Epidemiology and risk factors of sepsis after multiple trauma: An analysis of 29,829 patients from the Trauma Registry of the German Society for Trauma Surgery*

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Objectives: **The objectives of this study were 1) to assess potential changes in the incidence and outcome of sepsis after multiple trauma in Germany between 1993 and 2008 and 2) to evaluate independent risk factors for posttraumatic sepsis.**

Design: **Retrospective analysis of a nationwide, population-based prospective database, the Trauma Registry of the German Society for Trauma Surgery.**

Setting: **A total of 166 voluntarily participating trauma centers (levels I–III).**

Patients: **Patients registered in the Trauma Registry of the German Society for Trauma Surgery between 1993 and 2008 with complete data sets who presented with a relevant trauma load (Injury Severity Score of ≥9) and were admitted to an intensive care unit (n = 29,829).**

Interventions: **None.**

Measurements and Main Results: **Over the 16-yr study period, 10.2% (3,042 of 29,829) of multiply injured patients developed sepsis during their hospital course. Annual data were summarized into four subperiods: 1993–1996, 1997–2000, 2001–2004, and 2005–2008. The incidences of sepsis for the four subperiods were 14.8%, 12.5%, 9.4%, and 9.7% (*p* < .0001), respectively. In-hospital mortality for all trauma patients decreased for the respective subperiods (16.9%, 16.0%, 13.7%, and 11.9%; *p* < .0001). For the subgroup of patients with sepsis, the mortality rates were 16.2%, 21.5%, 22.0%, and 18.2% (*p* = .054), respectively. The following independent risk factors for posttraumatic sepsis were calculated from a multivariate logistic regression analysis: male gender, age, preexisting medical condition, Glasgow Coma Scale score of ≤8 at scene, Injury Severity Score, Abbreviated Injury Scale$_{\mathrm{THORAX}}$ score of ≥3, number of injuries, number of red blood cell units transfused, number of operative procedures, and laparotomy.**

Conclusions: **The incidence of sepsis decreased significantly over the study period; however, in this decade the incidence remained unchanged. Although overall mortality from multiple trauma has declined significantly since 1993, there has been no significant decrease of mortality in the subgroup of septic trauma patients. Thus, sepsis has remained a challenging complication after trauma during the past 2 decades. Recognition of the identified risk factors may guide early diagnostic workup and help to reduce septic complications after multiple trauma. (Crit Care Med 2011; 39:621–628)**

Key Words: multiple trauma; sepsis; risk factors; incidence; outcome; mortality; multivariate analysis

Several factors have been recognized to substantially contribute to impaired outcomes after severe injury, but sepsis is one of the most significant in patients who survive initial trauma resuscitation since it represents the leading cause of death in noncardiac intensive care units (ICUs) (1, 2). However, while overall mortality from multiple trauma has gradually decreased in western countries over the past few decades (3–5), there is only limited information on the development of sepsis in injured patients over recent years. Epidemiologic data from the United States have shown a general decrease in the incidence of sepsis (2); however, comparable European investigations do not exist.

In addition, independent predictors for sepsis during trauma-associated hospitalization are debated controversially. Several authors have reported that the transfusion of allogenic blood during trauma resuscitation is associated with the systemic inflammatory response syndrome and infection (6–11). In a large trauma study, Osborn et al (12) identified the Injury Severity Score (ISS), the Revised Trauma Score, the Glasgow Coma Scale (GCS) score, comorbidities, and male gender as predictors for posttraumatic sepsis but were not able to adjust for transfusion or other therapy-related variables. Furthermore, the predictive value of specific injury patterns and the role of distinct anatomical regions have not been elucidated. Altogether, independent risk factors for postinjury sepsis are still poorly defined, although they might be useful adjuncts to identify high-risk patients at an early stage.

Therefore, using a large multicenter population-based trauma registry, the aims of the present study were 1) to investigate the incidence and outcome of sepsis after multiple trauma and potential

***See also p. 876.**

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temporal changes since the establishment of the database in 1993 and 2) to identify independent risk factors for sepsis after multiple trauma.

