The Severity of Injury and the Extent of Hemorrhagic Shock Predict the Incidence of Infectious Complications in Trauma Patients

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Abstract

Background: Trauma patients are at high risk of developing systemic inflammatory response syndrome (SIRS) and infections. The aim of this study was to evaluate the influence of the severity of injury and the extent of hemorrhagic shock at admission on the incidence of SIRS, infection and septic complications.

Methods: A total of 972 patients who had an injury severity score (ISS) of ≥ 17, survived more than 72 h, and were admitted to a level I trauma center within 24 h after trauma were included in this retrospective analysis. SIRS, sepsis and infection rates were measured in patients with different severities of injury as assessed by ISS, or with various degrees of hemorrhagic shock according to ATLS® guidelines, and were compared using both uni- and multivariate analysis.

Results: Infection rates and septic complications increase significantly ($p < 0.001$) with higher ISS. Severe hemorrhagic shock on admission is associated with a higher rate of infection (72.8%) and septic complications (43.2%) compared to mild hemorrhagic shock (43.4%, $p < 0.001$ and 21.7%, $p < 0.001$, respectively).

Conclusions: The severity of injury and the severity of hemorrhagic shock are risk factors for infectious and septic complications. Early diagnostic and adequate therapeutic work up with planned early "second look" interventions in such high-risk patients may help to reduce these common posttraumatic complications.

Key Words
Trauma · Infection · Systemic inflammatory response syndrome · Hemorrhagic shock · Injury severity score

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Introduction

Severe traumatic injury leads to a state of systemic inflammation (systemic inflammatory response syndrome, SIRS) followed by a period of recovery mediated by the counter-regulatory anti-inflammatory response syndrome (CARS) [1, 2]. SIRS promotes a number of beneficial effects such as the clearance of pathogenic organisms or the local sequestration of tissue factors to promote wound healing. Overactivation of this physiological mechanism, however, may lead to a dysfunction of vital organs (multiple organ dysfunction syndrome, MODS) and may ultimately result in multiple organ failure (MOF) [2, 3]. CARS, being a counter-regulatory cascade, can ultimately result in immunosuppression and increased susceptibility to infection, which may reactivate SIRS, leading to late MODS [2, 3]. Infections and SIRS are frequently observed problems in severely injured patients [1, 4–9]. Two or more SIRS criteria on admission and persistent SIRS postinjury were found to be predictive of infectious complications in previous studies, indicating a marked susceptibility for infection through prolonged SIRS [9, 10]. A number of studies describe the influence of hemorrhage on the incidence of infection and SIRS [5, 11–13]. Peitzman et al. [14] demonstrated that the presence of hemorrhagic shock increases the rate of bacterial translocation during hypotension and also the ischemic disruption of the intestinal mucosal

barrier, leading to systemic dissemination of intestinal bacteria. Clinical and experimental studies have shown that the rate of wound infection is increased after trauma and hemorrhagic shock [15, 16]. Other studies have shown that the requirement of blood transfusion as a surrogate index of hemorrhage is a risk factor for infection following trauma [8, 17–19]. Papia et al. [8] demonstrated a dose-dependent relationship between the number of units of packed red blood cells (PRBC) transfused and the subsequent incidence of infection. A recent prospective observational study by Beale et al. [18] on 120 trauma patients further showed that transfusion of > 4 units of blood was an independent risk factor for SIRS.

Similarly, a number of studies have shown that the ISS is associated with patient outcome following trauma. The ISS was found to be a good predictor of post-injury MOF, and was further found to be associated with the development of acute respiratory distress syndrome (ARDS) [3]. The mortality rate in trauma patients was reported to increase with higher ISS scores [20]. Conflicting data are available with respect to the relationship between ISS and the rate of infection [4–6, 8, 10]. Pories et al. [5], using a retrospective analysis of 2,496 patients, demonstrated a significant relationship between the development of infection and ISS. Furthermore, infected patients had suffered significantly more injuries to the spine, chest, abdominal and pelvic regions than those without subsequent infection. In contrast, Hurr et al. [4] failed to find a relationship between ISS and infection in their retrospective chart review of 113 patients. Also, Baker et al. [6] failed to find a statistically significant association between injury severity and incidence of pneumonia in 62 intubated trauma patients.

