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Research Article

All 744 patients admitted to a Respiratory-Surgical Intensive Care Unit (RSICU) were included in a prospective study of the effects of a polymyxin (2.5 mg/kg body wt/day in six divided doses) or a placebo aerosol sprayed into the posterior pharynx and tracheal tube (if present), during 11 alternating 2-mo treatment cycles. The incidence of upper airway colonization in the RSICU with *Pseudomonas aeruginosa* was 1.6% during the polymyxin treatment cycles (total 374 patients) and 9.7% during the placebo cycles (370 patients) (X^2 equals 23.2, P less than 0.01). 3 patients in the RSICU acquired *Pseudomonas pneumonia*, as defined by independent "blinded" assessors, during the polymyxin cycles while 17 acquired a *Pseudomonas pneumonia* during the placebo cycles (X^2 equals 10.2, P less than 0.01). The overall mortality was similar in both placebo and polymyxin-treated groups (12.2 vs. 12.0%). Systemic antibiotic usage was similar in the different cycles; 49% of patients in the placebo and 53% in the polymyxin-treated groups received systemic antibiotics while in the RSICU.

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Prevention of Gram-Negative Bacillary Pneumonia Using Polymyxin Aerosol as Prophylaxis

II. EFFECT ON THE INCIDENCE OF PNEUMONIA IN SERIOUSLY ILL PATIENTS

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ABSTRACT All 744 patients admitted to a Respiratory-Surgical Intensive Care Unit (RSICU) were included in a prospective study of the effects of a polymyxin (2.5 mg/kg body wt/day in six divided doses) or a placebo aerosol sprayed into the posterior pharynx and tracheal tube (if present), during 11 alternating 2-mo treatment cycles. The incidence of upper airway colonization in the RSICU with *Pseudomonas aeruginosa* was 1.6% during the polymyxin treatment cycles (total 374 patients) and 9.7% during the placebo cycles (370 patients) ($\chi^2 = 23.2$, $P < 0.01$). 3 patients in the RSICU acquired *Pseudomonas* pneumonia, as defined by independent "blinded" assessors, during the polymyxin cycles while 17 acquired a *Pseudomonas* pneumonia during the placebo cycles ($\chi^2 = 10.2$, $P < 0.01$). The overall mortality was similar in both placebo and polymyxin-treated groups (12.2 vs. 12.0%). Systemic antibiotic usage was similar in the different cycles; 49% of patients in the placebo and 53% in the polymyxin-treated groups received systemic antibiotics while in the RSICU.

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INTRODUCTION¹

An ever increasing problem in modern hospital care has been the development of nosocomial respiratory infections preceded by colonization of the upper respiratory tract (1). Sanford and Pierce have cited occurrences of nosocomial infections of the respiratory tract as ranging from 0.5 to 5.0% of all hospitalized patients (2). Much progress has been made in elucidating reservoirs of pathogens existing in the hospital environment, including anesthesia equipment, room humidifiers, disinfectants, water sources, and jellies (3-8). However, dangerous pathogens, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, still account for increasing morbidity and mortality in certain patient populations, particularly critically ill patients (9-11).

To assess the extent of nosocomial infection we previously carried out a 30-mo retrospective analysis of infection in our Respiratory-Surgical Intensive Care Unit (RSICU)² (12). During that time *P. aeruginosa* was the most common pulmonary pathogen (50% of 158 episodes of bacterial pneumonia). *Pseudomonas* pneumonia carried a 75% mortality rate as compared to 25% in other bacterial pneumonias. The mortality of pneumonia-free patients was only 3.8%. Consequently, analysis of the potential reservoirs from which *Pseudomonas* could be recovered became a major objective. We then

¹The opinions or assertions contained herein are those of the authors, and are not to be construed as official or necessarily reflecting the views of the Navy Department, or the naval service at large.

²Abbreviation used in this paper: RSICU, Respiratory-Surgical Intensive Care Unit.

undertook the monitoring of 640 patients and their environment in the RSICU during a 19-mo period. 71% of the sputum or throat isolates of *Pseudomonas* were clearly hospital acquired, and at least 10 of 16 patients who had *P. aeruginosa* on first culture were suspected of having hospital-acquired organisms. Pyocine type 10 was the "resident" strain, outbreaks of which tended to occur in clusters. Pyocine type 10 was regularly cultured from only one environmental source (the sinks), including 1-2-wk intervals during which no patient in the RSICU was colonized with *Pseudomonas*.

