Intensive Care Med (1994) 20:187–192

Intensive Care Medicine

Prevention of Gram negative nosocomial bronchopneumonia by intratracheal colistin in critically ill patients

Histologic and bacteriologic study

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Received: 6 August 1992; accepted: 14 June 1993

Abstract. *Objective:* To evaluate the efficiency of intratracheal colistin in preventing nosocomial bronchopneumonia (BPN) in the critically ill.
Design: Study evaluating the clinical incidence of nosocomial BPN in 2 groups of critically ill patients who receive or did not receive intratracheal colistin. BPN was assessed clinically in survivors and histologically in non-survivors.
Setting: A 14-bed surgical intensive care unit.
Patients: 598 consecutive critically ill patients were studied during a prospective non-randomized study over a 40-month period.
Interventions: 251 patients – 31 non-survivors and 220 survivors – did not receive intratracheal colistin and 347 – 42 non-survivors and 305 survivors – received intratracheal colistin for a 2-week period (1 600 000 units per 24 h).
Measurements and results: The incidence of nosocomial BPN was evaluated clinically in survivors, using repeated protected minibronchoalveolar lavages, and histologically in non-survivors via an immediate postmortem pneumonectomy (histologic and semi-quantitative bacteriologic analysis of one lung). The clinical incidence of nosocomial BPN was of 37% in coli (–) survivors and of 27% in coli (+) survivors ($p < 0.01$). This result was histologically confirmed in non-survivors, where the incidence of histologic BPN was of 61% in coli (–) patients and of 36% in coli (+) patients ($p < 0.001$). Emergence of BPN due to colistin-resistant micro-organisms was not observed. Because colistin was successful in preventing Gram-negative BPN and did not change the absolute number of Gram-positive BPN, the proportion of BPN caused by *staphylococcus species* was higher in group coli (+) patients (33% vs 16%). Mortality was not significantly influenced by the administration of colistin.
Conclusion: This study suggests that the administration of intratracheal colistin during a 2-week period significantly reduces the incidence of Gram-negative BPN without creating an increasing number of BPN due to colistin-resistant micro-organisms.

Key words: Nosocomial bronchopneumonia – Mechanical ventilation – Intratracheal colistin

For the past decade, pathogenic mechanisms of nosocomial bronchopneumonia (BPN) occurring in critically ill patients have been progressively elucidated. In intubated and tracheostomized patients, superinfection of the lung is mainly from bronchial origin. The tracheobronchial tree is continuously colonized by bacteria coming from the oropharynx, which has been identified as one of the main reservoirs from which lung infection occurs [2, 3]. In critically ill patients, the normal oropharyngeal flora is rapidly replaced by Gram-negative opportunist bacteria, issuing either from patients' digestive flora through a retrograde colonization of stomach and esophagus [4, 5], or from the external environment [6]. A better understanding of the infectious process leading to nosocomial BPN has enabled the setting up of methods of prevention. In the 80s, several prospective randomized studies had suggested that selective decontamination of intestine and oropharynx may decrease the incidence of nosocomial BPN in critically ill patients [7–12]. However, several criticisms were addressed as to the technique and its evaluation, although a recent prospective randomized multicenter study did confirm these initial results [13]. Because of the complex anatomy of the oropharynx, oropharyngeal decontamination using an antibiotic paste is not easy, cumbersome and can be source of discomfort for the patient. The risk of selecting resistant pathogens has been emphasized [14]. All published evaluations of selective decontamination of the digestive tract have used very poorly sensitive diagnostic criteria of BPN, generally based on the association of

Presented in part at the 33th Congrès National d'Anesthésie-Réanimation, Paris, September 20, 1991

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positive tracheal secretions with "evocative" clinical and radiologic signs [7–12]. As a consequence, the finding of a reduced incidence of BPN remains a subject of controversy.