Some studies have indicated that higher ISS scores may be a risk factor for the development of posttraumatic inflammatory complications, such as SIRS [1, 9, 20, 21]. Ertel et al. [21] determined that the severity of SIRS and the incidence of septic complications increased significantly with the severity of trauma as measured by ISS in 1,278 patients.

The aim of the present study was to evaluate the incidence of SIRS and infections in our database of severely traumatized patients and to determine whether an association exists between the ISS score and hemorrhagic shock on one side and the development of infection and SIRS on the other. It is our hypothesis that the rate of specific, clinical infections is independently associated with both the severity of injury as quantified by the ISS, and the severity of hemorrhage according to the Advanced Trauma Life Support (ATLS®) guidelines.

Patients and Methods

A total of 972 patients admitted to the emergency department of the University Hospital of Zürich were enrolled into the present study over a ten-year period. Admission criteria were an Injury Severity Score (ISS) ≥ 17 and admission to our level I trauma center within 24 h, followed by intensive care treatment and survival for more than 72 h to evaluate the occurrence of inflammatory complications. The treatment of all patients followed ATLS® guidelines and the previously outlined trauma management protocol [22–24].

Briefly, after establishing airway, ventilation and cardiovascular functions, life-saving procedures including decompression of body cavities, control of hemorrhage and contamination were conducted. This was followed by radical wound debridement, decompression of compartments, and primary stabilization of major fractures (''day-one surgery'') [22, 23]. The use of perioperative prophylactic antibiotics was generally based on the site and type of injury. All patients received enteral nutrition within 24 h following trauma to maintain normal intestinal flora and mucosa, thereby reducing or avoiding peritoneal bacterial translocation.

All data were prospectively collected regarding infection (as defined below), isolated pathogens, ISS, severity of hemorrhagic shock on admission, time from injury to admission, and other demographic, clinical and laboratory parameters. All patient data were retrieved following local Institutional Review Board (IRB) approval according to the University of Zurich IRB guidelines.

Scoring Systems

The abbreviated injury score (AIS) and ISS were used to define the severity of injury [25]. The Glasgow Coma Scale (GCS) and the Acute Physiology and Chronic Health Evaluation (APACHE) Score were used to quantify neurologic disability and overall health impairment upon admission and throughout the hospital stay [26, 27].

Definition of Hemorrhagic Shock

The severity of hemorrhagic shock was defined according to the guidelines of the ATLS® [28]. The patients were subdivided into four classes with class I and II as uncomplicated hemorrhage and a blood volume loss of up to 15 and 15–30%, respectively. Class III is a complicated hemorrhagic state with 30–40% blood volume loss. The degree of exsanguination in class IV hemorrhage is immediately life-threatening, with more than 40% blood volume loss [28]. For this study, we defined classes I and II as mild hemorrhage and classes III and IV as severe hemorrhage.

Definition of SIRS

Systemic inflammatory response syndrome and sepsis were defined according to the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, but modified in that these criteria had to be fulfilled for at least three continuous days to confirm the presence of SIRS or sepsis [1, 29]. SIRS was subdivided into four different grades (two positive SIRS criteria = SIRS 2, three positive SIRS criteria = SIRS 3, four positive SIRS criteria = SIRS 4). Sepsis was diagnosed if all criteria of SIRS (SIRS 4) were fulfilled for at least three days in combination with a proven infectious focus or positive blood cultures [1].

Diagnosis of Infection

Surveillance for infection was performed by intensive care physicians and institutional infectious disease specialists. Cultures were taken on admission and regularly during the ICU stay from sputum, tracheobronchial aspirate, wound exudates and urine. Blood and intravascular catheter tip cultures were taken when central venous catheter (CVC)-related infection and/or bacteremia was suspected. Diagnosis of infection was based on modified Center for Disease Control and Prevention (CDC) definitions of nosocomial and surgical site infection with the following modifications: CVC infection was defined as local signs of infection, a positive catheter tip culture but negative blood cultures [30]; bacteremia was defined as at least one positive blood culture with clinical findings (two or more SIRS criteria) for which antimicrobial therapy had to be initiated. Primary bloodstream infections (no focus of infection) and secondary bloodstream infections (with a focus of infection) were combined into this group. Pneumonia was diagnosed by the presence of a new or changing infiltrate on chest X-ray as well as clinical (two or more SIRS criteria) and laboratory findings. Wounds were considered to be infected in the presence of purulent exudates requiring surgical wound care.