We have presented data which show that treatment of *Pseudomonas* pneumonia with systemic antibiotics is at best minimally effective (12). Since the portal of entry is usually the upper respiratory tract, the feasibility of specific prophylaxis with localized antibiotic therapy was tested in a pilot study. Polymyxin B was given by aerosol to reduce colonization of the upper respiratory tract with nosocomial gram-negative bacilli. 58 high-risk patients from the RSICU entered the pilot trial. 33 were randomly selected to receive 2.5 mg/kg/day of polymyxin B by a hand atomizer into the pharynx and, if present, tracheal tube: 17 of 25 control patients became colonized with gram-negative bacilli as compared with 7 of 33 polymyxin-treated patients ($P < 0.01$). Polymyxin B was selected for reasons which have been previously detailed (13).

Since the upper respiratory tract is rapidly colonized during acute illness and hospitalization (1, 14) and since pneumonia often occurs before prolonged controlled ventilation is instituted (12), prevention must be attempted early in the course of a given critical illness (15). Thus, after completion of the pilot study, we received permission from the appropriate hospital committees to put all patients in our RSICU on 2-mo alternating cycles of placebo and polymyxin aerosols to determine the effect on the development of pneumonia.

METHODS

The present study was conducted in the RSICU at the Beth Israel Hospital where patients in respiratory distress are admitted from all services. The majority of the patients were those in whom respiratory impairment was anticipated postoperatively.

The interval from 23 October 1972 to 14 June 1974 was divided into 10 8-wk cycles; the last cycle, cycle 11, was 4 wk in duration. During this time, 744 patients were admitted to the RSICU, 370 during cycles when a normal saline placebo aerosol was administered (mean age 60 yr, average number patient days 5.3) and 374 during cycles when polymyxin was administered (mean age 57 yr, average number of patient days 5.1). The systemic antibiotics given to the patients were recorded. No attempt was made by anyone connected with the study to influence systemic antibiotic administration.

Within the first 24 h of admission to the RSICU all patients had their posterior pharynx and tracheal tube (if present) sprayed with an aerosol which consisted either of

normal saline (placebo) or a 0.5% polymyxin in normal saline aerosol every 4 h to a total daily dose of 2.5 mg/kg in the manner described by Greenfield, Teres, Bushnell, Hedley-Whyte, and Feingold (13). The placebo and polymyxin aerosols were alternated so that during each 8-wk period all patients admitted to or present in the RSICU received the same aerosol. The content of the aerosol was unknown to the RSICU staff, and the code was broken by one of us (J. H-W.) at the end of the study.

Tracheal aspirate and stool cultures were obtained within 24 h of admission. Daily tracheal aspirates for culture were usually collected in the morning from each patient following chest physiotherapy and within 1 h before the 10 a.m. aerosol treatment. Urine was cultured at the time of bladder catheterization and when clinically indicated.

The drains of the sinks used for handwashing in the RSICU were cultured at least biweekly, and the cultures were examined for the presence of gram-negative organisms, particularly *Pseudomonas*. During the duration of this study a daily practice of sink sterilization was in effect within the RSICU. This consisted of filling the sinks, which had previously been fitted with drain cutoff valves, with a 5% phenol solution and heating the disinfectant with a 500-W immersion heater to 70°C for 90 min. The sink overflow drains, reservoir nebulizers, and ventilator trap bottles were all cultured intermittently. During the twice yearly closing of the RSICU for cleaning, floors, beds, vents, etc. were cultured using cotton swabs moistened with dextrose-phosphate broth. Settling plates were positioned around the unit and exposed for 2 h during all stages of cleaning to monitor airborne contamination.

All bacteriology was performed by the same microbiologist (G. C. D.). The isolation media for *P. aeruginosa* was cetrimide agar, and identification was based on colony morphology, pigment production, and biochemical reactions in oxidative-fermentative media. Pyocine typing was done by the technique of Gillies and Govan (16). Fermentative gram-negative bacilli were identical by the criteria of Edwards and Ewing (17). The nonfermentative gram-negative bacilli were identified by the criteria of Weaver, Tatum, and Hollis.⁸ Polymyxin sensitivities were performed on all gram-negative bacilli using a modified method of disk diffusion antibiotic susceptibility testing as described by Bauer, Kirby, Sherris, and Turck (18).

