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Pneumonia in multiple injured patients: a prospective controlled trial on early prediction using clinical and immunological parameters

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Abstract. *Objective and design:* In a prospective trial 266 multiple injured patients were included to evaluate clinical risk factors and immune parameters related to pneumonia.
Methods: Clinical and humoral parameters were assessed and multivariate analysis performed.
Results: The multivariate analysis (odds ratio with 95% confidence interval (CI)) revealed male gender (3.65), traumatic brain injury (TBI) (2.52), thorax trauma ($AIS_{thorax} \geq 3$) (2.05), antibiotic prophylaxis (1.30), injury severity score (ISS) (1.03 per ISS point) and the age (1.02 per year) as risk factors for pneumonia. The main pathogens were Acinetobacter Baumannii (40%) and Staphylococcus aureus (25%). A tendency towards higher Procalcitonin (PCT) and Interleukin (IL)-6 levels two days after trauma was observed for pneumonia patients.
Conclusion: The immune parameters (PCT, IL-6, IL-10, soluble tumor necrosis factor p-55 and p-75) could not confirm the diagnosis of pneumonia earlier than the clinical parameters.

Key words: Pneumonia – Multiple trauma – Interleukin – TNF receptors – Procalcitonin

Introduction

Constant improvement of emergency and intensive care unit (ICU) management has increased the quality of outcome in multiple injured patients, however, infections and multiple organ failure continue to be the main causes of death in the late stage of multiple trauma [1]. With a reported incidence between 4% to 87%, pneumonia is the most common infection following multiple trauma [2–4]. Besides an increase in mortality [5], pneumonia causes a prolonged duration of intensive care and hospital stay, thus contributes to an increase in health care expenditure [6–9].

Several risk factors for development of pneumonia in multiple trauma patients have been identified, such as the type and severity of trauma (thorax trauma [3], neurotrauma [10], hypotension [11], intubation [12], days on ventilator [13], and also the misuse of pharmacotherapy [14], especially antibiotics [15]. Neurotrauma patients due to reduced airway reflexes with subsequent risk of aspiration and patients with severe thorax trauma and lung injury have been described to be associated with an increased risk for pneumonia [16, 17].

The use of prophylactic antibiotics is favoured by some authors [18], whereas others emphasise that resistances may support the development of pneumonia [19]. An increasing number of resistances to antibiotics, especially in hospital acquired pathogens, also poses therapeutic problems. The early use of antibiotics at the beginning of the exponential growth stage of bacteria is considered essential for fast recovery. Thus, an early diagnosis of pneumonia is of utmost importance. Common criteria for the diagnosis of pneumonia [13], such as changes in leukocyte count, body temperature, and CRP reveal a misdiagnosis rate of 38% along with low specificity and sensitivity in literature.

Multiple trauma also causes immune suppression which becomes apparent as impaired immune cell function with decreased proliferation and production capacity and subsequent changes in pro- and anti-inflammatory cytokines [11, 20, 21]. The susceptibility to the development of infections is reported to be particularly high on days 3 to 5 after trauma [14]. Thus, a peak incidence of pneumonia is expected to occur at this vulnerable stage in the clinical course after multiple trauma.

Recent findings related to immunological changes in multiple trauma patients may help to solve the problems of early diagnosis and prevention of pneumonia. Initially high levels of pro-inflammatory IL-6 and anti-inflammatory IL-10 [22] were reported to correlate with increased incidence

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of sepsis [23, 24]. Ertel et al. described a correlation between high sTNFR levels and mortality [25]. Thus, these parameters seem to influence the immune response, the development of infections, and outcome. Similar predictive and diagnostic qualities are attributed to procalcitonin [26–28]. Since its first description in 1993 by Assicot et al. [26] several authors described a correlation between initially high PCT levels and late complications such as sepsis and multiple organ dysfunction syndrome (MODS) [27, 28]. High PCT levels were reported to indicate the development of sepsis with a sensitivity of 97.8% and a specificity of 86.4% [28]. The purpose of the present study was to evaluate the early predictive value of several clinical and immune parameters for the development of posttraumatic pneumonia in a large prospective controlled trial.

Materials and methods

Patient population

From June 1996 to June 2001 622 multiple injured patients were admitted to the emergency rooms of the two university trauma centres in Cologne-Merheim and Cologne-Lindenthal. 332 did not perform the enrolment criterias. 266 patients were enrolled and analysed in the prospective clinical study. Of 133 patients blood samples of more than 6 time points during the early phase after trauma could be obtained for the immunological analyses. The common criteria for study enrolment were: patient age of >16 years, ISS >16 points, first blood sample within 24 h, and an expected minimum of survival for >3 days. Patients with acquired or inherited immunodeficiencies and patients receiving immunosuppressive therapy were excluded from the study. The traumatic brain injury (TBI) was defined by an Glasgow Coma Scale (GCS) value ≤8, or 24 h of coma, or an AIS for the head ≥3. Multiple trauma patients were defined by multiple injuries in at least two different body regions with two times an AIS of >3, or a sum of >6 for the two most severe injuries.

Clinical data including laboratory and vital parameters (ICU-daily data set) were prospectively collected in parallel with the equivalent plasma samples. However, we retrospectively analysed the incidence of pneumonia using the prospectively collected variables. The choice of intervals for age and ISS was made a priori obeying the proposals made by former publications [29].

