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Systemic and endotracheal antibiotic prophylaxis of nosocomial pneumonia in ICU

H. Lode, G. Höffken, B. Kemmerich and T. Schaberg

Department of Chest and Infectious Diseases, City Hospital Zehlendorf and Department of Internal Medicine, Klinikum Steglitz, Freie Universität Berlin, FRG

Abstract. Nosocomial pneumonias, especially in ventilated patients, are a continuing problem in modern medicine. Pathogens most commonly involved with these pneumonias are *Enterobacteriaceae*, *Ps. aeruginosa* and *S. aureus*. Several prevention measures for nosocomial pneumonia are possible such as parenteral and topical antibiotics – a very controversial issue. Several studies with parenteral antibiotics, starting as early as 1954, could not prove any benefit of parenteral antibiotics in pneumonia prevention. Topical antibiotics, starting with polymyxin or gentamicin via the endotracheal tube in the 70s, gave controversial results. In a prospective, randomized, double-blind placebo controlled study with gentamicin via the endotracheal tube in ventilated ICU patients we found no significant reduction of pneumonia rate and mortality. However, the combined approach (SDD) of oropharyngeal, gastrointestinal and parenteral use of certain antibiotics appears to give promising results in specific patient subgroups such as ventilated polytrauma patients in ICU.

Key words: Antibiotic prophylaxis – Nosocomial pneumonia

Nosocomial pneumonia represents a major threat to the recovery of patients receiving mechanical ventilation and a difficult diagnostic challenge for ICU physicians. Ventilator-associated pneumonia occurs in 9%–21% of patients with different varieties of respiratory failure [1, 2], and its incidence exceeds 70% in patients who die of adult respiratory distress syndrome (ARDS) [3–5]. Altered resistance of the oropharynx, digestive tract and major organ systems [6–8] and an increase of bacterial colonization [9, 10] are the main causes of the high infection rates. The length of time in the ICU, underlying disease, age, and medical interventions are determining factors [11]. Despite careful hygienic measures and a restricted antibiotic policy, reported colonization and infection rates indicate that 70%–90% of mechanically ventilated ICU patients have been colonized by hospital-acquired bacteria in the oropharynx, trachea and digestive tract [12, 13]. After two weeks, up to 80% of patients have developed one or more episodes of infection. Micro-organisms involved are mainly *Enterobacteriaceae*, *Pseudomonadaceae* and yeasts [14, 15] (Table 1).

Considering the unresolved problems of endotracheal procedures for isolation of the "real" pathogen, detection of bacteria in blood cultures could give the best results in identification of nosocomial pneumonia etiologies. Bryan and Reynolds [16] studied 172 episodes of bacteremia attributed to nosocomial pneumonia in 168 patients, observed in the 4 major hospitals of a single metropolitan area over a 5-year period. Overall mortality for these patients was 58%; leading pathogens were *Klebsiella, Enterobacter* spp. and *Serratia* spp., *Staph. aureus*, *Ps. aeruginosa*, *Strep. pneumoniae* and *E. coli* (Table 2). Hence all antibacterial prophylactic approaches have to consider these pathogens. Different measures have been suggested to reduce bacterial colonization and the frequency of pneumonia.

Results: parenteral antibiotics

In 1954 Lepper [17] treated 51 of 81 tracheotomized poliomyelitis patients with different kinds of antibiotics. Thus 30 patients served as control and received no treatment. The prophylaxis with various systemic antibiotics single or in combination resulted in no benefit to the rates

Table 1. Nosocomial pneumonia/NNIS 1984

Pathogens	Frequency (%)
Pseudomonas aeruginosa	16.9
Staphylococcus aureus	12.9
Klebsiella spp.	11.6
Enterobacter spp.	9.4
Escherichia coli	6.4
Serratia spp.	5.8
Proteus spp.	4.2
Candida spp.	4.0

of pneumonia. In several patients aerosolized polymyxin B effectively prevented *Ps. aeruginosa* colonization.