PATIENTS AND METHODS

The Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie. The Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie (German Society for Trauma Surgery) (TR-DGU) (13) was founded in 1993 as an initiative for prospective, standardized, and anonymous documentation of severely injured patients. At present, 166 trauma centers of all levels are participating voluntarily at the TR-DGU, mainly from Germany, but also 17 hospitals from Austria, Switzerland, The Netherlands, Belgium, and Slovenia (http://www.traumaregister.de). Recently, >6,000 patients have been registered annually, and it is estimated that the TR-DGU covers about 25% of all severe trauma cases in Germany (5). The data are collected prospectively and are structured into four consecutive time phases: 1) prehospital phase, 2) emergency room and initial treatment until ICU admission, 3) ICU, and 4) discharge and list of injuries and interventions. The registry contains detailed information on the demographics, injury severity and pattern, prehospital and in-hospital management, time course, and outcome of each patient. In 2002, data collection moved from paper form documentation to a central online registration system via the Internet. The documentation includes standardized scoring systems, e.g., the GCS and the Abbreviated Injury Scale (AIS) (14, 15).

This study was approved by the ethical board of our institution and is in accordance with the standards of the Helsinki Declaration of 1975.

Study Population. Until 2008, 42,248 patients have been registered in the TR-DGU database. For the present study, patients were excluded 1) if any data on demographics, injury severity, or prehospital and in-hospital course were missing (n = 7466), 2) if patients presented with mild injury defined as ISS <9 (n = 3068), and 3) if they were not admitted to the ICU (n = 1885). Therefore, a total of 29,829 patients remained for further analysis.

To evaluate temporal changes over the study period, annual data were summarized into four subperiods as described previously (2), for the complete study population (see Table 2) and for the subgroup of patients with sepsis (see Table 3).

Definitions of Sepsis and Organ Failure. In the data report form, the occurrences of sepsis and organ failure (cardiovascular, lungs, central nervous system, kidney, liver, coagulation) during the hospital course are documented dichotomously for each as either "yes" or "no." Sepsis was coded according to the criteria of Bone (16) during the complete study period. Organ failure was assessed by

Table 1. Basic demographic/clinical characteristics upon admission and outcomes of multiple trauma patients with and without sepsis (1993–2008)

Demographic/Clinical Characteristic, Outcome	Sepsis, 3,042 (10.2%)	No Sepsis, 26,787 (89.8%)	p
Age (yrs; mean ± SD)	44 ± 19	42 ± 21	<.0001
Male (%)	80.9	72.1	<.0001
Blunt/penetrating trauma (%)	95.9/4.1	95.5/4.5	.356
Open fracture (%)	12.7	9.0	<.0001
Injury Severity Score (points; mean ± SD)	33 ± 13	25 ± 13	<.0001
AIS_{HEAD} score of ≥3 (%)	54.6	50.5	<.0001
AIS_{THORAX} score of ≥3 (%)	67.8	49.5	<.0001
$AIS_{ABDOMEN}$ score of ≥3 (%)	29.8	18.0	<.0001
$AIS_{EXTREMITIES}$ score of ≥3 (%)	49.0	37.5	<.0001
SBP at the scene (mm Hg; mean ± SD)	112 ± 33	120 ± 32	<.0001
SBP at the scene of ≤90 mm Hg (%)	26.5	17.4	<.0001
heart rate at the scene (beats per minute; mean ± SD)	98 ± 25	93 ± 23	<.0001
Glasgow Coma Scale score at the scene (points; mean ± SD)	10.0 ± 4.8	11.1 ± 4.6	<.0001
Glasgow Coma Scale score at the scene of ≤8 (%)	39.4	29.3	<.0001
Intravenous fluids, prehospital (mL; mean ± SD)	1637 ± 1241	1294 ± 1055	<.0001
SBP at the ER (mm Hg; mean ± SD)	117 ± 30	124 ± 29	<.0001
SBP at the ER of ≤90 mm Hg (%)	20.9	11.2	<.0001
Heart rate at the ER (beats per minute; mean ± SD)	95 ± 23	90 ± 21	<.0001
Hemoglobin (g/dL; mean ± SD)	10.7 ± 2.8	11.8 ± 2.7	<.0001
Platelets (nL^{-1}; mean ± SD)	187 ± 82	206 ± 81	<.0001
Prothrombin time (Quick%; mean ± SD)	72 ± 23	80 ± 22	<.0001
Base excess (mmol/L; mean ± SD)	−4.2 ± 5.1	−2.9 ± 4.6	<.0001
Intravenous fluids, ER to intensive care unit (mL; mean ± SD)	3560 ± 3641	2457 ± 2547	<.0001
Preexisting medical condition (%)	35.4	28.3	<.0001
pRBC transfusion[a] (%)	45.4	24.9	<.0001
Massive transfusion[a] (≥10 pRBC units) (%)	15.2	5.8	<.0001
pRBC units[a] (n; mean ± SD)	4.3 ± 8.1	1.8 ± 5.1	<.0001
Fresh frozen plasma units[a] (n; mean ± SD)	2.3 ± 6.3	0.9 ± 3.5	<.0001
Operative procedures (n; mean ± SD)	5.9 ± 6.5	3.0 ± 3.4	<.0001
Laparotomy (%)	27.3	15.0	<.0001
Organ failure (%)	82.9	34.8	<.0001
Cardiovascular (%)	63.5	20.1	<.0001
Respiratory (%)	63.5	17.3	<.0001
Central nervous system (%)	35.4	18.4	<.0001
Hepatic (%)	21.2	2.4	<.0001
Renal (%)	20.9	2.6	<.0001
Hematologic (%)	18.5	5.2	<.0001
Multiple-organ failure (%)	63.2	17.3	<.0001
Intensive care unit length of stay (days; mean ± SD)	28 ± 22	10 ± 12	<.0001
In-hospital length of stay (days; mean ± SD)	45 ± 37	26 ± 28	<.0001
Ventilator days (mean ± SD)	22 ± 19	6 ± 9	<.0001
30-day mortality (%)	15.7	12.1	<.0001
In-hospital mortality overall (%)	19.5	12.5	<.0001