The abbreviated injury scale (AIS) and the injury severity score (ISS) were used to classify the severity of the injury [30]. Patients with ISS <25 were classified as moderately injured and all patients with ISS ≥25 were classified as severely injured. The patients were further classified into three age groups in order to evaluate the effects of age on clinical and immune parameters: group I: patients <30 years; group II: ≥30 and <60 years ; group III: ≥60 years. The diagnosis of pneumonia was based on the consensus statement of the American Thoracic Society [31] and required two of the following criteria presented for at least 3 days: 1) purulent tracheal secretion with culture positive for pathogens, 2) recent formation or persistence of infiltration on chest x-ray or 3) temperature >38 °C. The thorax trauma was considered to be relevant if the AIS_{thorax} on admission was ≥3.

Wound or urinary tract infection were defined by a positive wound or urinary bacteriology in addition to leukocytes >12.000/mm^3 or body temperature >38 °C. Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference in 1992 [32]: Positive blood culture plus two of the following four criteria: 1) body temperature >38 °C or <36 °C, 2) heart rate >90/min, 3) breathing frequency >20/min or PaO_2 <32 torr, 4) leukocytes >12.000/mm^{3}or <4000/mm^{3}or 10% immature leukocytes.

The management of study patients included an immediate surgical treatment of life threatening injuries and a primary or secondary stabilisation of major fractures depending on clinical criteria. As for control the blood samples from 48 healthy blood donors were analysed with a distribution of age and gender similar to that of the trauma patients.

Study design

Blood samples for the determination of mediator levels were obtained at prespecified time points (first sample three and six hours after injury, then every six hours until day three, then daily samples until day ten after injury. Blood samples from 133 patients (with permission by the Ethical Commission of the University of Cologne from 24.06.1996, Nr. 9642) were analysed after informed consent was obtained in all cases. Especially in the early phase, however, blood samples were missing in some patients for organisatory reasons. Other reasons for incomplete data include the patients death or discharge.

The systemic levels of IL-6, IL-10, sTNFR-p55, sTNFR-p75 and PCT were determined from the isolated plasma using ELISA-technique. All assays were standardised by including a titration of the appropriate purified recombinant mediator of known concentration. The levels of sensitivity of the ELISA assays were >1 pg/ml (IL-6), >3 pg/ml (IL-10) and >25 pg/ml (sTNFRs). PCT was kindly measured by BRAHMS diagnostica GmbH, Berlin, Germany, using a specific immunoluminometric assay (Lumi-Test™PCT). The sensitivity of the assay was 0.1 ng/nl.

Positive cultures of bacteria found in blood cultures, urine probes or tracheal aspirates as well as pulmonary infiltrates on the chest x-ray were recorded.

Statistics

The cytokine levels are presented as medians as well as 25 and 75 percentiles. The Mann-Whitney U test was performed to test differences of cytokine release between the group with and without pneumonia during the clinical course. To compare pneumonia incidence in univariate analysis, relative risks (RR) were calculated. Risk factor identified univariately were then tested multivariately. We used a multivariate logistic regression model to examine the independent influence of various variables on the incidence of pneumonia. As independent variables we included: Age (continuous), sex, and injury severity (ISS as continuous variable), thorax injury, TBI and prophylactic antibiotic therapy. All analyses were performed using SPSS (Inc., Chicago, Ill.) for Windows, Version 9.0.1.

Results

Among the 266 multiple injured trauma patients, 206 were males and 60 females with a mean age of 38 ± 15 years [range 16–83]. 26 patients died within 48 h of trauma. The mean injury severity calculated by the ISS was 25.7 ± 11.5 points [range 9–66]. The patients were treated in the ICU for a mean of 14 ± 12 days [range 1–90]. The mean APACHE-score was 8.7 ± 3.99 points (range 1–25) at admittance to the ICU and 6.33 ± 4.02 points [range 0–19] at discharge.

41.4% of the patients developed an infection during intensive care treatment. Pneumonia was the most common infection, developing in 38.8% of the patients. Wound infection occurred in 13.5% and urinary tract infection in 1.5% of the patients. The incidence of pneumonia was significantly higher in men (43.2%) than in women (21.7%) [$p < 0.01$]. Fig. 1 shows that posttraumatic pneumonia developed mostly within 4 days after trauma.

Influence of age and gender

The mean age of the group with pneumonia was higher (40.3 years ± 14) compared to those without pneumonia (36.3 years ± 15.5) (Table 1). Performing an univariate analysis (see Table 2) the highest relative risk (RR) to develop a pneumonia was observed in the age group of 30 to 60 years (RR = 1.7). The age group <30 years had a relative risk of 1.0 (reference) and patients ≥60 years of 1.3. Performing a multivariate analysis (see Table 2), the patients age did not play a major preconditioning role for pneumonia (Odds ratio with 95% CI = 1.02 [1.00–1.04]) compared to the other tested factors. In contrast to age, gender revealed a high significant value in the univariate as well as in the multivariate linear regression. For female the relative risk to develop a pneumonia was 50% lower than in males (RR = 0.5). Of all tested factors the odds ratio for gender revealed the highest value with 3.65 [1.72–7.76].

Influence of severity and type of injury

Classifying the injury severity using the ISS (ISS ≥25 vs. <25), it became obvious that the relative risk for developing pneumonia increases significantly in correlation to the ISS (RR = 2.4) (see Table 3). The incidence of pneumonia was 48.8% in the group of severely injured patients (ISS ≥25) while an incidence of 28.0% was found in less injured patients (ISS <25).