Colonization was defined as the isolation of a new organism from throat or sputum on more than one consecutive culture. If only a few colonies (nine or less on the primary plating) of bacteria were present in the throat culture on admission to the unit, any increase on subsequent culture was considered to represent colonization. For gram-negative bacilli this is an identical definition to that used in our pilot study (13). The diagnosis of pneumonia was based upon three separate opinions: that of the house officers in the RSICU having direct care for the patient; an independent physician reviewing the records of the patients at the end of every two cycles; and, finally, a third opinion from a group consisting of a different physician and paramedical personnel reviewing the records of the patients at the end of every two cycles. The treatment given during cycles was not known to those passing judgment on the presence or absence of pneumonia. Each group was asked to

⁸Weaver, R. E., H. W. Tatum, and D. G. Hollis. 1972. The Identification of Unusual Pathogenic Gram Negative Bacteria. Atlanta, Ga.: U. S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control. Preliminary revision.

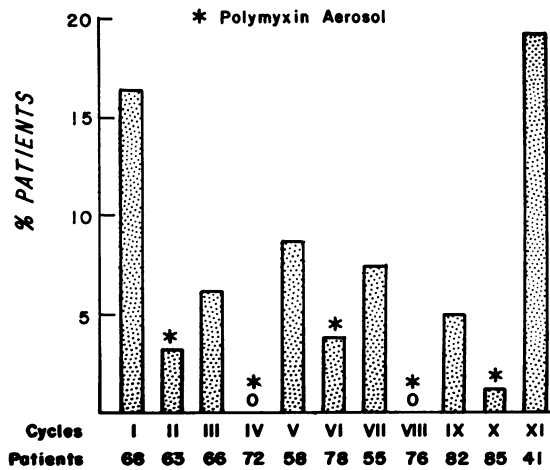


FIGURE 1 Upper airway colonization rate with *P. aeruginosa* in patients in the RSICU in each of the 11 cycles. Patients in the even-numbered cycles received polymyxin aerosol. Total number of patients in each cycle is indicated. 36 patients were colonized with *Pseudomonas* during the placebo cycles and 6 during the polymyxin cycles ($\chi^2 = 23.2, P < 0.01$).

decide whether the pneumonia was "probably" present or only "possibly" present and whether the pneumonia was present on admission to the RSICU or acquired while the patient was in the RSICU. Only cases of "probable" pneumonia were considered.

The criteria for the diagnosis of pneumonia were based on the presence of persistent X-ray evidence of an alveolar infiltrate on 2 or more consecutive days observed at a time when sputum cultures or tracheal aspirates were positive for potentially pathogenic organisms; an elevated alveolar-

arterial oxygen tension difference while breathing 100% oxygen ($AaDO_2^{1.0}$); and an evaluation of the temperature course, daily weights, central venous pressure, and Swan-Ganz catheter data (19).

The Beth Israel Hospital's Committee on Clinical Investigation and New Procedures and Forms of Therapy accepted this methodology and was kept abreast of results at intervals. The present study was terminated by the Chairman of the Committee on Clinical Investigation in the middle of the 11th cycle, a placebo cycle, because of the sudden increase in colonization and infection with *P. aeruginosa* (Figs. 1 and 2). Because of the number of patients at risk in the RSICU, the treatment code was broken, and all patients were placed on polymyxin aerosol, thus ending the blinded study.

At the end of our analysis to account for those patients who, during their stay in the RSICU, overlapped the 2-mo cycles, the data were reexamined with these patients excluded. This was done to rule out the possibility of a patient being colonized in one cycle and developing a pneumonia in the following cycle. The criteria for overlapping were strict in that, for example, a patient whose stay in the RSICU was 2 wk and who overlapped the following cycle by a day was considered as an "overlap".

