Prophylactic antibiotic therapy after inhalation injury

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A B S T R A C T

Objective: Inhalation injury is suspected in patients with facial and neck burn-injuries and in patients who suffered burns in an enclosed space. Inhalation injury is associated with a disappointingly high morbidity and mortality in spite of advances in diagnostics and therapy. Prophylactic antibiotic therapy in patients with diagnosed inhalation injury is still a controversial subject. The epidemiologic characteristics of the burn patients with diagnosed inhalation injury in our clinic receiving prophylactic antibiotic therapy and mortality of these patients will be referred in this study.

Methods: Patients >16 years of age admitted to the burn unit between January 2008 and December 2012 and fulfilling the burn center referral criteria according the German Burn Association were enrolled in the study.

Results: 58 patients (male:female 47:11) were diagnosed with an inhalation injury by their admission. The average length of hospital stay was 27.5 days, whereas of the patients with no inhalation injury was 16 days (p = 0.04). 56.9% of the patients underwent tracheostomy. An escalation of the antibiotic therapy was done in 39.7% of the patients with inhalation injury and in 20.3% of the patients without one. The mortality of inhalation injury patients was 12.1%.

Conclusions: The development of pneumonia is not influenced in a statistical significant way by the use of prophylactic antibiotics. We do recommend the administration of prophylactic antibiotic therapy to patients with diagnosed inhalation trauma, as the mortality of these patients was lower in comparison to other studies.

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1. Introduction

Inhalation injury should be suspected in patients with facial and neck injuries and those who suffered burns in an enclosed space.

Depending on the diagnostic criteria used, inhalation injury is reported in 0.3–43% of the patients with severe burn-injuries. It is one of the major (independent) risk factors for mortality, as it is associated with up to 8–10 fold increased mortality (1).
Patients with inhalation injury have a two time higher pneumonia rate compared with patients without inhalation injury ($p < 0.001$) (2).

The mortality of patients with pneumonia depends on the presence of inhalation injury. Lionello et al. published a study about the risk of death in severely burned patients in the period 1997–2000 and showed that the mortality rate among patients with inhalation injury was 4 times higher than patients without one (3).

MLCaK et al. found also a 40% increase in mortality rate in severely burned patients with pneumonia. However, the mortality rate went up to 60%, if the pneumonia occurred in patients with inhalation trauma (4).

The administration of prophylactic antibiotic therapy in patients with diagnosed inhalation injury is a subject of controversy.

Aim of our clinical study is to determine the epidemiologic characteristics of the patients with diagnosed inhalation injury in our burn care unit, the effect of administering prophylactic antibiotic therapy on developing pneumonia and on mortality of these patients. By comparing our data with other study we tried also to evaluate the necessity of the use of prophylactic antibiotics.

2. Materials and methods

A retrospectively maintained institutional database containing all patients in our burn care unit consisting of four one-patient rooms was reviewed. We selected all patients who were diagnosed with inhalation injury by their admission.

All patients >16 years of age admitted to the burn unit between January 2008 and December 2012 and fulfilling the burn center referral criteria to a burn care center according the German Burn Association [1] were enrolled in the study.

These conclude:

1. Partial thickness burns greater than 20% total body surface area (TBSA).
2. Burns that involve the face, hands, feet, genitalia, perineum.
3. Third degree burns in any age group.
4. Electrical burns, including lightening injury.
5. Chemical burns.

Exclusion criteria were immunosuppression, pregnancy and ICU admission 48 h after burn trauma.

Inhalation injury was suspected in patients with facial and neck burn injuries and in patients who suffered burns in an enclosed space. All suspected patients underwent bronchoscopy at their admission in our burn unit. The diagnosis of inhalation injury was made by demonstration of inflammatory changes in the respiratory tract such as mucosal erythema, edema, ulceration, or submucosal hemorrhages. All patients with diagnosed inhalation injury received intravenous prophylactic antibiotic treatment with piperacillin and tazobactam.

The following data was registered for each patient: age, gender, co-morbidities, total body surface area burned (TBSA), the American Society of Anesthesiologists (ASA) score, the abbreviated burn severity index (ABBSI), Zellweger index, length of stay, mortality, presence of tracheostoma, length of mechanical ventilation, presence of pneumonia, microbiology of pneumonia and burn wounds, the antibiotic therapy of the pneumonia and its length.