Tracheobronchial colonization and bronchiolitis are the last stages immediately preceding lung parenchymal infection. A logical approach in preventing nosocomial BPN would be to "decontaminate" the bronchial tree by the intratracheal administration of antibiotics. Recent experimental studies have clearly shown that the topical administration of antibiotics into the trachea largely prevents the onset of secondary lung infection [15, 16]. The aim of this study was to evaluate the efficiency of intratracheal (IT) colistin in preventing nosocomial BPN in a surgical intensive care unit (SICU). Colistin was selected for intratracheal administration for several reasons. First, a previous study had shown that the lungs of the patients who died in the SICU of La Pitié Hospital over a one-year period were mainly infected by Gram-negative bacteria [17], with a predominance of *Pseudomonas species* which are always sensitive to colistin. Second, experimental studies have recently shown that IT colistin can significantly reduce the incidence of nosocomial BPN [15, 16]. Third, clinical studies performed 20 years ago, had suggested that polymyxins administrated intratracheally could reduce nosocomial BPN rate for *Pseudomonas aeruginosa* [18, 19]. Last but not least, most Gram-negative bacteria do not easily acquire resistance to polymyxins. The results of the study, based on clinical and histologic criteria, suggest that a 2-week administration of IT colistin significantly reduces the incidence of Gram-negative BPN.

Methods

Patients

From April 1988 to August 1991, 598 consecutive critically ill patients who received mechanical ventilation for more than 72 h in the SICU of La Pitié Hospital in Paris (Department of Anesthesiology) were included in a prospective non-randomized study. From April 1988 to July 1989, 251 patients did not receive IT colistin. From July 1989 to August 1991, 347 patients received IT colistin during a 15-day period. The ability of IT colistin in preventing nosocomial BPN was evaluated during the 2 weeks following the first colistin administration and was based either on the clinical evolution of patients who survived or on the histologic examination of the lungs of those patients who died in the SICU between the third and the fifteenth day following the first colistin administration. In patients who did not receive IT colistin, the same evaluation was performed in survivors and non-survivors during the first 2 weeks following the admission to the SICU. In both groups, patients initially admitted for an acute BPN and patients whose lungs were mechanically ventilated for more than 2 days before the admission to the SICU were excluded from the analysis. These criteria of evaluation and selection were aimed at excluding patients with BPN preexisting to the administration of colistin as well as patients developing nosocomial BPN after the cessation of IT colistin. Finally, 2 groups and 2 sub-groups of patients were analyzed: group coli (−) patients, made up of patients who did not receive IT colistin and who survived or died during the 2-week period of evaluation (sub-groups coli (−) survivors and coli (−) non-survivors), and group coli (+) patients, made up of patients who received IT colistin and who survived or died during the 2-week period of evaluation (sub-groups coli (+) survivors and coli (+) non-survivors). For each patient included in the study, the chart was reviewed for the following data: sex, age, severity score on admission (as assessed by the simplified acute physiology score, SAPS), duration of mechanical ventilation, antibiotics received during the 2-week period of evaluation, ARDS and multiorgan failure.

Intratracheal administration of colistin

Colistin was administrated intratracheally as follows: after careful suctioning of the upper airways, 2 ml of saline containing 200000 units of colistin were directly instilled into the endotracheal tube, using a 5 ml-syringe. The patient was then reconnected to the ventilator and IT administration of colistin was repeated every 3 h (8 doses/24 h). A total dose of 1.6 million of units per 24 h was administrated during a 15-day period, the first instillation being given during the first 2 h following admission to the SICU. During the entire study period, from April 1988 to August 1991, selective decontamination of the digestive tract of all patients included in the study was performed using the intragastric daily administration of 2 g of erythromycin base. This selective digestive decontamination had been proved successful in controlling and preventing an outbreak of *Klebsiella pneumoniae* resistant to cefotaxime during the period 1986–1987 [20].