RESULTS

Systemic antibiotic usage. Full information on systemic antimicrobial therapy prescribed by the patient's physician was available for 331 of 371 (89.5%) of the patients in the placebo aerosol cycles and for 324 of 374 (86.6%) of the patients in the polymyxin aerosol cycles. 49% of those patients given the placebo saline aerosol were being treated with systemic antibiotics vs. 53% during the polymyxin periods. During the placebo aerosol cycles systemic antibiotics were given as follows: oxacillin 19% of patients, ampicillin 13%, cephalothin

TABLE I
Number of Acquired Microorganisms Other than *P. aeruginosa* by Cycle

Cycle.....	Polymyxin											Placebo total	Polymyxin total
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI		
Patients with acquired GNB	22	19	24	13	23	25	18	12	22	17	15	124	86
I. Polymyxin-sensitive organisms													
<i>Enterobacter</i> species	6	0	14	4	15	8	12	7	10	3	5	62	22
<i>Acinetobacter</i> species	8	1	3	0	4	1	6	0	8	1	2	31	3
Other GNB*	2	1	22	3	12	5	6	6	6	2	3	51	17
II. Polymyxin-resistant organisms													
<i>Serratia</i> species	0	6	4	3	4	2	2	1	2	1	0	12	13
<i>Proteus</i> species	3	10	4	2	3	10	3	4	8	6	2	23	32
<i>Flavobacterium</i> species	11	15	9	7	5	10	1	3	8	9	4	38	44
<i>Pseudomonas maltophilia</i>	0	0	0	0	0	0	0	0	0	0	2	2	0
III. Gram-positive organisms													
<i>Staphylococcus aureus</i>	1	0	2	3	5	9	6	12	5	8	1	20	32
<i>Enterococcus</i>	5	4	0	0	0	0	2	1	7	1	3	17	6
IV. Yeast													
<i>Candida albicans</i>	0	0	0	0	1	4	4	12	5	23	2	12	39
<i>Candida</i> species	0	0	0	0	0	0	0	1	2	6	0	2	7

* *Escherichia coli*, *Citrobacter*, *Klebsiella*.
GNB, gram-negative bacilli.

TABLE II
Summary of Pneumonias Acquired within the RSICU

	Placebo cycles	Polymyxin cycles
<i>Pseudomonas aeruginosa</i>	17	3
<i>Enterobacter</i> species, <i>Klebsiella pneumoniae</i> and <i>Escherichia coli</i>	3	1
<i>Staphylococcus aureus</i>	2	5
<i>Serratia</i> species or <i>Proteus</i> species	6	8
<i>Flavobacterium meningosepticum</i>	0	1
<i>Pseudomonas maltophilia</i>	1	0
<i>Candida albicans</i>	1	0
Total	30	18

13%, and kanamycin 6%. During the polymyxin aerosol cycles corresponding percentages were 20, 12, 9, and 6. Systemic gentamicin, systemic carbenicillin, and/or systemic polymyxin were used in 11.8% of the placebo aerosol patients and 6.5% of the polymyxin aerosol patients: this difference may be a response of the patient's primary physicians to the increased incidence of *P. aeruginosa* infection in the placebo aerosol periods.

Colonization rate. Fig. 1 shows the colonization rate of *P. aeruginosa* in RSICU patients during each of the 11 cycles. The overall rate of upper airway colonization with *Pseudomonas* was 5.6%. During the placebo cycles, the upper airways of 36 patients (9.7%) were colonized with *Pseudomonas* while during the polymyxin aerosol cycles the upper airways of 6 patients (1.6%) were colonized ($\chi^2 = 23.2, P < 0.01$). This decrease in colonization is consistent with the previous investigation by Greenfield et al. (13). As expected, the incidence of airway colonization with other species of Enterobacteriaceae sensitive to polymyxin was also diminished during those cycles in which polymyxin was employed (Table I). Colonization with *Escherichia coli*, *Enterobacter* species, and *Klebsiella* species occurred on 22 occasions during the polymyxin cycles and on 62 occasions during the placebo cycles ($\chi^2 = 22, P < 0.01$).

Perhaps of equal importance is the colonization rate with those organisms resistant to polymyxin. Eight patients were colonized with *Staphylococcus aureus* during the placebo cycles, and nine were colonized during polymyxin cycles (Tables I). 38 patients (9.5%) in the placebo cycle were colonized with *Serratia* species or *Proteus* species while 44 patients (12.0%) were colonized during the use of the polymyxin aerosol (NS). The most common nonfermentative gram-negative bacillus in the RSICU was *Flavobacterium* species. 10.3% of the patients were colonized with this organism during the placebo cycles, and 11.8% were colonized during the polymyxin cycles (Table I).