AIS, Abbreviated Injury Scale; ER, emergency room; pRBCs, packed red blood cells; SBP, systolic blood pressure. The small p values are based on the large sample size, and interpretation has to consider the clinical importance of the observed difference.

[a]Blood products transfused between ER arrival and intensive care unit admission.

using the revised multiple-organ failure (MOF) score of Goris et al (17). Since the introduction of the online version of the registry in 2002, the Sequential Organ Failure Assessment score was used to determine organ function status (18). MOF was defined as organ failure for at least two of the listed organs/systems.

Statistical Analysis: Univariate and Stratification. For categorical variables, data were compared between groups using the chi-square test. For continuous variables, the Mann-Whitney U test was applied for comparison of two groups (sepsis vs. nonsepsis patients; Table 1) and the Kruskal-Wallis test for comparison of more than two groups (four subperiods of trauma years; Tables 2 and 3). Data are presented as mean ± SD for continuous variables and as percentages for incidence rates.

Statistical Analysis: Multivariate. A multivariate analysis was performed by stepwise logistic regression with sepsis as the dependent variable to identify independent risk factors for the development of posttraumatic sepsis. The variables that were analyzed as potential predictors for sepsis were selected from the literature and from the clinical experience of our research group. These variables consisted of patient characteristics (age, gender, preex-

Table 2. Basic characteristics, injury patterns, and outcomes of the complete study population, stratified according to their respective trauma years (n = 29,829)

Characteristic, Injury Pattern, Outcome	1993–1996	1997–2000	1997–2000	2005–2008	*p*
n	1,543	3,771	8,403	16,112	
Participating hospitals	19	72	104	166	
Age (yrs; mean ± SD)	39 ± 19	39 ± 19	42 ± 20	44 ± 21	<.0001
Male (%)	71.4	72.5	73.2	73.2	.414
Injury Severity Score (points; mean ± SD)	24 ± 12	27 ± 14	25 ± 13	27 ± 13	<.0001
AIS_{HEAD} score of ≥3 (%)	43.3	49.9	50.4	52.2	<.0001
AIS_{THORAX} score of ≥3 (%)	48.9	46.1	48.9	54.1	<.0001
$AIS_{ABDOMEN}$ score of ≥3 (%)	20.9	21.3	20.2	18.0	<.0001
$AIS_{EXTREMITIES}$ score of ≥3 (%)	46.1	44.0	38.1	37.0	<.0001
Glasgow Coma Scale score at the scene of ≤8 (%)	30.4	34.9	30.6	29.0	<.0001
Preexisting medical condition (%)	1.5	17.4	29.4	34.8	<.0001
Packed red blood cell transfusion[a] (%)	41.3	37.4	25.7	23.9	<.0001
Operative procedures (n; mean ± SD)	3.5 ± 3.3	3.6 ± 3.6	3.1 ± 3.8	3.3 ± 4.1	<.0001
Laparotomy (%)	19.8	18.7	16.5	15.2	<.0001
Sepsis (%)	14.8	12.5	9.4	9.7	<.0001
Organ failure (%)	37.0	34.6	38.7	45.6	<.0001
Multiple-organ failure (%)	22.3	18.3	20.5	27.0	<.0001
Intensive care unit length of stay (days; mean ± SD)	13 ± 16	13 ± 15	12 ± 15	11 ± 13	<.0001
In-hospital length of stay (days; mean ± SD)	31 ± 31	30 ± 31	29 ± 33	26 ± 27	<.0001
30-day mortality (%)	16.3	15.1	12.8	11.3	<.0001
In-hospital mortality overall (%)	16.9	16.0	13.7	11.9	<0.0001

AIS, Abbreviated Injury Scale.
[a]Packed red blood cells transfused between emergency room arrival and intensive care unit admission.