Diagnosis of nosocomial BPN in survivors

Nosocomial BPN was clinically defined as the association of clinical signs of sepsis with new evocative radiologic pulmonary infiltrates and a positive protected minibronchoalveolar lavage [17]. As previously described [21], the sample obtained from the protected minibronchoalveolar lavage was immediately transported to the bacteriology laboratory, a Gram stain was performed and the number of polymorphonuclear leukocytes and bacteria per oil immersion field were counted. Cultures were performed on the following plates: blood agar for aerobic and anaerobic cultures, chocolate agar for culture in CO_2 (5%) incubator, and Sabouraud agar containing chloramphenicol. Grow density was determined after an incubation of 24–48 h at 37 °C by a semi-quantitative technique. Results were expressed as rare, few or many colonies forming units (cfu) on each plate. Isolates were identified by the usual bacterial methods, and antibiotic sensitivity was determined with a standardized disc diffusion method. In patients not receiving antibiotics, only protected minibronchoalveolar lavage demonstrating many cfu/plate were considered positive. In patients already treated by antimicrobial agents for extrapulmonary reasons, no semi-quantitative criteria was required, because it has been demonstrated that lung bacterial burden can be markedly decreased by the intravenous administration of antibiotics [16, 17]. For each patient included in the protocol, nosocomial BPN was systematically looked for during the 14-day period of evaluation by daily clinical examination and chest X-ray.

Post mortem pneumonectomies and pathologic studies in non-survivors

Post mortem pneumonectomies were performed in non-survivors according to French legislation which allows removal of organs for the purpose of transplantation or scientific research unless the patients prohibits it before death (law no 781181, December 22, 1976 followed by the statutory order no 78501 march 31, 1978 and the implementation order of April 3, 1978). As previously described, a thoracotomy was performed at the bedside under surgical conditions within 20 minutes following death while maintaining mechanical ventilation [17, 21]. A right thoracotomy was performed when radiologic infiltrates were bilateral or predominant on the right. A left thoracotomy was performed when radiologic infiltrates were predominant on the left. The patient was positioned in the lateral decubitus and a large posterior incision was performed in the 5th intercostal space. After opening the pleura, the entire lung was largely exposed using a thoracic retractor, and the 3 lobes of the right lung or the 2 lobes of the left lung were individualized and carefully examined. Mechanical ventilation was then stopped, and, in consolidated areas suspected of infection, a small specimen (approximately 1 cm^3) was cut from each lobe (including occasionally the left lingula) and immediately transported to the bacteriology laboratory. After careful dissection, the main bronchus and the pulmonary vessels

were ligatured and sectioned, and the entire lung was removed, weighed and immediately transported to the pathology laboratory. There were 48 right lungs and 35 left lungs obtained for histologic evaluation.

The entire unfixed lung was dissected as during autopsy, enabling a study of arteries, bronchial tree and lung sements. The external aspect of the lung was carefully examined, and each segment was sectioned into 5–10 mm thick sections to localize inflammatory areas and subsequently fixed in 10% formalin for 24 h. Tissue blocks were then taken from the margin as well as from the centers of all grossly normal and abnormal areas of each segment. All tissue blocks were embedded in paraffin and cut into sections at 4 μm. A total of 5–10 sections were obtained per segment and each deparaffined section was stained with hematoxylin-eosin-safran. If gross examination and the clinical signs were suggestive of mycotic or parasitic lesions, a Schiff's periodic acid, a Giemsa, and a Grocott's stain were used. The presence or absence of bronchopneumonia was determined histologically in each lung as the presence of at least one of the following histologic feature: foci of bronchopneumonia, defined as the presence of neutrophilic infiltrates localized to terminal bronchioles and surronding alveoli: confluent bronchopneumonia, defined as an extension of these elementary lesions to several adjacent lobules; lung abscess, defined as confluent bronchopneumonia associated with tissue necrosis and disappearance of the normal lung architecture. The same pathologist (EML) performed all histologic evaluations without knowledge of the bacteriologic results or antibiotics the patient had received before death.