The most common injuries in 112 patients with thorax trauma (AIS_{thorax} ≥3) (see Table 3) were lung contusion and multiple rib fractures. The relative risk to develop a pneumonia in patients with relevant thorax trauma was 1.7 times higher than in the none thorax trauma group. For that issue the logistic regression revealed significance (Odds ratio = 2.05 [0.99–4.22]) (see Table 2). Performing subgroups of increasing thorax injury severity there was a strong correlation to the incidence of pneumonia as derived from Fig. 2. The group without thorax trauma (AIS_{thorax} = 0) had an incidence of 38%, those with a low AIS_{thorax} (1–3) 48%, with relevant AIS_{thorax} (4–6) 67%, and with maximal AIS_{thorax} (7 – > 9) about 70% incidence of pneumonia during their ICU period.

Besides thoracic injury, TBI contributed to a higher risk for developing pneumonia. As we could show by univariate statistics, the selective TBI group had an elevated relative risk (RR = 1.2) for pneumonia as well as the combination of severe injury plus TBI (RR = 1.7) both compared to the group of severe injured patients without TBI (reference group). Head injury as special item solely or in combination with further severe injuries raised the incidence of pneumonia significantly also performing the multivariate linear regression analysis (2.52 [1.31–4.85]) (Table 2).

Table 1. Clinical data of the multiple trauma patients with and without pneumonia.

	Patients with pneumonia	Patients without pneumonia
Total numbers	102	164
ISS [mean ± SD]	29.5 ± 12.2	23.4 ± 10.4
Subjects with		
ISS < 25 and	38 (37)	97 (59)
ISS ≥ 25 [n] (%)	64 (63)	67 (41)
Subjects with AIS_{thorax} ≥ 3 [n] (%)	57 (56)	55 (34)
Subjects with TBI [n] (%)	71 (70)	90 (55)
Age [mean ± SD]	40.3 ± 14.3	36.3 ± 15.5
Subjects in studied age groups		
< 30 y	27 (26)	71 (43)
30–59 y	64 (63)	73 (45)
≥ 60 y [n] (%)	11 (11)	20 (12)
Subjects with antimicrobial prophylaxis [n] (%)	70 (67)	85 (52)
Gender [male/female]	89/13	117/47
Death [n] (%)	8 (7.8)	20 (12.2)
Apache [mean ± SD]	9.6 ± 4.1	8.2 ± 3.9
ICU time [mean ± SD]	23.2 ± 12.5	7.8 ± 6.7
Time on respirator (days)	16.3 ± 12.0	4.7 ± 5.3

Table 2. Univariate and multivariate statistical analysis of the risk factors age, gender, injury severity, thorax trauma, traumatic brain injury and antibiotic prophylaxis.

	Univariate statistics (RR = Relative Risk)	Multivariate statistics (Odds Ratio with 95% confidence interval)[a]
Age <30 years (n = 98)	RR = 1.0 (reference)	1.02 [1.00–1.04] per year
≥30 and < 60 years (n = 137)	RR = 1.7	
≥60 years (n = 31)	RR = 1.3	
Gender (female vs. male)	RR = 0.5	3.65 [1.72–7.76]
Injury severity score (ISS) (≥25 vs. <25)	RR = 2.4	1.03 [0.99–1.06] per ISS point
Thorax trauma (yes vs. no)	RR = 1.7	2.05 [0.99–4.22]
Traumatic brain injury (TBI) with a Glasgow coma score ≤8		2.52 [1.31–4.85]
Severe trauma without TBI	RR = 1.0 (reference)	
Selective TBI	RR = 1.2	
TBI plus severe trauma	RR = 1.7	
Antimicrobial prophylaxis (AP) in thorax trauma patients (AP vs. no AP)	RR = 1.2	1.30 [0.72–2.35]

[a] –2 Log Likelihood 286.7; Correct prediction 68%.

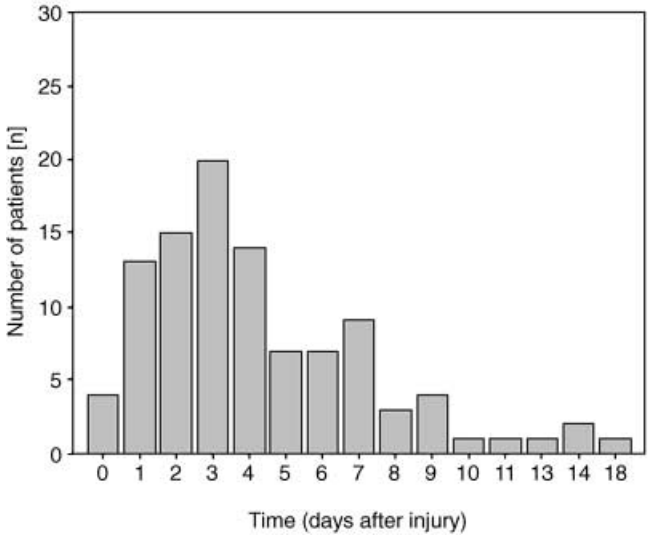

Fig. 1. Time course of the pneumonia onset. Most patients develop pneumonia within the first four days after trauma. The maximum of pneumonia onset was on day three after trauma.