Table 3. Basic characteristics, injury patterns, and outcomes of the subgroup of patients who developed sepsis during the hospital course, stratified according to their respective trauma years (n = 3042)

Characteristic, Injury Pattern, Outcome	1993–1996	1997–2000	2001–2004	2005–2008	*p*
n	228	470	786	1558	
Age (yrs; mean ± SD)	38 ± 16	41 ± 17	43 ± 19	45 ± 20	<.0001
Male (%)	75.7	80.4	81.7	81.5	.195
Injury Severity Score (points; mean ± SD)	28 ± 11	33 ± 13	31 ± 13	34 ± 13	<.0001
AIS_{HEAD} score of ≥3 (%)	43.9	52.1	48.2	60.1	<.0001
AIS_{THORAX} score of ≥3 (%)	60.1	63.0	64.6	71.9	<.0001
$AIS_{ABDOMEN}$ score of ≥3 (%)	32.0	33.4	29.4	28.5	.189
$AIS_{EXTREMITIES}$ score of ≥3 (%)	61.0	54.3	50.1	45.1	<.0001
Glasgow Coma Scale score at scene of ≤8 (%)	33.3	43.4	39.0	39.2	.13
Preexisting medical condition (%)	1.3	21.7	37.8	44.3	<.0001
Packed red blood cell transfusion[a] (%)	57.5	52.3	41.5	43.6	<.0001
Operative procedures (n; mean± SD)	5.7 ± 4.4	6.0 ± 5.5	5.6 ± 7.2	6.0 ± 6.7	.001
Laparotomy (%)	31.6	31.1	24.4	26.9	.031
No organ failure (%)	17.7	22.2	17.2	13.1	<.0001
Single-organ failure (%)	19.9	22.7	20.4	16.7	.014
Multiple-organ failure (%)	62.4	55.1	62.4	70.2	<.0001
Intensive care unit length of stay (days; mean ± SD)	26 ± 23	30 ± 24	29 ± 24	27 ± 20	.012
In-hospital length of stay (days; mean ± SD)	51 ± 42	45 ± 33	47 ± 40	43 ± 35	.14
30-day mortality (%)	15.4	16.6	17.6	14.5	.258
In-hospital mortality overall (%)	16.2	21.5	22.0	18.2	.054

AIS, Abbreviated Injury Scale.
[a]Packed red blood cells transfused between emergency room arrival and intensive care unit admission.

isting medical condition), type and severity of injury (ISS, body regions, open vs. closed fracture, etc.), early physiology (GCS, blood pressure), and early treatment (operative procedures, laparotomy, transfusion). Additional adjustment was performed for the trauma year. Measures of discrimination (e.g., Nagelkerke's r^2, area under the receiver operating characteristic curve) were calculated.

Where appropriate, mortality and other incidence rates are presented with 95% confidence intervals. A *p* value of <.05 was considered significant. Statistical analysis was performed using standard statistical software (SPSS Version 15.0, SPSS, Chicago, IL).

RESULTS

Univariate Analysis. From the total of 29,829 eligible multiple trauma patients during the entire study period, 3,042 (10.2%) developed sepsis during their hospital stay. Patients had a mean age of 42 (±20) yrs and were injured substantially (mean ISS = 26 ± 13). Detailed characteristics for patients with vs. patients without sepsis are summarized in Table 1.

In both groups, patients were predominantly male with significantly more males among septic trauma patients (80.9% vs. 72.1%; $p < .0001$). Patients with sepsis were injured more severely as indicated by a higher ISS (33 vs. 25; *p* <

.0001). Figure 1 depicts the association between the incidence of sepsis and trauma severity as reflected by stratification for ISS, in both male and female patients. Furthermore, the occurrence of sepsis during posttraumatic hospitalization was associated with more deranged physiologic and laboratory values during the initial trauma resuscitation. Patients developing trauma-associated sepsis had received significantly higher rates of transfusion of packed red blood cell units between emergency room arrival and ICU admission than nonseptic patients; furthermore, they underwent surgery more frequently.