Statistical Analysis

Continuous data are provided as mean ± standard deviation (SD) and compared between groups using the Mann–Whitney test and the Kruskal–Wallis test. Categorical data are presented as numbers with percentages and are compared using Pearson's chi-square test. Differences are considered significant at $p < 0.05$. Multiple logistic regressions were performed to assess the impact of ISS and degree of hemorrhagic shock on infection and sepsis. In this case, ISS and degree of hemorrhagic shock were analyzed as continuous and categorical variables, respectively. All statistical analyses were performed using the SPSS software package (SPSS 13.0, SPSS Inc., Chicago, IL, USA).

Results

Patient Collective

A total of 972 trauma patients were included in this study (Table 1). The majority of injuries were the result of blunt trauma (n = 888, 91.4%). Intensive care unit (ICU) stay was 13.5 ± 11.7 days and the mean length of hospital stay was 25.5 ± 18.9 days. Overall mortality in the entire study population was 10.5% (n = 102).

Infection Rate

An infection was diagnosed in 446 patients (45.9%), with a mean time to infection of 11.3 ± 9.9 days.

Table 1. Patient collective. (ISS: Injury Severity Score; GCS: Glasgow Coma Scale; APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: intensive care unit).

Characteristics	All patients	Infected patients	Noninfected patients	p value
Number (% of total)	972	446 (45.9)	526 (54.1)	
Age (years)[a]	40.2 ± 17.0	40.6 ± 16.7	39.9 ± 17.3	ns
Males (% of males)	746	349 (46.7)	397 (53.3)	ns
Females (% of females)	226	97 (42.9)	129 (57.1)	ns
ISS (points)[a]	31.9 ± 10.9	34.3 ± 11.7	29.9 ± 9.8	< 0.001[b]
GCS (points)[a]	8.6 ± 5.5	7.5 ± 5.3	9.6 ± 5.5	< 0.001[b]
APACHE II (points)[a]	14.5 ± 7.8	16.8 ± 7.5	12.6 ± 7.5	< 0.001[b]
ICU (days)[a]	13.5 ± 11.8	20.8 ± 12.9	7.3 ± 5.4	< 0.001[b]
Mortality	102 (10.5)	60 (13.5)	42 (8.0)	0.006[c]

[a]Mean ± SD. Values in parentheses are percentages

[b]Mann–Whitney test

[c]Pearson chi-square test

Patients developing posttraumatic infections had significantly higher ISS and APACHE II scores and significantly lower GCS scores than noninfected patients ($p < 0.001$). Also, ICU length of stay and mortality were significantly increased in infected patients compared to the noninfected group. In contrast, age and gender did not have any significant influence on the infection rate (Table 1).

Sites of Infection

The sites of infection and the most commonly isolated microorganisms are summarized in Table 2. The most frequent type of infection was pneumonia (34.3%), followed by bacteremia (14.7%), wound infections (13.4%), catheter-related infections (11.4%), and urinary tract infections (9.0%). Primary bloodstream infections (n = 45) occured in 35.7% of cases. The foci of secondary bloodstream infections (n = 81, 64.3%) were mainly catheter infections (n = 40, 49.4%), pneumonia (n = 24, 29.6%), and central nervous system (CNS) infection (n = 6, 7.4%). 48.9% of the isolated microorganisms were Gram-positive, 49.3% Gram-negative, 1.7% were fungi, and 0.1% were viruses. The most commonly recovered pathogens included *Staphylococcus aureus* (n = 176, 15.5%), coagulase-negative staphylococci (CNS, n = 162, 14.3%), *Pseudomonas aeruginosa* (n = 115, 10.1%), *Enterococcus* spp. (n = 113, 10.0%), *Escherichia coli* (n = 104, 9.2%), and *Enterobacter* spp. (n = 94, 8.3%).