The TBSA was calculated by adding percentages of dermal and subdermal burns with the help of the program BurnCase® (RISC Software GmbH, Hagenberg, Austria).

To assess the injury severity for each patient, the ABBSI was used. The index is a scoring system based on sex, age group, presence of inhalation injury and full thickness burn, and total body surface burn area in percent.

The Zellweger index represents a prognosis in lethality and is calculated by adding TBSA in % with the age of the patients.

Microbiological examination of the tracheal secretion of the patients in our burn care unit was made every 3 days in the patients with an inhalation injury. The swabs and trials were sent for cultivation in the Department of Microbiology. Candida antigen titer detection in serum is a reliable method of diagnosis of systemic candidiasis and the elevated titer indicate the antifungal treatment.

Antimicrobial therapy was instituted with the help of an infectious disease consultant from the Department of Microbiology.

SPSS (version 20, SPSS GmbH Software, Illinois, USA) was employed for data analysis. Variables were analyzed using contingency tables and chi-square and Fisher’s exact test. $p$-Values lower than 0.05 were regarded as statistically significant.

3. Results

In total 201 patients fulfilling our study criteria were treated in our burn care unit between January 2008 and December 2012 (male:female 151:50) with a mean age of 47.7 years.

In 58 patients (male:female 47:11) an inhalation injury was diagnosed by their admission in our Burn Unit. The incidence was 28.9%, the mean TBSA 20.5, the mean ASA score 1.55, the mean ABSI score 7, the mean Zellweger index 74.5. The average length of hospital stay of the inhalation injury group was 27.5 days, whereas of the non-inhalation injury it was 16 days ($p = 0.04$). 33 (56.9%) of the patients needed a temporary tracheostomy with a mean duration of 24.4 days. (Table 1)

Microbiological examination of the tracheal secretion of the patients in our burn care unit was made every 3 days in the patients with an inhalation injury. In 30/58 patients microorganisms were isolated in the tracheal secret and in 14/30 patients there were more than microorganisms isolated in the tracheal aspirate. The most common isolated microorganisms were gram positive bacteria as Staphylococcus and Streptococcus species (isolated in 18 patients) and Candida albicans and non-albicans species isolated as well in 18 patients (Fig. 1). In the non-inhalation injury group only 3.5% of the patients (5/143) had gram positive bacteria isolated in their tracheal secret and 2.8% (4/143) Candida albicans species, so that the isolation of these microorganisms from tracheal secret of patients with inhalation injury differed in a statistical significant manner in comparison to patients without inhalation injury. The incidence of pneumonia is higher in patients with isolated
microorganisms in their tracheal secret than in others without \((p < 0.01)\) and in all the 14 patients in which multiple microorganisms were isolated became a pneumonia implicating the immunosuppression of the burn patients. 34% of the patients with inhalation trauma became a pneumonia whereas only 14% of the patients without an inhalation trauma were diagnosed with a pneumonia during their stay in our burn care unit \((p < 0.01)\). The patients with isolated microorganisms had slightly higher mortality rates but in no statistical significant manner comparing with the patients without isolated microorganisms in tracheal secret. The mortality of patients with inhalation injury and no pneumonia was 9.7% and of patients with inhalation injury and pneumonia was higher at 12.1% but showing no statistical significance between these two groups \((p = 0.42)\).

In 5.2% of the patients with and in 2.1% of the patients without inhalation injury multi-resistance organisms (MRSA, ESBL, multiresistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*) have been isolated in the burn wounds or in the respiratory tract \((p = 0.23)\). The presence of the multiresistance organisms was determined on the 7th–23rd day after the admission of the patients (mean time: 15.7 days) and is higher in the inhalation trauma injury group due to the prolonged hospital stay of these patients and due to the immunocompromising effects of the combined burn trauma and the inhalation injury. In the three patients with inhalation injury and multiresistant microorganisms the antibiotic therapy had to be escalated and the antibiotic therapy was in each case vancomycin, imipenem and cholinist respectively.

11 of the 18 patients with isolated *Candida* in their tracheal aspirate required systemic antifungal therapy, as the *Candida* antigen titer in serum in the rest 7 patients not receiving systemic therapy was negative. 4 of the 143 non inhalation injury patients were diagnosed with systemic *Candida* \((p < 0.01)\).

An escalation of the antibiotic therapy was done in 39.7% (23/58) of the patients with inhalation injury and in 20.3% (29/143) of the patients without one \((p < 0.01)\).