Table 3. Incidence of observed thoracic injuries.

Thoracic Injury	Incidence (n)
Rib Fractures	66
Lung Contusion	61
Hematopneumothorax	25
Hematothorax	21
Pneumothorax	17
Thorax Contusion	17
Scapula Fracture	7
Pleural Effusion	4
Heart Contusion	5
Atelectasis	2
Tension Pneumothorax	2
Thoracic Emphysema	2
Pulmonary Haemorrhage	1
Lung Rupture	1
Pneumomediastinum	1
Sternal Fracture	1
Burn	1
Aspiration Pneumonia	1
Gunshot Wound	1

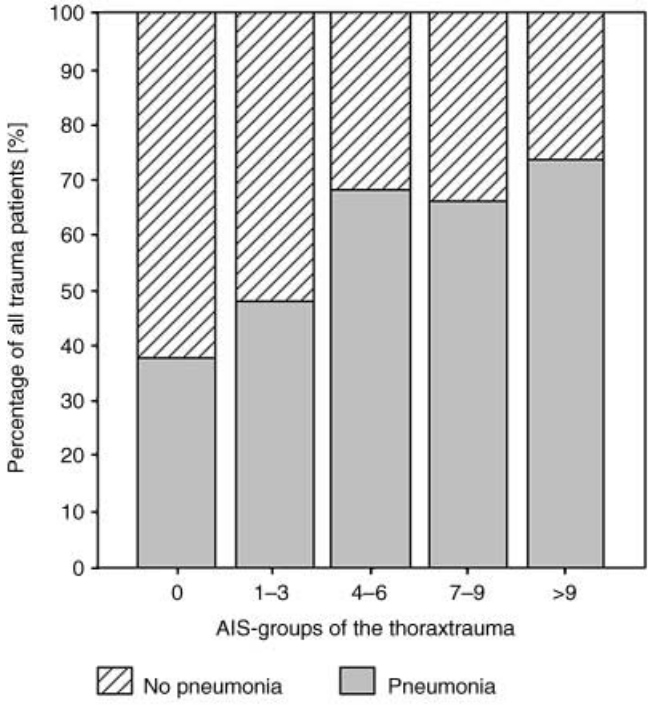

Fig. 2. Incidence of pneumonia in dependence of the thorax trauma severity measured by the abbreviated injury scale (AIS_{thorax}).

Influence of prophylactic antibiotics

Among 112 patients with a relevant thorax trauma ($AIS_{thorax} \geq 3$), 74 patients received prophylactic antibiotics and 38 did not. Pneumonia occurred in 54% of patients with prophylactic antibiotics, whereas only 45% of the patients without prophylactic antibiotics developed pneumonia (Table 4). Comparing the descriptive clinical data of the patients with and without prophylactic antibiotics there was no evident difference between the injury severity (ISS: 33 ± 10 vs. 35 ± 13), the age (37 ± 15 vs. 38 ± 12) or the gender distribution (55/15 vs. 29/9). In the group of prophylactically antimicrobial treated patients with relevant thorax trauma a higher incidence of TBI was seen (67% vs. 52%) (see Table 4). But performing the univariate analysis (Table 2) the relative risk to develop a pneumonia in patients who received prophylactically antibiotics was 1.2 compared to those without prophylaxis. Multivariate linear regression analysis showed a higher risk for pneumonia in the thorax trauma group which received prophylaxis (Odds ratio = 1.3 [80.72–2.35]). Thus, the prophylactic application of antibiotics did not reduce the incidence of pneumonia in severe injured patients with additional thorax trauma.

Pathogens in pneumonia

In a total of 102 patients with pneumonia a pathogen could be isolated. The most common pathogen which could be identified in the tracheal aspirate was in 40% of all cases Acinetobacter Baumanii (n = 41), followed by Staphylococcus aureus in 25% (n = 26) and Candida albicans 24% (n = 25), which was most often a contamination of the probe by oral resident flora (Table 5) and did not cause a candida pneumonia in these patients. As can be derived from Table 5 in detail, these pathogens were found in comparable incidences in all three injury groups (TBI isolated, multiple trauma with TBI and multiple trauma without TBI).

Humoral immune response

Regardless of age and gender (see Figs. 3 A–D), all mediator plasma levels of 133 trauma patients were clearly elevated within the 24 h period after trauma compared with plasma levels of control group patients. The injury severity stimulat-

Table 4. Clinical data of the multiple trauma patients with and without antimicrobial prophylaxis.

	Patients with antimicrobial prophylaxis		Patients without antimicrobial prophylaxis	
	All patients	Patients with thorax trauma ($AIS_{thorax} \geq 3$)	All patients	Patients with thorax trauma ($AIS_{thorax} \geq 3$)
Total numbers	155	74	111	38
Pneumonia [n] (%)	104 (67)	40 (54)	37 (33)	17 (45)
ISS [mean ± SD]	27 ± 11	33 ± 10	25 ± 13	35 ± 13
Subjects with TBI [n] (%)	104 (67)	39 (53)	58 (52)	12 (32)
Age [mean ± SD]	37 ± 15	37 ± 15	38 ± 15	38 ± 12
Gender [male/female]	124/31	55/15	80/31	29/9