Incidence of SIRS, Bacteremia and Sepsis

Table 3 shows the incidence of systemic inflammation SIRS and a comparison of SIRS criteria between infected and noninfected patients. SIRS ≥ 2 was present in 81.9% (n = 796) of all included patients, most of whom had SIRS 3 or 4. 228 (51.1%) of all infected patients developed 234 septic episodes, the majority of which were associated with pneumonia (n = 120, 51.3%), bacteremia (i.e., positive blood culture; n = 30, 12.8%), wound infection (n = 20, 8.5%), catheter-related infection (n = 12, 5.1%) or intracranial infection (n = 12, 5.1%).

Influence of ISS on Incidence of Infection, SIRS and Sepsis

The associations between ISS and infection, SIRS and sepsis are shown in Figures 1 and 2 using different ISS groups. ISS scores significantly predicted the overall infection rate ($p < 0.001$; Table 1; Figure 1). The percentage of patients with low systemic inflammation (no

Table 2. Main types of infections and predominant microorganisms.

Infection	N infections (% of total)	Predominant microorganism (% of subgroup)
Pneumonia	294 (34.3)	*Staphylococcus aureus* (13.2)
		Hämophilus spp. (8.9)
		Pseudomonas aeruginosa (7.7)
Bacteremia	126 (14.7)	Coagulase-negative staphylococci (24.9)
		Staphylococcus aureus (11.2)
Wound infection	115 (13.4)	*Enterococcus* spp. (12.5)
		Bacillus cereus (12.5)
		Coagulase-negative staphylococci (12.1)
Catheter infection	98 (11.4)	Coagulase-negative staphylococci (33.9)
		Enterobacter spp. (8.9)
		Staphylococcus aureus (8.9)
Urinary tract infection	77 (9.0)	*Escherichia coli* (35.6)
		Enterococcus spp. (21.8)
CNS infection	56 (6.5)	Coagulase-negative staphylococci (31)
		Enterococcus spp. (14.3)
Intra-abdominal infection	28 (3.3)	*Enterococcus* spp. (24.2)
		Coagulase-negative staphylococci (12.1)
Bone or joint infection	12 (1.4)	*Enterococcus* spp. (11.8)
		Coagulase-negative staphylococci (11.8)
Other[a] or unknown infection site	51 (6.0)	*Clostridium difficile* (33.3)
		Candida albicans (25)

[a]Other sites of infection include *Clostridium difficile*-associated colitis (n = 8), esophagitis and oral candidiasis (n = 4), thoracic infections (pericarditis and pleural empyema) (n = 4), soft tissue infections (myositis, fasciitis, parotitis) (n = 5), genital tract infections (vaginitis, colpitis) (n = 3), infected hematoma (n = 2) and eye infections (keratitis, conjunctivitis) (n = 2). Infection site unknown (n = 23). CNS: central nervous system.

Table 3. Incidence of systemic inflammatory response syndrome (SIRS).

	All patients (n = 972)	Infected patients (n = 446)	Noninfected patients (n = 526)	p value
No SIRS	176 (18.1)	16 (3.6)	160 (30.4)	< 0.001[a]
SIRS 2	187 (19.2)	32 (7.2)	155 (29.5)	< 0.001[a]
SIRS 3 and 4	381 (39.2)	170 (38.1)	211 (40.1)	ns
Sepsis	228 (23.5)	228 (51.1)	0 (0)[b]	

Values in parentheses are percentages
[a]Pearson chi-square test
[b]By definition

SIRS, SIRS 2) was lower in patients with increasing ISSs ($p < 0.001$). In patients with low (< 2) SIRS, moderately injured patients (ISS 17–19) accounted for 52% of patients, whereas more severely injured patients (e.g., ISS 50–75) accounted for only 10.9%. The incidence of SIRS 3/4 did not show a similar distribution. However, the rate of septic complications significantly increased with increasing ISS scores ($p < 0.001$; Figure 2).