The mortality of inhalation injury patients was 12.1% \((p = 0.09\) in comparison to patients without inhalation injury). The mean length of stay of the non-surviving patients with inhalation injury in our burn care unit was 25.8 days.

In order to avoid statistical bias due to the factor of TBSA and in order to have comparable groups, we examined the subgroup of patients with TBSA between 10 and 50%, under this condition there was no statistical significant difference of the TBSA between the inhalation and the non inhalation group. In that case there was as well a statistical significant difference of the pneumonia rate, the mortality of the patients between our two subgroups. As far as the length of stay is concerned in that case there was no difference between that the two subgroups.

### 4. Discussion

Inhalation injury is associated with a disappointingly high morbidity and mortality rate inspite of advances in diagnostics and therapy [2].

Several pathophysiologic mechanisms have been reported as responsible for inhalation injury, including toxins, anoxia and airway obstruction. The primary site of injury in smoke inhalation appears to be the small airway rather than the alveoli. These small airway occlusions caused by edema and pseudomembrane formation are the primary mechanisms of progressive hypoxia. Smoke exposure is a trigger for the sequence of events responsible for the development of inhalation injury. The inhalation of smoke triggers the release of the vasoconstrictor thromboxane, which causes an increase in pulmonary artery pressure. In addition, noxious chemicals generated by incomplete combustion injure the exposed bronchoepithelium and stimulate the release of chemical mediators that cause a progressive inflammatory process. Inhalation injury impairs surfactant production and can ultimately lead to a proinflammatory cytokines cascade altering the integrity of the capillary membrane [3,4]. Airway inflammation and pulmonary edema impair gas exchange and increase the susceptibility to pulmonary infection.

### Table 1 – Patients’ characteristics of the inhalation injury and the non inhalation injury group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Inhalation injury-group</th>
<th>Non-inhalation injury-group</th>
<th>p-Wert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>58</td>
<td>143</td>
<td>~</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>47.11</td>
<td>104:39</td>
<td>0.009</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.4 ± 18.3</td>
<td>46.8 ± 19.4</td>
<td>0.50</td>
</tr>
<tr>
<td>TBSA (%)</td>
<td>20.5 ± 20.4</td>
<td>11 ± 13.8</td>
<td>0.02</td>
</tr>
<tr>
<td>ABSI score</td>
<td>7 ± 3.0</td>
<td>6 ± 2.7</td>
<td>0.12</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>25.5 ± 18.9</td>
<td>16 ± 13.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Zellweger index</td>
<td>74.5 ± 27.8</td>
<td>63 ± 24.1</td>
<td>0.20</td>
</tr>
<tr>
<td>ASA score</td>
<td>1.5 ± 0.7</td>
<td>1.6 ± 0.9</td>
<td>0.97</td>
</tr>
</tbody>
</table>

### Fig. 1 – In 30/58 patients microorganisms were isolated in the tracheal secret. In 14/30 (46.7%) patients there were more than microorganisms isolated in the tracheal aspirate. In these 30 patients 26.7% of them had gram positive microorganisms in their tracheal secretion, 6.7% gram negative, 13.3% *Candida albicans*, 6.7% *Candida non albicans*.
In the retrospective studies of Edelman and Shirani, the incidence of inhalation injury in burn patients was shown to be 27% and 35% respectively [3,5]. Although mortality from smoke inhalation alone is low (0–11%), smoke inhalation in combination with cutaneous burns is fatal in 30–90% of the patients [6]. Cancio et al. stated that patients with inhalation injury are at high risk for bronchopneumonia, beginning 3–10 days after burn [7]. The contribution of inhalation injury and pneumonia to mortality were found to be independent and additive [8]. This was also shown in our statistical analysis when we compared the inhalation and non inhalation subgroup with the same mean TBSA. A statistical correlation was shown between inhalation injury and the presence of pneumonia. Expected mortality in patients with very small or very large burns appeared to be relatively uninfluenced by these pulmonary complications except at the extremes of age [8].

Administration of prophylactic antibiotics is a subject of controversy, as there are no clear recommendations. In the metanalysis of Anvi et al., the use of systematic antibiotics in the general or perioperative setting showed a significant reduction in the development of pneumonia. According to this study, there is a discrepancy between current guidelines for management of burn patients recommending against antibiotic prophylaxis and the evidence showing a reduction of about 50%. Anvi et al. recommend an antibiotic therapy with ampicillin and clavulanic acid [9].