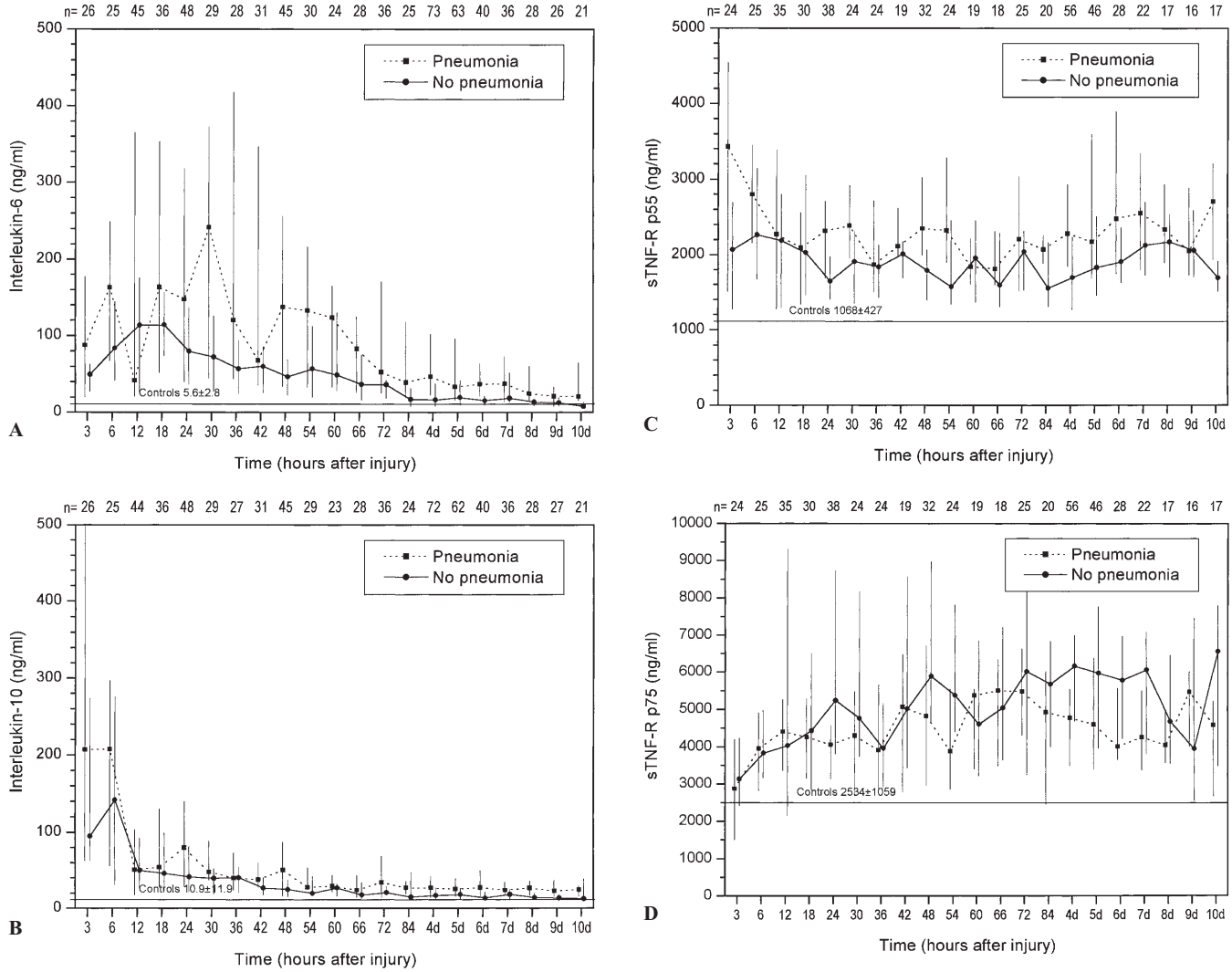

Fig. 3. Time course of interleukin (IL)-6, IL-10, soluble tumor necrosis factor receptor (sTNFR) p55, and sTNFR p75 levels in patients who developed pneumonia (n = 51) in the later course of trauma and patients who did not (n = 82). A tendency towards higher values could be seen two days after trauma for IL-6 in patients which developed pneumonia.

Table 5. Pneumonia pathogens accessed in the tracheal aspirate.

Pathogen	Incidence (n)
Acinetobacter Baumanii	41
Staphylococcus aureus	26
Candida albicans	25
Klebsiella pneumoniae	17
Escherichia coli	17
Enterobacter cloacae	14
Pseudomonas aeruginosa	14
Enterococcus	13
Haemophilus influenza	12
Stenotrophomonas maltophilia	9
Streptococcus pneumoniae	9
Serratia marcescens	6
Morganella morganii	6
Proteus mirabilis	4
Citrobacter diversus	4
Klebsiella oxytoca	3
Proteus vulgaris	3
Enterobacter aerogenes	2
Flavimonas oryzihabitans	2
Haemophilus parainfluenza	2
Serratia fonticola	1
Enterobacter amnigenus	1
Enterobacter hormaechei	1
Neisseria	1
Staphylococcus haemolyticus	1
Hafnia alvei	1
Yeast	1
Torulopsis glabrata	1

ed an intensive immune response. Comparing the mean mediator levels of patients with and without pneumonia, no significant differences between both groups could be detected. In both groups, plasma levels of pro-inflammatory IL-6 and anti-inflammatory IL-10 showed a marked initial increase caused by the trauma. IL-10 levels from patients with pneumonia were less pronounced as compared to plasma levels for patients without pneumonia. This could be observed directly after trauma but did not reach significance. In patients with pneumonia, which has most commonly been acquired during the first week after trauma (Fig. 1), levels of sTNFR p55 and p75 increased within the first 12 h after trauma and did not come back to normal values until the end of observation on day 10 (Figs. 3C–D).