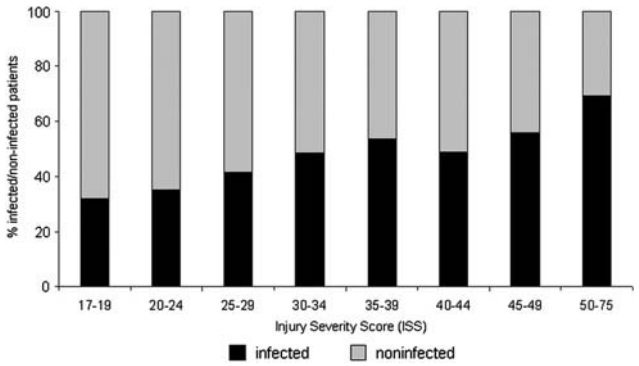

Figure 1. Influence of injury severity score (ISS) on the incidence of infection. Incidence of infection in patients with ISS ≥ 17 points for different ISS groups. Data represent percentages.

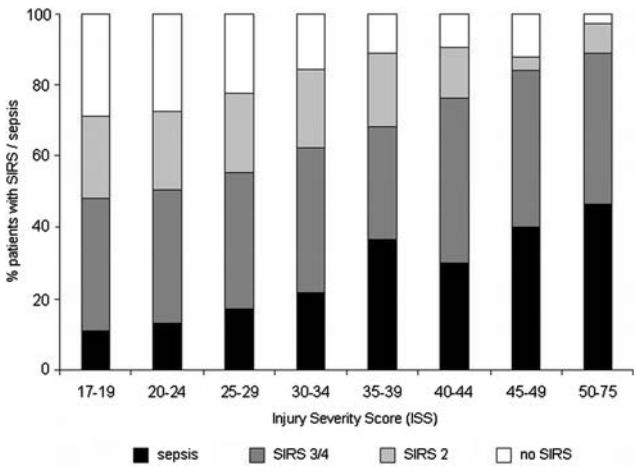

Figure 2. Influence of injury severity score (ISS) on incidence of SIRS and sepsis. Incidence of SIRS and sepsis in patients with ISS ≥ 17 points for different ISS groups. Data represent percentages. *SIRS*, systemic inflammatory response syndrome.

Influence of Hemorrhagic Shock on Incidence of Infection, SIRS and Sepsis

Mild hemorrhagic shock (class I and II) on admission was present in 891 patients (91.7%), whereas 81 patients (8.3%) suffered from severe hemorrhagic shock (class III and IV). ISS scores were significantly related to the severity of hemorrhagic shock, ranging from 29.9 ± 9.7 points in class I to 40.9 ± 14.2 points in class IV ($p < 0.001$; Table 4). Class I and II hemorrhage were associated with infection rates of 39.7 and 50.5%, respectively, whereas significantly higher infection rates were observed in patients with severe hemorrhagic shock (class III, 69.6%; class IV, 80.0%; $p < 0.001$). This was also evident in the relative accumulation of infectious foci depending on the severity of hemorrhage (Table 4; Figure 3). A significant increase

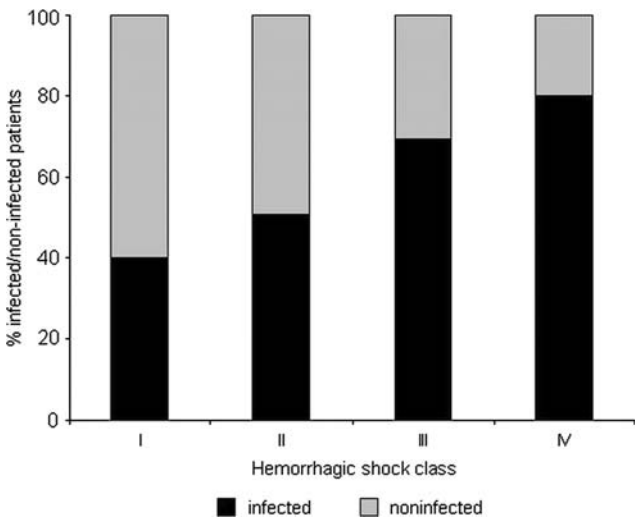

Figure 3. Influence of hemorrhagic shock on incidence of infection. Incidence of infection in patients with ISS ≥ 17 points for the different hemorrhagic shock groups (according to ATLS®). Data represent percentages.