Sepsis after trauma was significantly associated with prolonged ICU/hospital stay and with increased rates of single-organ failure (82.9% vs. 34.8%) and MOF (63.2% vs. 17.3%; both $p < .0001$). The organs that failed most frequently in patients with sepsis were the cardiovascular system and the lungs (both 63.5%; Table 1). The overall hospital mortality totaled 19.5% in the sepsis group vs. 12.5% in patients without sepsis ($p < .0001$).

Stratification for Trauma Years. Table 2 displays the basic characteristics for the complete study population stratified into four subperiods according to the trauma year. Most changes observed from 1993 through 2008 were statistically significant, e.g., a decreasing rate of packed red blood cell transfusions and fewer laparotomies. The incidence of sepsis declined until the third subperiod but then remained on a comparable level during the two latest subperiods (Fig. 2). Overall mortality in all multiple trauma patients (Fig. 3, *light gray columns*) declined from 1993 through 2008.

Table 3 lists the relevant data on the subgroup of septic trauma patients correspondingly stratified into the four trauma year subperiods. As for the entire study population, the incidence of MOF significantly increased from 1993 until 2008, and over time, progressively fewer sepsis patients presented without organ failure. The development of mortality rates in septic trauma patients is also demonstrated in Figure 3 (*dark gray columns*), showing no significant changes regarding the complete study period. However, when the two latest subperiods were compared, the mortality rate decreased significantly.

Predictors of Sepsis from Multivariate Analysis. A total of 19 variables were entered into the stepwise logistic regression. The final model is presented in Table 4. The following independent risk factors for the development of sepsis after multiple trauma were calculated: male gender, age, preexisting medical condition, GCS score of ≤8 at the scene, ISS, AIS_{THORAX} score of ≥3, number of injuries, number of red blood cell units transfused, number of operative procedures, and laparotomy ($r^2 = 0.124$; area under the receiver operating characteristic curve of 0.727; 95% confidence interval of 0.717–0.738). For the model, the percentage of correctly predicted cases was 89.4% and Cohen's κ coefficient was 0.20 if p(sepsis) of ≥20% was used as the cutoff. The following variables were excluded by the model: systolic blood pressure at the scene of ≤90 mm Hg vs. >90 mm Hg; systolic blood pressure at emergency room admission of ≤90 mm Hg vs. >90 mm Hg; AIS_{HEAD} score of ≥3; $AIS_{ABDOMEN}$ score of ≥3; $AIS_{EXTREMITIES}$ score of ≥3; blunt vs. penetrating mechanism; open vs. closed fracture; fresh frozen plasma transfusion vs. no fresh frozen plasma transfusion.

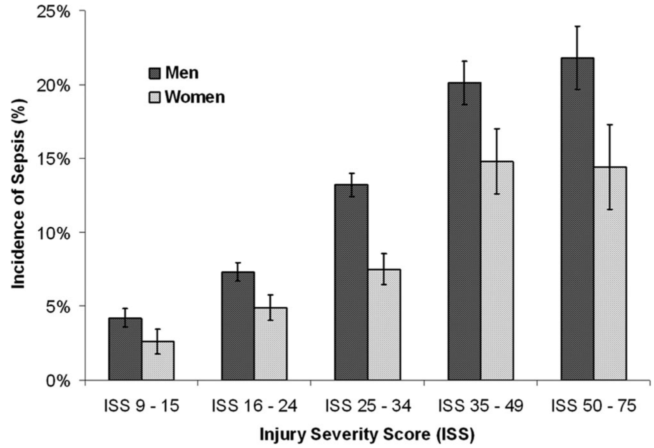

Figure 1. Incidence of sepsis in multiple trauma patients, grouped for male and female gender and stratified for Injury Severity Score subgroups (n = 29,829; 1993–2008); $p < .0001$. Error bars represent 95% confidence intervals.

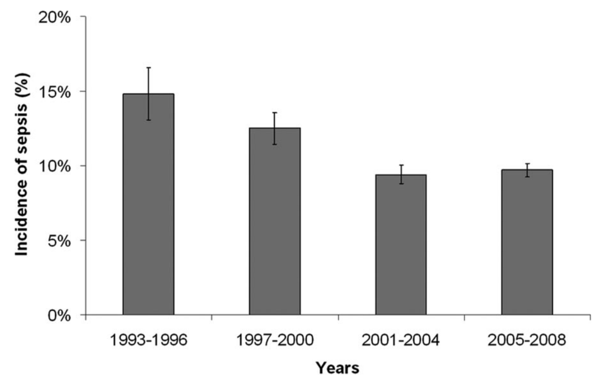

Figure 2. Incidence of sepsis after multiple trauma from 1993 to 2008 (n = 29,829); $p < .0001$. Linear regression analysis showed a decrease of −0.46% per year for sepsis incidence. Error bars represent 95% confidence intervals.