Procalcitonin is reported being an indicator for an bacterial infection. Peak plasma levels of procalcitonin occurred on days two to three after trauma (Fig. 4). There was no significant difference between patients with or without pneumonia. However, plasma levels are clearly higher in patients with pneumonia from day 2 on and the following days after trauma. Thus, procalcitonin but not IL-6, IL-10, sTNFR p55 and p75 may serve as an additional indicator for bacterial infections including pneumonia which onset reached the peak also on day three after trauma (Fig. 1).

Discussion

Infections and multiple organ failure are the most common late complications in patients with multiple trauma. Pneumonia has the highest incidence of all posttraumatic infec-

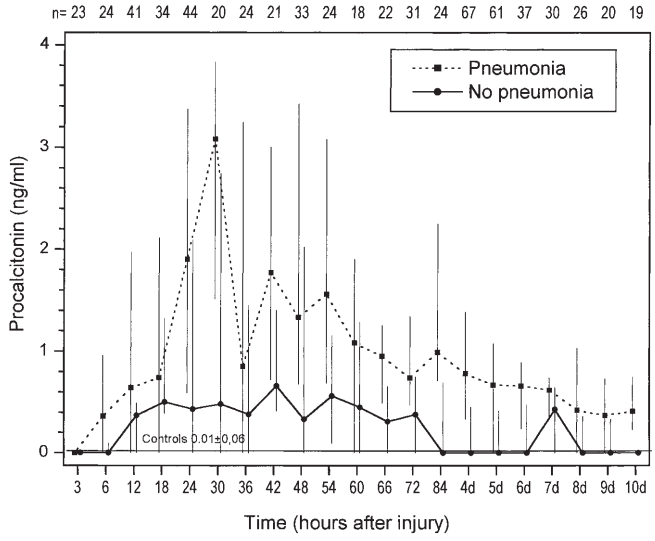

Fig. 4. Time course of procalcitonin plasma levels in patients who developed pneumonia (n = 51) and those who did not (n = 82). A tendency towards higher values could be seen two days after trauma for PCT in patients with pneumonia.

tions and early diagnosis as well as specific treatment is mandatory.

A logistic regression analysis was performed to identify risk factors for the development of pneumonia during the later clinical course. The main risk factors were (listed in descending odds ratio order): Gender (males), TBI (with or without multiple trauma), additional thorax trauma, antibiotic prophylaxis, a high total injury severity (ISS > 25) and an age between 30–60 years.

Injury severity

Several studies demonstrated a correlation between the severity of trauma and the incidence of infections [8, 12]. In our patient population we found that patients with severe trauma (ISS ≥ 25) had a more than two times higher relative risk for developing pneumonia. It can be assumed that tissue injuries are more extensive in patients with a high ISS, providing a larger surface for possible pathogen invasion**.** Since several immunological changes are induced by trauma [14], the severity of trauma correlates with both the immune suppression and the susceptibility to infections. In addition, the duration of ICU treatment, which is longer in severely injured patients than in less injured patients in our study, is an additional indirect variable that indicates a higher incidence of pneumonia due to risk factors such as ventilation, and secondary operations [33].

Thorax trauma

Several studies described an increased incidence of posttraumatic pneumonia in patients with thorax trauma [3, 34]. The data of the present study confirm a distinct correlation: Patients with thorax trauma had an almost two times higher risk for develop pneumonia (Table 2). Multiple rib fractures

and lung contusion have been described as the most common thoracic injuries, which was supported by the data of the present study. It has been described that lung contusions with disruption of capillaries and alveoli and subsequent oedema formation [17] enhance pathogen invasion and the development of pneumonia [2]. The necrotic tissue, which results from lung contusion, is an additional variable which produces an environment that supports pathogen growth. Along with possibly reduced airway reflexes, the impairment of ciliar function, which is supposed to occur in trauma patients [16], supports the invasion of pathogens into lung parenchyma. The severity of thorax trauma correlated positive with the incidence of pneumonia in our study (Fig. 2).

Traumatic brain injury

As well as thorax trauma contributing to pneumonia, TBI raised the risk especially in combination with multiple trauma. As we could show previously, TBI leads to remarkably changes in the immune response after trauma [10, 35]. Besides the longer respirator time, an immune response in TBI patients seem to contribute to the development of infections such as pneumonia. Some involved factors may be: the disturbed blood brain barrier, activation of micro- and macroglia and the release of humoral inflammatory factors into the blood as well as into the liquor [25]. The present data provide some evidence that the main cause of higher incidence of pneumonia in TBI patients was not the longer respirator time (9.7 ± 10,4 vs. 6.8 ± 8.6 days), because the peak onset of pneumonia in patients with and without TBI was always the third day after trauma. We could not identify any difference in the spectrum of pathogens in both groups.