Table 4. Influence of hemorrhagic shock on the incidence of infection and SIRS/sepsis. (ISS: Injury Severity Score; APACHE II: Acute Physiology and Chronic Health Evaluation II; SIRS: systemic inflammatory response syndrome).

Hemorrhagic shock class	I	II	III	IV	p value
Number	582 (59.9)	309 (31.8)	56 (5.8)	25 (2.5)	
ISS (points)[a]	29.9 ± 9.7	34.3 ± 11.8	36.1 ± 10.9	40.9 ± 14.2	< 0.001[b]
APACHE II (points)[a]	13.1 ± 7.1	15.3 ± 7.5	19.9 ± 9.3	26.0 ± 7.6	< 0.001[b]
Infected patients	231 (39.7)	156 (50.5)	39 (69.6)	20 (80.0)	< 0.001[c]
Pneumonia	146 (25.1)	99 (32.0)	22 (39.3)	11 (44.0)	0.01[c]
Wound infection	40 (6.9)	39 (12.6)	14 (25.0)	11 (44.0)	< 0.001[c]
Bacteremia	57 (9.8)	43 (13.9)	13 (23.2)	8 (32.0)	< 0.001[C]
CNS infection	32 (5.5)	18 (5.8)	3 (5.4)	1 (4.0)	ns
Catheter infection	40 (6.9)	37 (12.0)	13 (23.2)	6 (24.0)	< 0.001[c]
No SIRS	133 (22.9)	41 (13.2)	2 (3.6)	0 (0)	ns
SIRS 2	126 (21.6)	50 (16.2)	9 (16.0)	2 (8.0)	ns
SIRS 3 and 4	227 (39.0)	121 (39.2)	22 (39.3)	11 (44.0)	< 0.001[c]
Sepsis	96 (16.5)	97 (31.4)	23 (41.1)	12 (48.0)	< 0.001[c]
Mortality	60 (10.3)	27 (8.7)	11 (19.6)	4 (16.0)	ns

[a]Mean ± SD. Values in parentheses are percentages
[b]Kruskal–Wallis test
[c]Pearson chi-square test

in septic complications was found with more severe hemorrhagic shock (class I, 16.5%; class II, 31.4%; class III, 41.1%; class IV, 48.0%, $p < 0.001$; Figure 4).

Multiple logistic regression analysis showed that ISS and the degree of hemorrhagic shock were independent risk factors for infection as well as sepsis (all $p < 0.001$).

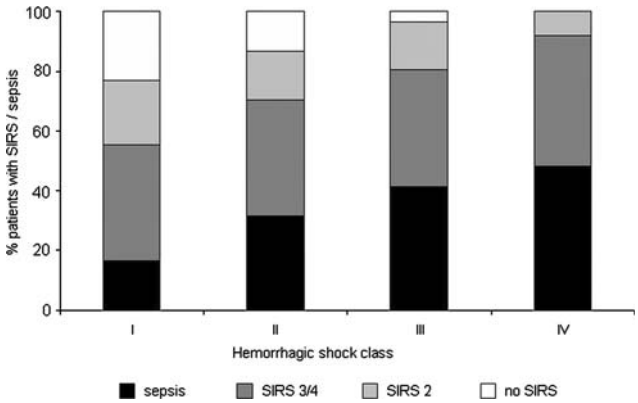

Figure 4. Influence of hemorrhagic shock on the incidence of SIRS and sepsis. Incidence of SIRS and sepsis in patients with ISS ≥ 17 points for the different hemorrhagic shock groups (according to ATLS®). Data represent percentages. *SIRS*, systemic inflammatory response syndrome.

Discussion

The activation of the inflammatory response following trauma depends on the severity of trauma and on the individual patient's physiological condition [3]. The extent and duration of early SIRS depends on the magnitude of the initial traumatic load [3]. Within this inflammatory process, a fine balance exists between the beneficial effects of local and systemic inflammation and the potential to cause and aggravate tissue injury leading to MOF [2]. Negative feedback mechanisms (CARS) downregulate SIRS to limit this potentially autodestructive inflammation, resulting in a state of delayed immunosuppression [2, 3]. During CARS, subsequent infection represents an important cause of mortality in patients who initially survive severe trauma but later develop sepsis and late MODS [6].

