal activity.44 Treatment with recombinant human activated protein C (drotrecogin alfa activated) showed a significant reduction of mortality in patients with severe sepsis.14 However, criticisms concern data consistency, unclear mechanism of action and the increased risk of bleeding, which restricts its use in injured patients, especially with severe head injuries.14,48 Although the effects of steroids in patients with sepsis are controversial, low doses of corticosteroids seem to reduce the mortality rate in patients with septic complications.7,191 Insulin has recently been shown to decrease mortality and to prevent the incidence of multiple organ failure in critically ill patients.96 It seems that insulin attenuates the inflammatory response by decreasing the pro-inflammatory, and increasing the anti-inflammatory, cascades, thus restoring systemic homeostasis, which has been shown to be critical for organ function and survival in critically ill patients.96

Although some successful progress in clinical trials is obvious, better understanding of the pathophysiological mechanisms at local site of injury would identify exact primary targets for drug interventions. However, progress in diagnostic tools for the monitoring of the immune status (beside immuno-monitoring) may become more successful for the management of severely injured patients in the near future. Parallel monitoring of pro-inflammatory (e.g. IL-6) and anti-inflammatory (e.g. IL-10) cytokines, as well as acute phase proteins (e.g. CRP, procalcitonin), or other factors, could help us in the decision making for optimal secondary operative interventions to limit second hits.71,170 However, more prospective diagnostic studies have to be conducted, to understand the kinetics and significance of these factors in order to optimize the concept of damage control.

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