Since the start of sink decontamination, sink drain and overflow drain cultures have been taken twice weekly. Only occasional cultures positive for *Pseudomonas* have

been obtained. Routine cultures of heated nebulizers have been consistently negative, and only rare positive cultures have been obtained from the expiratory trap of the ventilator.

Pneumonia (Table II). During the placebo periods, 30 patients acquired pneumonia while in the RSICU; 17 of these were due to *Pseudomonas* (4.6% of the 370 patients), and 4 of these latter patients died (Fig. 2). In the polymyxin cycles, 18 acquired pneumonia, 3 due to *Pseudomonas* (0.8% of the 374 patients; $\chi^2 = 10.2, P < 0.01$) 2 of whom died. Five patients acquired staphylococcal pneumonia while in the RSICU during the polymyxin cycles, two of whom died, while two acquired a staphylococcal pneumonia during the placebo cycles (NS), one of whom died. There was a single case of pneumonia attributed to polymyxin-resistant *Flavobacterium meningosepticum*, subtype D during a polymyxin cycle (20). The number of patients with pneumonia acquired in the RSICU due to *Serratia* species and *Proteus* species during the placebo and polymyxin cycles was six and eight, respectively. During polymyxin cycles there was one case of pneumonia attributed to *K. pneumoniae*. During the placebo cycles, one case of acquired pneumonia was attributed to *Enterobacter* species, and two cases of pneumonia were attributed to *K. pneumoniae* (Table II).

Cycle-overlapping patients. A total of 52 patients were found to overlap two cycles: none overlapped three. 33 patients began in placebo periods and completed their stay in the RSICU in polymyxin periods. 19 pa-

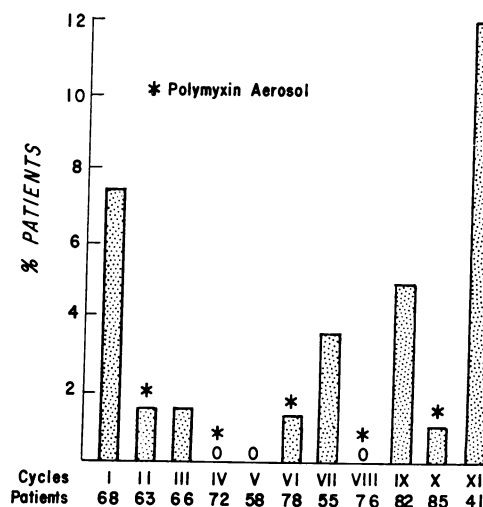


FIGURE 2 Incidence of *Pseudomonas* pneumonia acquired by patients in the RSICU during each of the 11 cycles. Total number of patients in each cycle is indicated. 17 patients acquired *Pseudomonas* pneumonia during the placebo cycles and 3 acquired *Pseudomonas* during the polymyxin cycle ($\chi^2 = 10.2, P < 0.01$).

tients began in the polymyxin-cycles and overlapped into a placebo period. Six patients in the placebo cycles acquired pneumonia and then overlapped into polymyxin cycles. Three of these pneumonias were due to *P. aeruginosa*, two were due to *Proteus* species, and one was due to *Serratia* species. Only two patients began in the RSICU in polymyxin cycles, developed pneumonia, and then completed their RSICU stays in placebo cycles. One of these two patients had a *P. aeruginosa* pneumonia, and the other pneumonia was due to *Proteus* species. No patient was free of pneumonia in the first cycle and then developed pneumonia in the next cycle. Thus with all cycle-overlapping patients excluded, 14 patients acquired *P. aeruginosa* pneumonias during the placebo periods, and two acquired *P. aeruginosa* pneumonias during the polymyxin periods ($\chi^2 = 9.3$, $P < 0.01$).

DISCUSSION

Patients in the RSICU were placed on alternating polymyxin-placebo aerosol treatments to determine if the incidence of gram-negative bacillary pneumonia is reduced by polymyxin. Such aerosol treatment with polymyxin B has previously been shown not to contaminate the culture media so as to inhibit the growth of viable organisms deposited in the plate (13). There is therefore no diminution in the ability to culture existing polymyxin B sensitive gram-negative bacilli after such treatment. As shown by other studies (21), inhibition of gram-negative bacteria by commensal flora in the respiratory tract has been presumed to be a factor in the determination of colonization. The majority of patients entering the RSICU, however, had recent prior antibiotic administration and consequently showed little "normal flora" on their original plates. We thus concluded that interbacterial inhibition would not play a significant role in this study.