Recent investigations using modern microarray-based technology suggest that CARS may further be promoted by the specific depression of genes responsible for the transcription of proinflammatory cytokines such as TNF-α, IL-1β, or chemokines such as IL-8. This genetic reprogramming or ''silencing'' may develop rapidly (3–5 h) after the initial activation phase that generates the overexpression of proinflammatory cytokines [31]. In addition, the absolute concentrations of pro- and anti-inflammatory cytokines are influenced by polymorphisms in cytokine genes, which in the cases of TNF-α and TNF-β have been shown to affect mortality in sepsis patients [32]. Currently, high-throughput genomic studies are being performed to analyze inflammatory leukocyte gene expression patterns on a genome-wide basis, such as by investigators of the Glue Grant Consortium [33].

Several other studies have demonstrated high infection rates in the posttraumatic course of severely traumatized patients. Papia et al. and Bochiccio et al. reported overall infection rates in trauma ICU patients of 37% (mean ISS 24 pts, range 1–75 pts) and 41.3% (mean ISS 23 ± 12 pts), respectively [8, 9]. Appelgren et al. [7] found that almost 50% of trauma patients eventually developed infections. Early recognition of risk factors for subsequent infection in this group of high-risk patients may therefore reduce mortality by allowing early initiation of preventive surgical and antibiotic measures.

The most common infectious complication observed in our trauma patient population was pneumonia, followed by bacteremia, wound infection, catheter infection and urinary tract infection. The rates and foci of infections were in general accordance with the results of previous studies, even though nosocomial infection rates from different ICUs are difficult to compare because of varying study populations, surveillance methods and different diagnostic criteria. Obviously, the high rate of respiratory tract infections is a consequence of frequent ventilator support in trauma patients.

With respect to isolated microorganisms, results vary by nature in studies from different institutions. However, the distribution of organisms isolated at our department was similar to that reported by Papia et al. [8]. In their study, *S. aureus* (19%), *E. coli* (16%) and *P. aeruginosa* (10%) were the most commonly recovered pathogens. Again, *S. aureus* remains the most frequently observed pathogen, and has been partially responsible for most kinds of localized infections in our patient collective, except maybe in the urinary tract.

The ISS is the scoring system most widely used to quantify the extent of injury in a specific patient [25]. Several studies have examined the predictive value of the ISS as a risk factor for infection [4–6, 8, 10]. While most of these demonstrated a significant association between ISS and infection, a few failed to find such a relationship [4, 6, 27]. Croce et al. [11] reported that the ISS was a predictor of abdominal septic complications in a subset of patients with penetrating abdominal trauma. Papia et al. [8] found that infected patients tended to have more severe or extensive injuries, as demonstrated by a mean ISS of 30 compared with a mean ISS of 21 in noninfected patients ($p < 0.01$). Heckbert et al. [13] reported a statistically significant relationship between ISS in patients with hypotension and infection. On the other hand, Hurr et al. [4] failed to verify that ISS was an independent predictor of nosocomial infections in his study of 113 severely injured patients. In this report, only the length of ICU stay independently predicted the occurrence of subsequent nosocomial infections. However, the incidence of infection in our collective was higher with increasing ISS.

Systemic inflammation is common during the posttraumatic period and correlates well with the severity of injury [9, 20, 21, 34]. We have previously demonstrated that the ISS represents a potent risk factor for SIRS 3/4 and sepsis in trauma patients [34]. In a retrospective study of 1,273 patients, ISS and severe (AIS ≥ 3 pts) head injuries were potent independent risk factors for SIRS 3/4, MODS and death. With respect to the site of injury, patients with isolated abdominal and pelvic injuries had the highest rates of septic complications. In the present study, we did not assess the influence of different anatomic regions or injury patterns, but we could again demonstrate that the incidence of sepsis significantly correlates with the ISS.