DISCUSSION

Incidence. To our knowledge, the current analysis is the largest study on sepsis in severely injured patients. The only comparable study, by Osborn et al (12), included 30,303 trauma patients from Pennsylvania over a 2-yr period; however, their study population was rather heterogeneous since the majority of the patients were injured only mildly (mean ISS = 13 ± 11) and therefore only 40% were admitted to the ICU. Consequently, the authors reported an incidence of posttraumatic sepsis of only 2%, which probably underestimates septic complications in populations of critically injured patients. Since in the present study only patients with a relevant trauma load indicated by an ISS of ≥9 were considered, the mean ISS was 26 ± 13, with the overall incidence of sepsis totaling 10.2%.

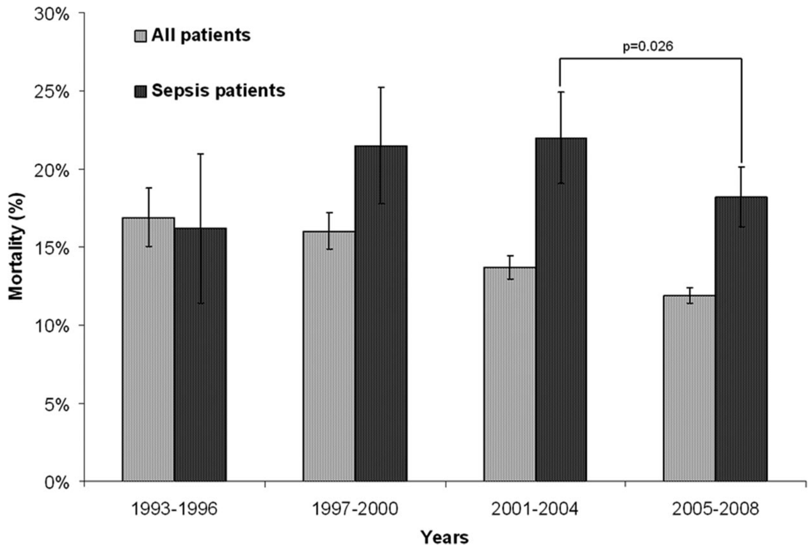

Figure 3. Mortality in all trauma patients (*light gray columns*; n = 29,829; $p < .0001$) and in the subgroup of trauma patients who developed sepsis (*dark gray columns*; n = 3042; $p = .054$) from 1993 until 2008. In patients with sepsis, differences between two subsequent periods did not reach statistical significance except for the two latest subperiods, as depicted ($p = .026$). Linear regression analyses showed a slope of −0.433% per year for overall mortality and a slope of +0.155% per year for sepsis mortality. Error bars represent 95% confidence intervals.

Table 4. Independent risk factors for the development of sepsis after multiple trauma, derived from a multivariate analysis using a stepwise logistic regression model with forward variable selection

Variable Entered	Regression Coefficient β	Odds Ratio (e^{β}; 95% Confidence Interval)	*p*
Male gender (vs. female gender)	0.59	1.81 (1.61–2.03)	<.0001
Preexisting medical condition (vs. none)	0.48	1.62 (1.45–1.80)	<.0001
Injury Severity Score (points)	0.01	1.01 (1.01–1.02)	<.0001
Number of operative procedures			
0			
1	0.52	1.69 (1.37–2.07)	<.0001
≥2	0.86	2.37 (1.98–2.83)	<.0001
Number of packed red blood cell units[a]			
0			
1–9	0.35	1.41 (1.27–1.58)	<.0001
≥10	0.47	1.60 (1.37–1.88)	<.0001
Abbreviated Injury Scale (thorax) score of ≥3 (vs. <3)	0.26	1.30 (1.17–1.45)	<.0001
Glasgow Coma Scale score of ≤8 at the scene (vs. >8)	0.28	1.32 (1.19–1.46)	<.0001
Age (yrs)	0.01	1.01 (1.00–1.01)	<.0001
Laparotomy (vs. no laparotomy)	0.16	1.18 (1.05–1.32)	.007
Number of injuries	0.09	1.09 (1.07–1.11)	<.0001
Trauma years			
1993–1996			
1997–2000	−0.28	0.76 (0.62–0.93)	.007
2001–2004	−0.50	0.61 (0.50–0.74)	<.0001
2005–2008	−0.55	0.58 (0.48–0.70)	<.0001
Constant	−4.63		

Backward variable selection yielded the same results. The logistic regression model was started with 19 variables (see text). The standard category is included in parentheses behind the variable name and does not receive a coefficient in the model. Odds ratios have to be interpreted in relation to this standard category.

