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MINIREVIEW

Prevention of Hospital-Acquired Pneumonia in Critically Ill Patients

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Hospital-acquired pneumonia causes considerable morbidity and mortality and adds appreciably to the costs of health care (40, 69). Pneumonia accounts for approximately 10 to 15% of hospital-acquired infections, and mortality rates range from 15 to 50% (5, 24, 37, 40, 69), although the rates of mortality directly attributable to pneumonia may be lower (40). Facultative gram-negative bacilli are isolated in 40 to 60% of these infections (5, 9, 12, 24, 37). Risk factors for colonization and infection of the respiratory tract by facultative gram-negative rods include intubation and tracheostomy, severe underlying disease, especially chronic lung disease, prolonged hospitalization, prior aspiration of gastric contents, and exposure to antibiotics (5, 12, 18, 30, 42, 59, 69).

Since gram-negative bacilli account for a major portion of isolates in hospital-acquired pneumonia, efforts to prevent this infection have focused on the elimination of these pathogens. These efforts have been aimed at the elimination of exogenous sources of gram-negative organisms by encouraging regular hand washing by health care workers, the use of aseptic techniques for tracheal suction, and the sterilization of respiratory equipment (37). Although these efforts have had an impact, nosocomial pneumonia remains a major problem. Recently, the focus of intervention has shifted from exogenous sources to the patient's fecal flora as a potential source of gram-negative bacilli that may colonize the nasopharynx and cause pneumonia. This shift has led to renewed interest in the use of topical and systemic antimicrobial prophylaxis to prevent pneumonia.

The purpose of this review is to examine the assumptions that underlie the use of antimicrobial prophylaxis to prevent nosocomial pneumonia and to review the results of comparative studies in terms of the efficacy and risks of prophylaxis. The lack of a "gold standard" for the diagnosis of hospital-acquired pneumonia as well as variability in the definition of nosocomial pneumonia makes a comparative analysis of prophylaxis studies difficult. Differences in the patient populations studied provide a source of sample bias that makes generalization of the study results problematic. The focus of this review will be on critically ill or high-risk patients, i.e., patients requiring intensive care unit (ICU) admission and, frequently, mechanical ventilation, because these patients have been the most carefully studied population. Neutropenic patients, who constitute a separate risk group, will not be considered here.

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PATHOGENESIS OF NOSOCOMIAL PNEUMONIA

Infection of the lower respiratory tract of hospitalized patients by facultative gram-negative organisms is usually preceded by colonization of the oropharynx or stomach (2, 8, 14, 28, 30, 43, 52, 59, 68). The prevalence of oropharyngeal colonization by gram-negative bacilli in nonhospitalized healthy people ranges from 2 to 9% (29, 64) but was as high as 18% in one study (49). The rate among hospitalized patients is much higher (29, 39, 64) and is closely correlated with the intensity of patient care and the severity of the underlying illness of the patient (29, 64). For example, in one study, 22% of patients were colonized by gram-negative bacilli on admission to the ICU, and 45% were colonized after 4 days of residence in the ICU (29). Colonization is probably favored by the systemic administration of antibiotics but occurs even without this provocation (29, 39).