The sinks used for handwashing continued to undergo a daily sterilization program throughout this study. They were previously identified as the only known reservoir of *Pseudomonas* within the RSICU (8), their drains being a source of pyocine type 10 *P. aeruginosa*. This pyocine type previously accounted for 57.5% of the upper airway isolates acquired within the RSICU, while following sink sterilization, pyocine type 10 was responsible for only 10% of the acquired isolates. The diminished colonization by gram-negative bacilli of the upper respiratory tract has again been demonstrated in those patients receiving polymyxin aerosol, the incidence of *Pseudomonas* colonization being 9.7% in the placebo cycles vs. 1.6% in the polymyxin cycles ($\chi^2 = 23.2$, $P < 0.01$). Our initial concern that we would see a large increase in the number of patients colonized with polymyxin-resistant organisms was unfounded during

the use of alternating polymyxin and normal saline placebo cycles. Of particular concern to us was the possibility that patients might become colonized with staphylococci, *Proteus* species, *Serratia* species, or other resistant organisms during a polymyxin cycle only to develop pneumonia during a subsequent placebo cycle. Analysis of the overlapping patients showed that this infection pattern did not occur to any significant extent. Cycle-overlapping patients were not at greater risk of developing pneumonia than comparably sick patients in the placebo cycles. Overall conclusions about our study were not altered by excluding cycle-overlapping patients.

In a recent study using endotracheal gentamicin prophylaxis, some selection of resistant organisms occurred. In particular, gentamicin-resistant *Providencia* strains emerged (15). During the use of polymyxin, there was an insignificant increase in colonization of *Serratia* species and *Proteus* species of 2.5% and an increase in colonization with *Flavobacterium* species of 1.5%, while only one additional patient was colonized with *S. aureus*. It is possible that having used such antibiotics prophylactically in an alternating manner with a placebo, we were able to minimize colonization with resistant organisms.

Despite the significant decrease in *Pseudomonas* pneumonia acquired within the RSICU, we were unable to demonstrate any effect on the overall mortality. 12.2% of the patients (45) died during placebo cycles and 12.0% (45) during the polymyxin cycles. That the equality in overall mortality rates is to some extent due to the difference in mortality of *Pseudomonas* pneumonia acquired in the RSICU during placebo vs. polymyxin cycles should be considered. Two of the three patients acquiring *Pseudomonas* pneumonia died during the use of polymyxin prophylaxis, while 4 of the 17 patients (24%) acquiring *Pseudomonas* pneumonia died in the placebo group (NS). That three patients acquired *Pseudomonas* pneumonia during polymyxin prophylaxis and that two of them died may be a reflection of their degree of illness. One of these patients was hospitalized with a large intracerebral hemorrhage and renal failure; he succumbed to a cardiac arrest following an acute tension pneumothorax. The other death occurred in an elderly man following massive peritonitis and shock. Both patients required mechanical controlled ventilation; the neurosurgical patient, in addition, required positive end-expiratory pressure.

In addition to the *Pseudomonas* pneumonia acquired by patients while in the RSICU, there were 13 cases of acquired pneumonia during the placebo cycles and 15 cases during the polymyxin cycles of etiology other than *P. aeruginosa* (Table II). The most striking difference in acquired pneumonias other than those due to *Pseudomonas* were the five cases of *S. aureus* pneumonia

during the polymyxin cycles and two cases during the placebo cycles (NS). The mortality rate for patients with pneumonia was 30.4% vs. the 12.1%. Pneumonia was a diagnosis in 18.1% of the 744 patients in the study, and 35.5% of the pneumonias were acquired while the patients were in the RSICU.

At present we are encouraged that the incidence of *Pseudomonas* pneumonia acquired within the intensive care setting can be reduced by the techniques we have employed. We are continuing our efforts to reduce the incidence of nosocomial pneumonias and the evaluation of uninterrupted polymyxin prophylaxis.

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