Prophylactic antibiotics

Since there was no specified criterion for the indication of antibiotic prophylaxis, 58% of patients were treated with prophylactic antibiotics, while 42% received no antibiotics (see Table 1 and 4). The effectiveness of antibiotic prophylaxis is still a subject of debate [13]. While Rodriguez et al [11] regarded this prophylaxis as imperative, other authors disagree [31]. A strong argument against antibiotic prophylaxis is the increasing occurrence of resistant pathogens [6, 7] which leads to an increased incidence of pneumonia caused by multi-resistant nosocomial pathogens. We observed an incidence of pneumonia of 54% in thorax trauma patients who received prophylaxis, whereas only 45% patients without prophylaxis acquired pneumonia, although the injury severity of both groups was comparable (ISS: 33 ± 10 vs. 35 ± 13) (Table 4). Regarding previous studies as well as the results of the present study, we propose that there is no benefit for the prevention of pneumonia in the prophylactic application of antibiotics after thorax trauma.

Age and gender

Recent studies propose an influence of age and gender on the development of infections [36]. A study by Wichmann et al revealed an increased incidence of posttraumatic infections in males compared with females [21]. The incidence of pneumonia in the present study was significantly higher in males (43.2% in males, vs. 21.7% in females), who had a two times higher risk to develop pneumonia. Multivariate analysis revealed the highest odds ratio for that issue. One could speculate on a protective quality of female hormones (e.g. oestrogen) which may lead to a reduction of inflammatory complication in females [19, 21, 36, 37].

Besides gender differences, age differences concerning outcome and immune response after multiple trauma have been described in the past. In this context Kahlke et al reported a significantly higher incidence of pneumonia in patients older than 60 years [37]. The present study confirms age differences, whereas the logistic regression analysis revealed the worst odds ratio of all tested factors (1.02 [1.00–1.04]) (Table 2). Patients 30–60 years of age had an almost two fold higher risk to develop posttraumatic pneumonia than patients younger than 30 years. Similar to gender, the age difference may be caused by decreased immune functions in elderly patients. These assumptions are supported by the observation of increasing cell defects with advancing age [37]. In addition, the higher average prevalence of various diseases in older patients may contribute to a bad outcome in these patients as shown for the increased lethality.

Inflammatory mediators

The humoral parameters IL-6, IL-10, sTNFR p55 and p75, and PCT, had no predictive capacity for the development of pneumonia. This may be due to the presence of additional risk factors in the later course of disease such as ventilation and pharmaceutical agents, which have a greater influence on the development of pneumonia than immunological imbalances. According to Ertel et al [25] we found a remarkable elevation of IL-6 in the pneumonia group during the first three days after trauma. Nevertheless, looking at the time course of IL-6 elevation and pneumonia onset, there was no significant rise in serum levels before clinical signs of pneumonia such as fever and infiltrates in the chest x-ray appeared. A similar course was found for serum PCT levels. According to Wanner et al [28], elevated PCT levels indicate a bacterial infection such as sepsis. We could show for the first time that PCT levels in multiple trauma patients with pneumonia were remarkably elevated compared to patients without pneumonia during the clinical course. These findings did not reach significance and PCT elevation did not occur prior to clinical signs of pneumonia. These results suggest that the investigation of immune parameters [38] is inferior to the assessment of clinical variables using the ISS, AIS_{thorax} or Age and gender as well as TBI concerning the prediction of pneumonia. Using multivariate linear regression of the presented clinical parameters we could made a correct prediction in 68% of the cases. In order to predict infection in general as well as sepsis and systemic inflammatory response syndrome (SIRS) the immunological parameters may be useful tools [22–25] but to predict pneumonia in multiple trauma patients they are not.