Prophylactic antibiotics do not seem to prevent the development of pneumonia. The incidence of pneumonia in patients with inhalation trauma in our study was 34% (p < 0.01) while in the study of Edelman, in which no prophylactic antibiotic therapy was given, the incidence was 27%. The fact that prophylactic antibiotics do not prevent from the development of pneumonia is also reported in the review of Cancio et al. [7].

According to Edelman et al., the presence of pneumonia among inhalation injury patients significantly increased length of stay and doubled mortality rate [3]. The mortality rate of patients with inhalation injury in the study of Shirani was 20% [5]. The pneumonia rate was two times higher in the subset of patients with inhalation injury compared with the group of patients without inhalation injury (p < 0.001) [8].

The mortality of inhalation injury patients in our study was 12.1%. In the Swedish study of Appelgren, the mortality of the patients with inhalation injury was reported to be higher reaching 16.7%. In that study, no prophylactic antimicrobial therapy was given. In the study of Edelman, the mortality of patients with inhalation injury and no pneumonia was 9% (8/85) and of patients with inhalation injury and with pneumonia was 19% (6/32), whereas the incidence of pneumonia was 27% (32/117) [3]. No statistical significance was found between our study and the study of Edelman regarding the mortality of patients with inhalation injury and pneumonia (p = 0.307), whereas there was a statistical significant difference in the mortality of patients with inhalation injury without pneumonia (p = 0.01). In our study the mortality of patients with inhalation injury and no pneumonia was 9.7% and of patients with inhalation injury and pneumonia was 12.1% showing no statistical significance between these two groups (p = 0.42).

According to de la Cal, the mortality of patients with inhalation injury and pneumonia was 19%, double the mortality rate of 9% found in patients with inhalation injury and no pneumonia [3]. In the study of Edelman the mortality rate was also doubled by the addition of pneumonia to inhalation injury [3]. On the other hand, we showed that in our patient sample there was no statistical significant correlation (p = 0.608) between the mortality of the patients with pneumonia with (12%) and without inhalation trauma (10%).

Due to fear of developing antibacterial resistance and Candida infections, some investigators suggested no antibiotic usage in burn patients initial few days [10].

Appelgren et al. stated, that one of the reasons is that their strict antibiotic agents promote proliferation of yeast and fungi in burn wounds [11]. Candida spp. are increasingly important nosocomial pathogens representing the fourth leading cause of nosocomial bloodstream infections in the US, accounting for 8% of all bloodstream infections acquired in hospitals [12]. Candida bloodstream infections are associated with hospital mortality of 39% [13]. The point of initiating the Candida therapy is very important. Carey et al. used in their cohort analysis different time categories and found that delays in the initiation of antifungal therapy beyond 24 h after blood sampling significantly increased the mortality from 15% to 24% and 37% [13].

Candida infections were not a great problem in that study, as the mortality of the patients with Candida infections was only 0.9%.

According to the practice guidelines of the American Burn Association for ventilator-associated pneumonia (VAP) in burn patients, the isolation of Candida from endotracheal aspirates is common, but unusually represents colonization of the airway and rarely requires treatment with antifungals [14]. In our study in 31% of the inhalation injury patients Candida albicans and non-albicans species were isolated, whereas in only 4.1% of the non-inhalation burn patients were isolated (p < 0.01). We found that the diagnosis of candidaemia based on the elevated Candida antigen titer in serum was more common in inhalation injury patients, as in our study its incidence was 18.97% versus 3.5% in non-inhalation injury patients.

Antibiotic resistance was not a great problem in our study, since only in 5.1% of the patients with inhalation injury multi-resistant organisms were responsible. As already documented, there was no statistically significant difference to the patients without inhalation injury who did not receive a prophylactic antibiotic therapy.

5. Conclusion

The administration of prophylactic antibiotic therapy in case of an inhalation trauma is a controversial matter. In our study we showed that the incidence of pneumonia and the mortality of patients with pneumonia after inhalation injury are not influenced by the administration of prophylactic antibiotics. The controversial data presented show the need for a metanalysis about the issue of prophylactic antibiotics in burn patients with inhalation injury providing more evidence in order to add this extremely important issue. Nevertheless, since there are no clear recommendations it is up to the experience of the burn surgeons to decide for prophylactic antibiotics administration.
Conflict of interest statement

No conflict of interest.

Acknowledgement

No acknowledgments.

REFERENCES