[a]Packed red blood cells transfused between emergency room arrival and intensive care unit admission.

This result is consistent with results from a South African study on 450 severely injured patients (mean ISS = 18 ± 8) where 14.4% developed sepsis (19) or from a prospective, observational investigation that found a sepsis rate of 12.4% among 454 surgical and medical ICUs across Germany (20).

In the current study, the incidence of postinjury sepsis decreased significantly over time; however, regarding this decade (2001–2008), the incidence rates remained constant. In contrast to our findings, a large epidemiologic study from the United States indicated that the incidence of sepsis increased progressively from 1979 until 2000 (2). The declining incidence of sepsis over the 16-yr study period in our analysis can partially be attributed to various nonspecific improvements in intensive care medicine over the past 2 decades, e.g., with respect to mechanical ventilation (21, 22) and weaning (23, 24). However, the impacts of these potential advances were neither investigated nor substantiated by our analysis since the respective data are not documented in the TR-DGU.

With respect to packed red blood cell transfusion and operative procedures, we observed substantial changes regarding these sepsis predictors from 1993 to 2008, particularly a dramatic reduction in the packed red blood cell transfusion rate. Therefore, this observation represents another possible reason for the decline in sepsis incidence, as discussed previously (25).

Outcome. Previous reports have suggested a decrease in mortality after severe injury over recent years (3–5). However, similar findings in our present study were not accompanied by improved outcomes in those patients with sepsis. Although overall mortality from multiple injury declined significantly from 1993 until 2008, we could not determine a significant decrease of mortality in the subgroup of septic trauma patients regarding the entire study period. Similarly, there was no significant change in the length of hospital stay among sepsis patients although demonstrated for the complete study population. Interestingly, the occurrence of MOF increased significantly in both the entire cohort and the subgroup with sepsis, which has been reported by other authors as well (2). These temporal changes with respect to organ failure, which is an indicator of the severity of illness, are likely to have contributed to the relatively static mortality rates among sepsis patients over the study period. Another potential explanation might be associated with the emergence of fungal pathogens and increasing microbial resistance (2, 26). However, information on causative microorganisms or the site of infection is not documented at all in the TR-DGU database, which represents one major weakness of the current investigation.

Osborn et al (12) found a mortality of 23.1% in trauma patients with sepsis, which resembles the overall mortality rate of 19.5% in septic patients of the current study considering the higher age as compared to that of our study population (49 ± 21 yrs vs. 44 ± 19 yrs). In 1995, Angus et al (1) calculated an annual mortality of 28.6% in a nontrauma population; however, only patients with severe sepsis were studied, and the mean age was 64 yrs.

While general long-term data on sepsis are available from the United States showing a declining mortality in sepsis patients (27.8% during the period of 1979–1984 to 17.9% during 1995–2000) (2), further comparison remains difficult as no other trauma study exists assessing epidemiology of sepsis over a long study period. We found a trend toward increasing mortality in sepsis patients in each subsequent period, but interestingly, a significant decrease was observed when the two latest subperiods were compared (2001–2004 vs. 2005–2008). Certainly, the interpretation of outcome data must take into account that new insights from clinical trials have enhanced sepsis therapy over recent years (27–30). Accordingly, as a key effort of the Surviving Sepsis Campaign, evidence-based clinical practice guidelines were developed and published in 2004 (31), and first analyses demonstrated that increasing compliance with the guidelines was associated with improved outcomes (32). However, regarding the role of these initiatives for the current study, the grade of adherence to sepsis guidelines among the participating centers cannot be abstracted from our database. However, it remains to be seen whether future advances in critical care will be accompanied by temporal changes observable in our and other trauma registries.

Sepsis Risk Factors. As the second objective, the present study was conducted to determine independent risk factors for sepsis after severe injury. In the investigation by Osborn et al (12), the following predictors of sepsis were identified: ISS, Revised Trauma Score, GCS score, comorbidities, and male gender. However, information on transfusion requirement, operative procedures, or organ failure was not documented in their database.

Regarding the multivariate analysis of the current study, we detected male gender as a significant predictor for sepsis as well, and large epidemiologic studies have already demonstrated the same disparity between men and women (1, 2), which has been attributed to genetic (33), endocrine (34), and socioeconomic (1, 2) aspects. Corresponding to prior studies, both age and preexisting medical conditions were also identified as independent predictors of sepsis in our analysis (1, 7, 12).