In 1952 Petersdorf et al. [18] undertook a non-randomized comparative study in 72 comatose general medicine patients and treated 32 of these with penicillin and streptomycin or tetracycline alone, 10 patients with sulphonamides and 30 received no treatment. These authors could not detect any benefit of their antibiotic prophylaxis, instead they found higher rates of pneumonia, more cutaneous infections and bacteremias as well as more Gram-negative rod overgrowth occurring with antibiotic prophylaxis. The same authors [19] included 150 patients with acute heart failure in another randomized, double-blind, placebo-controlled trial and treated 72 with chloramphenicol and 78 with placebo. Again they could not detect any benefit of the prophylaxis measures.

Mandelli and co-workers [20] reported recently on a large study including 70 patients from 23 ICUs of whom 181 were treated with cefoxitin, 196 with penicillin G and 193 received no treatment. Again in this study no statistical significant difference in rates of pneumonia or death were found among the three different study groups.

Results: topical antibiotics

Topical antibiotics are one measure to avoid nosocomial pneumonias (Table 3) [21]. The SENIC study found nosocomial pneumonias to be the least preventable. The study concluded that up to 22% of nosocomial pneumonias were potentially preventable with an intense surveillance and control program and one infection control practitioner for every 250 beds [22]. Theoretically, prevention of colonization of the respiratory tract should be an effective means of preventing nosocomial bacterial pneumonias. Topical antibiotics have been used to suppress colonization of the oropharynx and gastrointestinal tract. Several studies have used polymyxin B, since polymyxin B can absorb to epithelial cells without being absorbed systemically, and is effective against most Gram-negative bacilli at low concentrations [23, 24]. Initial studies with polymyxin B showed a decrease in Gram-negative colonization, especially in those patients requiring ventilation for more than 72 h. However, in subsequent studies, with prolonged use, resistant strains emerged that were associated with a higher mortality.

Aerosolized gentamicin has also been used in the study of burn patients with pulmonary injury [25]. Pulmonary and septic complications were not reduced in the gentamicin group. Like the polymyxin studies, gentamicin aerosol was associated with the emergence of resistant flora. Klastersky et al. [26, 27] studied the effect of endotracheal gentamicin versus endotracheal placebo in a randomized double-blind placebo controlled trial in comatose tracheotomized neurosurgical ICU patients. They found a significant reduction in pneumonia rate in the gentamicin group but colonization of Gram-negative resistant bacteria developed. Comparing, in the same patient groups, endotracheal polymyxin B plus kanamycin versus endotracheal gentamicin alone in a total of 47 patients the same results hold true with both regimens although the combination treatment prevented severe Gram-negative bacterial colonization and reduced pneumonia risk; however, resistance developed with both regimens, more with gentamicin alone than with the combination of polymyxin and kanamycin. Another approach was to use polymyxin E and tobramycin in an adhesive paste and smear this on the oral mucosa four times per day [27]. With this regimen colonization of the oropharynx with Gram-negative bacilli was virtually eliminated, and no patient developed a nosocomial pneumonia. In a more recent study, animals in acute respiratory distress, requiring mechanical ventilation, were treated with a combination of topical polymyxin B and systemic ampicillin [28]. This combination lowered the rate of Gram-negative pneumonias to 19%, compared with 100% in the non-treated control animals. More recently, a combination of polymyxin B, tobramycin and amphotericin B was administered down the nasogastric tubes and applied topically to the oral mucosa in critically ill patients to prevent colonization [29]. This concept was recently further developed as selective intestinal decontamination with use of topically and parenterally administered antimicrobial drugs and gave promising results in polytrauma patients [30, 31].