Bacteriologic processing for lung cultures

Immediately after death, small specimens (1 cm^3) sampled from each lobe (two or three from the left lung, and three from the right lung), were transported to the bacteriology and the pathology laboratory. Each lobar specimen was aseptically divided in two parts: one for bacteriologic culture, the second for histologic analyis. A Gram stain was performed on a small fragment and the number of polynuclear cells and bacteria per oil immersion field were estimated. The rest of each sample, placed in a sterile tube, was weighed and covered with 1 ml of tripticase soja broth supplemented with glucose, L-cysteine and vitamine K_3. The vial was vortexed vigorously for 1 min and an aliquot of 0.1 ml was streaked on the surface of the following plates: blood agar for aerobic and anaerobic cultures, chocolate agar for culture in CO_2 (5%) incubator and Sabouraud agar containing chloramphenicol. In addition, one buffered charcoal yeast extract media with or without antibiotics for isolation of *Legionella species* was cultured at 37 °C in a CO_2 enriched atmosphere for at least 48 h. Growth density was estimated by a semiquantitative method consisting of counting colonies forming units on each plate (rare, few, many). Isolates were identified by the usual bacterial methods and antibiotic sensitivity was determined with a standardized disc diffusion method.

Statistical analysis

All data are expressed as mean±SD. The χ^2 (and for small numbers, Fisher's exact test) and the Student's *t*-test for unpaired data were used to compare patients who received or did not receive intratracheal colistin. Results were considered significant at $p<0.05$.

Results

Comparison of patients groups

During a 40-month period, the incidence of nosocomial BPN was clinically evaluated in 525 survivors and histologically assessed in 73 non-survivors; 220 survivors and 31 non-survivors did not receive IT colistin (group coli (−), period April 1988–July 1989), whereas 305 survivors and 42 non-survivors received IT colistin (group coli (+), period August 1989–August 1991). As shown in Tables 1 and 2, these 2 groups of patients were comparable as far as age, incidence of MOF and ARDS and cause of admission to the SICU. Survivors in both groups had a significantly lower SAPS, were treated less frequently with intravenous antibiotics, and had a significant lower incidence of MOF and ARDS than non-survivors ($p<0.05$). Coli (−) survivors were mechanically ventilated for a longer time than coli (+) survivors. Among non-survivors, the proportion of females was significantly greater in the coli (−) group and lung weight was significantly lower in the coli (+) group. Mortality was not influenced by the administration of colistin (14% in both groups).

Table 1. Clinical characteristics of survivors in both groups

	Group coli (−)	Group coli (+)	
n	220	305	
Sex (F/M)	109/111	159/146	NS
Age	51±12	53±16	NS
Duration of mechanical ventilation (days)	18±12	12±14	$p<0.05$
ARDS	36	38	NS
MOF*	33	40	NS
IV antibiotics	176 (80%)	228 (74%)	NS
SAPS*	12±5	11±7	NS
Causes of admission			
MT*	59	95	NS
SC*	117	178	NS
M*	24	32	NS

MT = multiple trauma; SC = surgical complications; M = medical disease; MOF = multiorgan failure; SAPS = simplified acute physiologic score at admission

Characteristics of nosocomial BPN in both groups

As shown in Table 3, the incidence of nosocomial BPN was of 37% in coli (−) survivors and of 27% in coli (+) survivors ($p<0.01$). This result was histologically confirmed in non-survivors, where the incidence of histologic BPN decreased from 61% in coli (−) non-survivors to

Table 2. Clinical characteristics of non-survivors in both groups

	Group coli (−)	Group coli (+)	
n	31	42	
Sex F/M	15/16	9/33	$p<0.01$
Age	56±18	58±16	NS
Duration of mechanical ventilation (days)	9±5	8±4	NS
ARDS	7	9	NS
MOF*	15	19	NS
IV antibiotics	31 (100%)	42 (100%)	NS
SAPS*	18±6	19±8	NS
Causes of admission to the SICU			
MT	8	10	NS
SC	18	23	NS
M	5	9	NS
Lung weight (kg)	0.671±0.351	0.503±0.258	$p<0.05$