Still, activation of the inflammatory response is determined not only by these individual host factors but also by the magnitude of the initial trauma load (35), preferably quantified using the ISS as a surrogate (15). Our present analysis supports earlier findings that the ISS represents a potent predictor of infection and sepsis (7, 11, 12). However, only a few authors have investigated the influence of the injury pattern on the development of sepsis. First, we could demonstrate that the incidence of sepsis significantly correlates with the number of injuries. According to AIS scores, the anatomical region with the highest predictive value for postinjury sepsis was the thorax. Chest injuries have frequently been reported to contribute significantly to increased rates of acute respiratory distress syndrome, sepsis, and MOF (7, 36, 37). Accordingly, the highest rate of organ failure in our study was observed for the respiratory system (63.5%).

Several authors have recognized allogenic blood transfusion as an independent predictor of posttraumatic infection (7, 11) and systemic inflammatory response syndrome (6, 8). We observed similar results and a dose-dependent relationship regarding posttraumatic sepsis, with massive transfusion (≥10 red blood cell units) approaching a doubling of the risk. Potential underlying mechanisms are associated with contaminating leukocytes and inflammatory mediators within packed red blood cell units (9, 10) and with the widespread depression of the immune system through hemorrhagic shock (6, 11, 37–39).

As discussed above, we could assess a decreasing number of operative procedures and fewer laparotomies from 1993 through 2008. This reflects the changing practice regarding splenic and hepatic injuries with a more frequent use of nonoperative treatment strategies, which have been associated with lower rates of abdominal infection and sepsis in previous reports as well (7, 40, 41). Multiple surgical procedures have been described to affect the immune system as "second hits" (7, 11, 38, 42).

Several limitations must be considered regarding this study. Only basic admission laboratory values are documented; further values that might be of interest (procalcitonin, C-reactive protein) are not documented in our registry. During the initial years, comorbidities were registered very inconsistently, and only their presence or absence was documented. Thus, further information with respect to specific diseases was not available. Accordingly, the occurrences of sepsis and MOF during trauma-associated hospitalization are documented only dichotomously as either "yes" or "no" without information on the respective day of onset or the duration. Therefore, it cannot be abstracted from the TR-DGU data set whether the operative procedures occurred before or after the onset of sepsis. In the interpretation of incidence data, it should be considered that the sepsis definition according to Bone (16) has been applied throughout the complete study period. Just recently, the TR-DGU data set has been revised; thus, in the future sepsis is going to be defined according to the recommended American College of Chest Physicians/Society of Critical Care Medicine consensus criteria (43). As mentioned above, the definition for organ failure was updated for the TR-DGU participants in 2002, which might bias statistics related to the incidence of organ failure. The following aspects might be further potential sources for bias: The mode of data entry changed in 2002 from paper form to online registration via the Internet. A total of 7,466 patients with missing data were excluded from the analysis. Participation at the TR-DGU is voluntary; as estimated, only about 25% of German multiple trauma patients are registered. There is a significant imbalance in the patient numbers among the four subperiods, which reflects the progressively increasing number of trauma centers participating in the registry since 1993. The resulting unequal sample sizes of the groups and subgroups studied might bias the results. Also, death was attributed to sepsis just on the basis of the mortality rates in patients diagnosed with sepsis, since the direct cause of death is not documented in the TR-DGU. It must be considered that information on "do not resuscitate" decisions is not registered as well. Finally, we conducted a retrospective analysis, and only associations are reported that do not necessarily represent causal relationships.

Despite these shortcomings, the present analysis remains the largest study on sepsis epidemiology in critically injured patients and is derived from a representative database with respect to the general German trauma population. Additionally, early recognition of the identified risk factors for sepsis may allow prognostic considerations, guide early diagnostic workup, and help to reduce septic complications after multiple trauma.

CONCLUSIONS

Although the incidence of posttraumatic sepsis decreased from 1993 until 2008, the general outcome improvement in multiply injured patients seen over recent years has not been accompanied by significant changes in the subgroup of patients with sepsis. Therefore, sepsis after severe trauma remains a substantial challenge, and further efforts are necessary to reduce morbidity and mortality. Predictors for sepsis after severe trauma derived from multivariate analysis were male gender, age, preexisting medical condition, GCS score of ≤8 at the scene, ISS, AIS_{THORAX} score of ≥3, number of injuries, number of red blood cell units transfused, number of operative procedures, and laparotomy. Identification of injured patients at risk for sepsis at an early stage may help to decrease this deadly complication in trauma populations.

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