In the last ten years Vogel et al. [32, 33] reported several controlled and uncontrolled studies using gentamicin four times 40 mg daily endotracheally in ventilated ICU patients to prevent pneumonia. They found a significant reduction in bacterial colonization of the trachea and reduced frequency of pneumonia with this approach. Since

Table 2. Mortality associated with bacteremic nosocomial pneumonia, according to micro-organisms isolated from blood cultures

Micro-organisms[a]	Deaths attributed to pneumonia +		Deaths attributed to all causes[b]	
Escherichia coli	5/16	(31)	10/16	(63)
Klebsiella, Enterobacter, Serratia	20/50	(40)	34/50	(68)
Other *Enterobacteriaceae*	3/7	(43)	4/7	(57)
Pseudomonas aeruginosa	18/25	(72)	19/25	(76)
Other aerobic Gram-negative micro-organisms	2/8	(25)	5/8	(63)
Streptococcus pneumoniae	6/21	(29)	9/21	(43)
Other *Streptococci*	1/17	(6)	8/17	(47)
Staphylococcus aureus	15/46	(33)	24/46	(52)
Staphylococcus epidermidis	0/2	(0)	1/2	(50)
Anaerobic micro-organisms	0/4	(0)	2/4	(50)

After Bryan and Reynolds, ARRD 1984

[a] The number of micro-organisms (196) exceeds the number of patients (168) because some patients experienced polymicrobial and/or more than one clinical occurrence of bacteremic nosocomial pneumonia

[b] Number of deaths per number of episodes (percent mortality)

Table 3. Prevention of nosocomial pneumonia

- Effective infection control program
- Prevent colonization
- Topical antibiotics (??)
- Prevent aspiration
- Improve host defense mechanisms

these studies were not blinded and due to the conflicting results in the above mentioned investigations the Paul-Ehrlich-Society study group "Endotracheal Pneumonia Prophylaxis" performed a prospective randomized double-blind multi-centre study to investigate the effect of endotracheal gentamicin on colonization, infection and mortality in ventilated ICU patients: during a time period of 2 years from August 1985 to September 1987 patients ventilated mechanically for a period of at least 4 days, from 5 ICUs were included in the study protocol [34]. Study medications (gentamicin, 40 mg q.i.d. endotracheally) or placebo (0.9% sodium chloride q.i.d. endotracheally) were started after intubation; randomisation was done by the Institute of Biomathematics in Heidelberg. Study medication was continued until the time of extubation; study endpoint was day 14 of continued ventilation. Registration of pneumonia was followed until day 16, and mortality was registered for 4 weeks after ventilation was started – a total of 199 patients were included in the study protocol. There were 37 patients (20 treatment, 17 placebo) excluded from final analysis due to protocol violation. Assessable patients could be divided into 85 patients in the treatment group and 77 patients in the placebo group. Both patient groups were comparable for underlying diseases and Apache II scores. Significant reductions in bacterial colonization could be determined in the gentamicin group (Table 4), but a reduction in the incidence of pneumonia could not be demonstrated in comparison with the placebo group ($p = 0.57$) (Table 5). The mortality analysis until day 28 after the start of ventilation resulted in a lower death rate in the treatment patients (27% versus 39%), however this difference was not statistically significant. The conclusion of this study was that endotracheal topical application of gentamicin in intubated and ventilated ICU patients was not effective for the prevention of pneumonia and the reduction of mortality in this prospective randomized placebo-controlled study.

Table 4. Maximal colonization of the trachea during ventilation

	Treatment group (%)	Placebo group (%)
Candida spp.	10.6%	10.4%
Ps. aeruginosa	2.4%	7.8%
E. coli	1.2%	9.1%
Klebsiella spp.	0%	5.2%
Enterobacteriaceae	1.2%	3.9%
Enterococci	5.9%	6.5%
Staph. aureus	11.8%	28.6%

Table 5. Incidence of pneumonia (during 16 days after start of ventilation)

	Days under risk	Pneumonia		Rate/day
		No.	Raw rate	
Verum ($n = 85$)	685	29	34%	0.042*
Placebo ($n = 77$)	476	25	32%	0.053*

*$p = 0.57$

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Prof. Dr. H. Lode
Department of Chest und Infectious Diseases
City Hospital Zehlendorf
affil. Freie Universität Berlin
Zum Heckeshorn 33
1000 Berlin 39
FRG