It is unclear what proportion of gram-negative bacilli that colonize the oropharynx and the trachea arise from exogenous sources as opposed to the patient's own intestinal flora (14, 43, 68). It is also not known whether organisms that originate in the fecal flora reach the oropharynx primarily by being carried externally from the perianal area to the mouth or by migrating retrograde up the gastrointestinal tract. For example, Du Moulin et al. found that the gram-negative pathogens isolated from the trachea of patients with hospital-acquired pneumonia were the same as those found in the stomach and inferred that gastric colonization with gram-negative bacilli was a prerequisite for the development of pneumonia (via aspiration), even though the trachea was colonized before the stomach in some of their patients (14). However, they did not culture the oropharynx, which could have been the proximate source of bacteria found both in the stomach and in the trachea. A study of enteral nutrition in mechanically ventilated patients that evaluated simultaneous cultures of the oropharynx, stomach, and trachea found that tracheal colonization was equally likely to be preceded by oropharyngeal colonization as by gastric colonization (44). A recent study of mechanically ventilated patients with nasogastric tubes used a technetium-99m–sulfur colloid to quantitate the aspiration of gastric contents into the trachea (60). Subjects in the supine position had higher mean radioactive counts in endobronchial secretions than subjects who remained semirecumbent, and aspiration increased with time in both groups. The same microorganisms were isolated from the trachea, pharynx, and stomach in 68% of the supine patients as opposed to only 32% of the semirecumbent patients. While this study showed that the aspiration of gastric contents into the upper airway of mechanically ventilated patients with nasogastric tubes readily occurs, especially in the supine position, the aspiration of oropha-

ryngeal contents into the trachea may occur as well. Indeed, another study of patients admitted to an ICU found a strong correlation between oropharyngeal and tracheal floras (68). The authors inferred that colonization of the oropharynx preceded colonization of the trachea. Surveillance cultures of the stomach were not done, so the role of this organ cannot be determined. Reusser and colleagues concluded that the stomach was the source of infection in only 1 of 15 intubated patients who acquired pneumonia in the hospital (47). Although gastric colonization was common, it did not appear to be a significant risk factor for tracheal colonization or pneumonia. Rodriguez-Roldan and colleagues reported that pharyngeal or tracheal colonization preceded gastric colonization in six of seven patients not given antimicrobial prophylaxis (48).

In summary, the majority of the studies suggest that although oropharyngeal colonization often precedes gastric colonization, the reverse may also occur. Moreover, the sequence of events may differ in different populations. For example, it may be important that Du Moulin et al. (14) studied older patients who had respiratory failure and were admitted to a respiratory-surgical ICU, whereas Reusser et al. (47) were dealing with young patients who had undergone neurosurgical operations. Given the continuity of the upper intestinal and respiratory tracts, it will be necessary to sample the floras of the oropharynx, trachea, and stomach simultaneously and often to elucidate the various sequences of events. It appears likely that the results will be influenced by many risk factors, including endotracheal intubation or tracheostomy, nasogastric feeding, the usual position of the patient, the age of the patient, and the administration of antibiotics by various routes.

ROLE OF GASTRIC ACIDITY

Physicians who have focused attention on the stomach as a potential source of organisms colonizing the respiratory tract have emphasized the role of stomach acid and intestinal motility in preventing bacterial colonization or overgrowth (53). An in vitro study of the bactericidal activity of hydrochloric acid found that whereas enteric diarrheal pathogens were highly sensitive to a low pH, *Escherichia coli* and *Staphylococcus aureus* were relatively resistant (50). Nevertheless, alkalinization of the stomach rapidly leads to colonization with coliform bacteria, especially when the pH is higher than 2.5 (11, 14, 20, 28, 51, 60). A recent study of mechanically ventilated ICU patients found a significantly higher rate of gastric colonization with gram-negative bacilli in subjects treated with an H_2 receptor blocker than in those who received sucralfate (15). An increase in gram-negative colonization correlated well with the higher pHs found in the group receiving H_2 receptor blockers.