Several authors have examined the association between hypotension (defined as a systolic blood pressure below 90 mmHg) on admission and infection [5, 11–13, 16]. Patients who were hypotensive upon admission were generally more likely to develop hospital-acquired pneumonia, wound infection and bacteremia than normotensive patients [5, 7, 12, 13, 16]. Several trials have reported a depression of both the innate and acquired immune system as a result of acute hemorrhage causing an increased susceptibility to infection, SIRS and sepsis in affected patients [15, 35]. Angele et al. demonstrated that wound exudate cells harvested on the first and third postoperative days from hemorrhaged animals exhibit an impaired release of proinflammatory cytokines and chemokines such as IL-1β and IL-6 in response to a second stimulus (lipopolysaccharide, LPS) in vitro [15]. They concluded that this dysfunction of wound exsudate cells could provide a potential mechanism by which to explain the impaired bacterial resistance in wounds of trauma patients, resulting in a higher rate of wound infections. Other clinical studies found only a weak association between shock and infection, but a strong correlation between blood transfusions on admission and subsequent infection, especially pneumonia [11]. Therefore, the recent trauma literature has focused extensively on blood transfusion and adverse outcome in trauma. In a study by Heckbert et al. [13], the requirement for large volumes of intravenous fluid as a surrogate index of hemorrhagic shock was associated with an increased risk of infection, organ failure and death. Edna et al. [17] demonstrated, in a prospective study in 868 patients with acute injuries, an obvious relationship between blood transfusions and infectious

morbidity independent of ISS, age, and surgical procedure. They found a corrected odds ratio for infection of 1.6 when 1–4 units of blood were given and 6.4 when more than four units were used. Papia et al. [8] demonstrated a dose-dependent relationship between number of units transfused and risk of infection, with an odds ratio of 7.71 when more than ten units of blood were transfused. Beale et al. [18] identified, in a previous prospective study of 120 patients, that multiple transfusions (> 4 units) are a risk factor for the development of posttraumatic SIRS. Higher transfusion volumes were also associated with a trend towards a higher rate of septic complications and organ failure, although this failed to reach statistical significance. The association between blood transfusion and risk for SIRS was also the focus of a study by Malone et al. performed in 9,569 trauma patients. Patients who received blood transfusions had a three- to fivefold increased risk for SIRS and a tenfold increased risk for mortality. In a subsequent study in a larger cohort of trauma patients (n = 15,534), the same authors confirmed that blood transfusion was a strong independent predictor of SIRS. SIRS was present in 28% of patients who underwent blood transfusion within the first 24 h compared to 15% of patients without transfusion ($p < 0.001$) [19]. Potential reasons for higher rates of infection and SIRS in patients receiving blood transfusions include contaminating leucocytes and inflammatory mediators within red blood cell units [36, 37]. A large body of evidence from animal and ex vivo laboratory studies supports a shift towards a Th_2-type immune response with increased levels of IL-4 and IL-10, and at the same time diminished levels of IL-2, IL-12 or interferon-γ. Combined, these changes lead to an impaired proinflammatory response to bacterial endotoxins and affect monocyte function such as phagocytosis or killing of microorganisms [37, 38]. However, the potential benefits of leukoreduced red cell transfusions remain intensely debated [39, 40].

Fewer reports exist on the use of the hemorrhagic shock classification according to ATLS® criteria as a predictor of infection in severely injured patients. In our patient collective, 80% of patients with class IV hemorrhage did develop infectious complications and 48% developed septic complications. Frequently observed infections in class IV hemorrhage were pneumonia and wound infections. To the authors' knowledge, a detailed analysis of the influence of the different ATLS shock grades on infection and SIRS has not yet been reported. The results of our study, therefore, support the relevance of hemorrhagic shock on the incidence of infection and SIRS in patients with significant hemorrhage. In addition, ATLS criteria for the severity of hemorrhage are simple to use in clinical practice, providing an excellent tool for rapid assessment of the severity of hemorrhage in acutely injured patients.

In summary, our data show a distinct relationship between the severity of injury, the extent of hemorrhage, and the subsequent incidence of posttraumatic infections. It emphasizes timely and adequate resuscitation not only to restore patient physiology and minimize day-one mortality, but also to reduce long-term infectious morbidity in trauma patients.

Conflict of interest statement

The authors declare that there is no actual or potential conflict of interest in relation to this article.

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