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References

[1] Acosta JA, Yang JC, Winchell RJ, Simons RK, Fortlage DA, Hollingsworth-Fridlund P et al. Lethal injuries and time to death in a level I trauma centre. Am Coll Surg 1998; 186: 528–33.
[2] Antonelli M, Moro ML, Capelli O, De Blasi RA, D'Errico RR, Conti G et al. Risk factors for early onset pneumonia in trauma patients. Chest 1994; 105: 224–8.
[3] Aufmkolk M, Neudeck F, Voggenreiter G, Schneider K, Obertacke U, Schmitt-Neuerburg KP. Einfluss der primären Oberschenkelplattenosteosynthese auf den Verlauf polytraumatisierter Patienten mit oder ohne Thoraxtrauma. Unfallchirurg 1998; 101: 433–9.
[4] Trinkle JK, Richardson JD, Franz JL. Management of flail chest without mechanical ventilation. Ann Thorac Surg 1975; 19: 355–63.
[5] Walker WE, Kapelanski DP, Weiland AP. Patterns of infection and mortality in thorax trauma. Ann Surg 1985; 291: 752–7.
[6] Craig CP, Connely S. Effect of intensive care unit nosocomial pneumonia on duration of stay and mortality. Am J Infect Control 1984; 12: 233–8.
[7] Haley RW, Schaberg DR, Crossley KB. Extra charges and prolongation of stay attributable to nosocomial infections: A prospective interhospital comparison. Am J Med 1981; 70: 51–8.
[8] Hoyt DB, Simons RK, Winchell RJ. A risk analysis of pulmonary complications following major trauma. J Trauma 1993; 35: 524–31.
[9] Toews GB. Southwestern internal medicine conference: nosocomial pneumonia. Am J Med Sci 1986; 291: 355–67.
[10] Hensler T, Sauerland S, Riess P, Hess S. Helling HJ, Andermahr J et al. The effect of additional brain injury on systemic interleukin (IL)-10 and IL-13 levels in trauma patients. Inflamm Res 2000; 49: 524–8.
[11] Rodriguez JL, Gibbons KJ, Bitzer LG. Pneumonia: incidence, risk factors and outcome in injured patients. J Trauma 1991; 31: 907–12.
[12] Waydhas C, Nast-Kolb D, Jochum M, Trupka A, Lenk S, Fritz H et al. Inflammatory mediators, infection, sepsis and multiple organ failure after severe trauma. Arch Surg 1992; 127: 460–7.
[13] Brun-Buisson C. Advances and controversies in the epidemiology, diagnosis, and prevention of nosocomial pneumonia in the ICU. Curr Op Crit Care 1995; 1: 341–8.
[14] Faist E, Storck M, Hultner L, Redl H, Ertel W, Walz A et al. Functional analysis of monocyte (M∅) activity via synthesis patterns of interleukin 1, 6, 8 (IL-1, IL-6, IL-8) and neopterin in surgical intensive care patients. Surgery 1992; 112: 562–72.
[15] Celis R, Torres A, Gatell JM, Almela M, Rodriguez-Roisin R, Augusti-Vidal A. Nosocomial pneumonia. Chest 1988; 93: 318–24.
[16] Chevret S, Hemmer M, Carlet J, Langer M. Incidence and risk factors of pneumonia acquired in intensive care units. Int Care Med 1993; 19: 256–64.
[17] Hsieh AH, Bishop MJ, Kubilis PS, Newell DW, Pierson DJ. Pneumonia following closed head injury. Am Rev Resp Dis 1992; 146: 290–4.
[18] Walker WE, Kapelanski DP, Weiland AP, Stewart JD, Duke JH. Patterns of infection and mortality in thorax trauma. Ann Surg 1985; 201: 752–7.
[19] Weber DJ, Raasch R, Rutala WA. Nosocomial infections in the ICU: the growing importance of antibiotic-resistant pathogens. Chest 1999; 115: 28–33.
[20] Kragsbjerg P, Holmberg H, Vikerfors T. Serum concentrations of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. Eur J Surg 1995; 161: 17–22.
[21] Wichmann MW, Zellweger R, DeMaso CM, Ayala A, Chaudry IH. Enhanced immune responses in females, as opposed to decreased responses in males following haemorrhagic shock and resuscitation. Cytokine 1996; 8: 853–63.
[22] Billiau A, Vandekerckhove F. Cytokines and their interactions with other inflammatory mediators in the pathogenesis of sepsis and septic shock. Eur J Clin Inv 1991; 21: 559–73.
[23] Bone RC. Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: What we do and do not know about cytokine regulation. Crit Care Med 1996; 24: 163–72.
[24] Sherry RM, Cué JI, Goddard JK, Parramore JB, DiPiro JT. Interleukin-10 is associated with the development of sepsis in trauma patients. J Trauma 1996; 40: 613–6.
[25] Ertel W, Keel M, Bonaccio M, Steckholzer U, Gallati H, Kenney JS et al. Release of anti-inflammatory mediators after mechanical trauma correlates with severity of injury and clinical outcome. J Trauma 1995; 39: 879–85.
[26] Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993; 341: 515–8.
[27] Gendrel D, Bohuon C. Procalcitonin, a marker of bacterial infection. Infection 1997; 25: 133–4.
[28] Wanner GA, Keel M, Steckholzer U, Beier W, Stocker R, Ertel W. Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure, and mortality in injured patients. Crit Care Med 2000; 28: 950–7.
[29] Neidhardt R, Keel M, Steckholzer U, Safret A, Ungethuem U, Trentz O et al. Relationship of interleukin-10 plasma levels to severity of injury and clinical outcome in injured patients. J Trauma 1997; 42: 863–71.
[30] Champion HR, Sacco WJ, Hunt TK. Trauma severity scoring to predict mortality. World J Surg 1983; 7: 4–11.
[31] American Thoracic Society. Hospital-acquired pneumonia in adults, November 1995: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. Am J Resp Crit Care Med 1996; 153: 1711–25.
[32] American College of Chest Physicans/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20: 864–74.
[33] Brown DL, Hungness ES, Campbell RS, Luchette FA. Ventilator-associated pneumonia in the surgical intensive care unit. 2001; 51: 1207–16.
[34] D'Alise MD, Demarest GB, Fry DE, Olson TM, Osler TM, Clevenger FW. Evaluation of pulmonary infections in patients with extremity fractures and blunt chest trauma. J Trauma 1994; 37: 171–5.
[35] Neugebauer E, Hensler T, Rose S, Maier B, Holonda M, Raum M et al. Severe head trauma in multiple injured patients: State of the art of interactions between local and systemic mediator response. Unfallchirurg 2000; 103: 122–33.
[36] Schroder J, Kahlke V, Staubach KH, Zabel P, Stuber F. Gender differences in human sepsis. Arch Surg. 1998; 133: 1200–5.
[37] Kahlke V, Angele MK, Ayala A, Schwacha MG, Cioffi WG, Bland KI et al. Immune dysfunction following trauma-haemorrhage: influence of gender and age. Cytokine 2000; 12: 69–77.
[38] Kragsbjerg P, Jones I, Vikerfors T. Diagnostic value of blood cytokine concentrations in acute pneumonia. Thorax 1995; 50: 1253–7.