* MT = multiple trauma; SC = surgical complications; M = medical disease; MOF = multiorgan failure; SAPS = simplified acute physiologic score at admission

Table 3. Incidence of nosocomial bronchopneumonia – (BPN+) – in survivors and non-survivors according to intratracheal administration of colistin – groups coli (−) and coli (+) – In survivors, the diagnosis of BPN was based on clinical and microbiological criteria. In non-survivors, the diagnosis of BPN was based on complete histologic examination of one lung

Patients	Group	BPN (+)	BPN (−)
Survivors	Coli (−) $n = 220$	81 (37%)	139 (63%)
$n = 525$	Coli (+) $n = 305$	82 (27%)*	223 (72%)*
Non-survivors	Coli (−) $n = 31$	19 (61%)**	12 (39%)**
$n = 73$	Coli (+) $n = 42$	15 (36%)*	27 (64%)*

*$p < 0.001$ group coli (+) vs group coli (−)
**$p < 0.001$ group coli (−) non-survivors vs group coli (−) survivors

36% in coli (+) non-survivors ($p < 0.001$). The incidence of BPN was significantly higher in coli (−) non-survivors than in coli (−) survivors (61% versus 37%, $p < 0.001$), and the difference observed between coli (+) non-survivors and coli (+) survivors (36% versus 27%) did not reach statistical significance. As shown in Table 4, the lower incidence of nosocomial BPN in coli (+) patients was related to a reduced incidence of Gram-negative and polymicrobial BPN without significant increase in Gram-positive BPN. Colistin-treated patients had a reduced incidence of BPN due to *Pseudomonas aeruginosa* when compared to non-treated patients, and did not show any increasing incidence in the number of BPN caused by other *Pseudomonas species, Proteus mirabilis* or *Serratia marcescens.* However, the proportion of BPN caused by *Staphylococcus species* was significantly higher (30%) in coli (+) patients than in coli (−) patients (18%). Surprisingly, a significant reduction in the incidence of BPN due to yeasts was observed in colistin-treated non-survivors.

Table 4. Incidence and microbiologic characteristics of nosocomial bronchopneumonia (BPN) in both groups of patients (survivors and non-survivors)

	Group coli (+)	Group coli (−)	p
Number of patients	347	251	
Nosocomial BPN	97 (28%)	100 (40%)	$p < 0.05$
GN BPN*	33 (9.5%)	46 (18%)	$p < 0.01$
GP BPN*	26 (7.5%)	13 (5%)	NS
Polymicrobial BPN	9 (2.6%)	14 (5%)	$p < 0.05$
BPN with negative lung culture	29 (8%)	27 (11%)	NS
Total number of microorganisms found in lung culture	71	76	
Total number of GNB*	40 (56%)	58 (76%)	$p < 0.01$
Pseudomonas species + Acinetobacter	12 (17%)	26 (34%)	$p < 0.01$
Proteus mirabilis + Serratia marscesens	13 (18%)	11 (14%)	NS
Staphyloccocus species	21 /30%)	14 (18%)	$p < 0.01$

*GN = Gram-negative; GP = Gram-positive; GNB = Gram-negative bacteria

Table 5. Sensitivity to colistin of the 15 bacteria isolated in lung cultures of 11 non-survivors of Group coli (+) with histologic BPN and positive lung culture

Patients	Microorganisms found in lung culture	Sensitivity to colistin	Semi-quantitative culture
1	*Pseudomonas aeruginosa*	Yes	Few
2	*Pseudomonas aeruginosa*	Yes	Rare
3	*Pseudomonas aeruginosa*	Yes	Rare
4	*Pseudomonas aeruginosa*	Yes	Few
5	*Escherichia coli*	Yes	Few
6	*Streptococcus hemolytica*	No	Many
8	*Staphylococcus aureus*	No	Few
9	*Pseudomonas aeruginosa*	Yes	Many
	Staphylococcus aureus	No	Many
10	*Proteus mirabilis*	No	Many
	Staphylococcus aureus	No	Few
11	*Escherichia coli*	Yes	Rare
	Hemophilus influenza	Yes	Few
	Staphylococcus aureus	No	Many

Susceptibility to antimicrobial agents of microorganisms infecting the lungs in non-survivors

In non-survivors with histologic BPN, microorganisms found in lung culture were resistant to antibiotics administered before death in similar proportions in both groups: 55% in coli (−) patients vs 67% in coli (+) patients (NS). Among the 15 BPN histologically diagnosed in group coli (+) non-survivors, 4 were associated with a negative lung culture. As shown in Table 5, 5 of these 11 BPN were caused by microorganisms sensitive to colistin and 3 of them were polymicrobial.

Discussion

This study strongly suggests that Gram-negative nosocomial bronchopneumonia can be partially prevented by the administration of intratracheal colistin in critically ill patients under mechanical ventilation. By using a 15-day regimen of intratracheal colistin, the incidence of GNB bronchopneumonia was reduced from 40–28% in a series of critically ill patients admitted to the SICU of La Pitié Hospital in Paris. This result was based on a clinical evaluation of the incidence of nosocomial BPN in survivors and on a multiple segmental histologic analysis of non-survivors' lungs. The incidence of nosocomial BPN was compared in a historical control group of 251 patients and in 347 subsequent patients who received IT colistin.

When considering causes of admission to the SICU, severity score on admission, age, incidence of MOF and ARDS and treatment by intravenous antibiotics, all factors which could have influenced the occurrence of bronchopneumonia, both groups of patients were similar. In survivors, the incidence of MOF and ARDS were significantly less than in non-survivors confirming that MOF and ARDS are critical factors influencing the prognosis of critically ill patients. In addition, mean lung weight was found to be higher in group coli (−) non-survivors than in group coli (+) non-survivors, a result reflecting

the lower incidence of lung superinfection in the latter group.

The reduced incidence of bronchopneumonias in group coli (+) patients was mainly due to a reduction in Gram-negative BPN with an unchanged absolute number of Gram-positive BPN. The total number of microorganisms found in lung cultures was significantly reduced in group coli (+) patients, essentially because of a significant reduction in the number of Gram-negative bacteria. In terms of bacteriologic characteristics, BPN observed in both groups were different. Although more than 50% of BPN were caused by Gram-negative bacteria in both groups, BPN in group coli (+) patients were less frequently due to Gram-negative bacteria and more frequently caused by *Staphylococcus aureus*. In fact, tracheal decontamination using colistin did not change the absolute number of Gram-positive BPN, and thereby increased the proportion of BPN caused by *Staphylococcus aureus*. This result is not surprising, since a reduction in BPN caused by *Staphylococcus aureus* could not be reasonably expected from the administration of intratracheal colistin. Other Gram-negative bacteria, naturally resistant to colistin, such as *Pseudomonas maltophilia, Pseudomonas cepacia, Serratia marscencens* and *Proteus mirabilis* did not show any increasing incidence in colistin-treated patients. These results do not support the idea suggested by Feeley et al. in 1975 [18, 19] that emergence of polymyxin-resistant pathogens is a serious complication of the long-term administration of intratracheal colistin. In their initial study [18], all patients admitted to the respiratory-surgical intensive care unit were treated either with polymyxin aerosol for a 2-month period and with an aerosol of physiologic saline for the next 2 months. Therapy was alternated in this manner for 11 two-month cycles. Using this mode of administration, a significant reduction in the incidence of acquired Gram-negative BPN was observed, without emergence of polymyxin-resistant pathogens [18]. In a second study [19], they confirmed that, when continuously administering polymyxin to all patients for a 7-month period, Gram-negative BPN were less frequent; however, this beneficial effect was offset by an increased mortality of those patients who acquired BPN caused by polymyxin-resistant microorganisms which were found with an "abnormally high incidence", according to the investigators. However, the absence of control group does not enable a definitive conclusion.

Our study suggests that over a period of 2 years, the daily administration of intratracheal colistin limited to a 2-week period for all patients admitted to the SICU, did not significantly increase the absolute number of BPN caused by colistin-resistant pathogens and significantly reduced the incidence of Gram-negative BPN. The absence of emergence of colistin-resistant microorganisms might be related to the small potential of colistin for selecting baterial resistance. Because colistin-resistance is not known to be mediated by transferable resistance factors, the emergence of resistant pathogens in humans is mainly due to the selection of micro-organisms that are intrinsically resistant to colistin, such as *Proteus species* or *Pseudomonas species* other than *Pseudomonas aeruginosa*. Because the major adverse effect of the administration of intratracheal antimicrobial agents is the possible development of a multiresistant Gram-negative bacteria flora within the intensive care unit, great attention should be paid both to antibiotics used and to the duration of intratracheal administration. Ideally, the antibiotic used should not be absorbed through the tracheal mucosa, should adsorb to bronchial epithelial cells, should be bactericidal at low concentrations and should not induce transferable resistance factors. Only a few microbial agents can fulfil these conditions and colistin appears one of them. Intratracheal gentamicin, previously used to prevent human and experimental nosocomial bronchopneumonias [16, 22], is associated with the development of a high percentage of Gram-negative bacteria resistant to this agent. When aminosides are administered in the oropharynx and in the digestive tract, detectable concentrations are found in distal bronchial secretions and in the serum [23]. Most often, these concentrations are below minimal inhibitory concentrations of Gram-negative bacteria, a fact which can potentiate the emergence of aminoside-resistant strains. This is one of the possible mechanisms by which topical aminosides might induce bacterial resistance. Another factor, critical to avoiding selection of colistin-resistant Gram-negative bacteria, is the duration of administration. Previous clinical studies, during which intratracheal antibiotherapy was administered daily for the entire stay of the patient in the intensive care unit, had suggested that emergence of resistant microorganisms was a serious complication of the method [19, 22]. In contrast, experimental studies had shown that the use of intratracheal antibiotherapy for 7 to 10-day periods for preventing nosocomial BPN in baboons, was not associated with the emergence of resistant micro-organisms [15]. In this study, where the period of colistin administration was limited to 15 days, no increasing incidence of polymyxin-resistant bacteria infecting patients' lungs was noted. If all these results are taken into consideration, then it appears wise to limit the intratracheal administration of colistin to one or two weeks in critically ill patients under mechanical ventilation.

It has to be pointed out that intratracheal colistin was not always successful in preventing BPN caused by *Pseudomonas aeruginosa* and other colistin-sensitive microorganisms. Among colistin-treated patients who developped BPN, 4 were infected by *Pseudomonas aeruginosa* and one by *Escherichia coli*, all bacteria sensitive to colistin. Among the 15 bacteria isolated in lung cultures, 8 were sensitive to colistin. This lack of efficiency could be related to the mode of administration, consisting of a direct injection within the endotracheal tube. As suggested by a recent study [24], administration by aerosol could be more performant in terms of the tracheobronchial area reached by the nebulized colistin, and consequently, more successful in preventing Gram-negative BPN. Further studies are required to determine the best mode of administration.

In conclusion, this study suggests that the administration of intratracheal colistin for a 2-week period decreases by half the incidence of Gram-negative BPN. Because

of the small potential of colistin for inducing bacterial resistance, no increase in the number of BPN caused by colistin-resistant microorganisms was observed. Since the study was consecutive and non-randomized using an historical control group, further studies are required to confirm these preliminary results.

Acknowledgment. The authors thank Dr. J. Amaro, A. Andreev, M. Benameur, E. Cantoni, J.L. Leguillou, T. Lherm and M. Moutafis for their direct participation to the study; the nurses of the surgical intensive care unit for their active cooperation; Corine Mataguez and Véronique Connan for typing and preparing the manuscript; Gillian Debrabander for her expert technical assistance and all members of the laboratory of bacteriology for their expertise and full participation.

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