The common practice of alkalinizing the stomach contents of patients in ICUs by means of antacids or H_2 receptor blockers to prevent stress ulcers could, at least theoretically, foster gastric colonization by gram-negative bacilli, which in turn could predispose the patients to pneumonia caused by aspiration of these organisms. In a well-done, prospective, randomized study of mechanically ventilated patients, Driks and coauthors found a lower rate of pneumonia ($P = 0.11$) and a lower mortality rate ($P = 0.07$) in patients treated with sucralfate, an agent that does not appreciably reduce gastric acidity, than in the combined group of patients treated with antacids, H_2 receptor blockers, or both agents (13). Paradoxically, the lowest rate of pneumonia was found for the subgroup given H_2 receptor blockers alone (5.9 versus 11.5% for those given sucralfate). The authors suggest that this finding may have been due to selection bias, as the subgroup of patients given H_2 receptor blockers alone may have been less severely ill than the other patients. A further confounding feature is that a higher proportion of patients receiving H_2 receptor blockers or antacids or both than sucralfate had tracheostomies done during the study and had nasogastric tubes. Both of these characteristics could have predisposed the patients to pneumonia. Because of these issues, we do not believe that a clear interpretation of the study done by Driks et al. (13) can be made. Other studies of mechanically ventilated patients have found that patients who received H_2 receptor blockers for stress ulcer prophylaxis had a higher incidence of pneumonia than patients who received sucralfate (31, 45). A randomized study of mechanically ventilated patients that compared stress ulcer prophylaxis with antacids, ranitidine, and sucralfate found no difference in the incidence of early-onset (within 4 days of entry into the ICU) nosocomial pneumonia among the three groups (45). However, the incidence of late-onset pneumonia was significantly lower in patients who received sucralfate. It is clear that more studies of the incidence of hospital-acquired pneumonia in patients receiving sucralfate therapy versus H_2 receptor antagonist therapy need to be performed to help resolve the controversy regarding differences in the predisposition to pneumonia. It has been suggested that sucralfate has antibacterial activity in vitro (11, 61), but the clinical significance of this observation remains to be shown.

ANTIMICROBIAL PROPHYLAXIS OF NOSOCOMIAL PNEUMONIA

Whether the oropharynx or stomach is the source of organisms causing pneumonia in hospitalized patients, there is a possibility of preventing infections by the application of antibiotics either systemically or topically in the form of oral pastes, tracheal solutions, and suspensions to be swallowed. Several early studies examined this issue.

Early studies. Klastersky and colleagues administered a solution of gentamicin via an endotracheal catheter in a randomized double-blind study of neurosurgical patients with tracheostomies (33). The treated group had significantly fewer episodes of colonization by gram-negative bacilli and of infection of the respiratory tract than the placebo recipients. However, for six strains of bacteria isolated from the gentamicin-treated group, the MICs were higher than 6 μg/ml; this was true for only two strains from the placebo-treated group. In a subsequent study by the same group, gentamicin was compared with a combination of aminosidin (an aminoglycoside) and polymyxin B given as an endotracheal aerosol (32). The number of infections in the two groups was similar, but all strains causing infections in the gentamicin-treated group were resistant to gentamicin, whereas those causing infections in the other group did not show such a high rate of resistance to aminosidin or polymyxin B. The authors concluded that, although both regimens were equally efficacious, the aminoglycoside-polymyxin B regimen was a more useful alternative, as it was less likely to promote resistance.

Aerosolized polymyxin B was applied to the pharynx of critically ill patients to decrease pharyngeal and tracheal colonization with gram-negative bacilli (34). When alternating 8-week cycles of treatment with polymyxin B versus treatment with placebo were compared, there was a significant decrease in the incidence of pneumonia caused by *Pseudomonas aeruginosa* but no appreciable effect on mor-

tality with the former. However, continued usage of the prophylactic regimen resulted in a 74% rate of colonization of the upper respiratory tract by polymyxin B-resistant gram-negative bacilli (16).

Recent studies. Following the above-described reports, which showed a worrisome increase in the incidence of recovery of resistant organisms with the use of prophylactic antibiotics to prevent pneumonia in critically ill patients, efforts in this direction were suspended. Recently, however, there has been a resurgence of interest in this approach, especially by physicians specializing in critical care. To minimize of the development of resistance, combinations of drugs are being used, sometimes with an additional drug being given parenterally. In the choice of antibiotics, attention is being paid to the maintenance of "colonization resistance," i.e., the resistance to colonization by new species that appears to be conferred by the normal flora (66). Although colonization resistance is attributed by some to an effect of the anaerobic flora (22, 66, 67), the facultative flora may play an important role as well (3, 19, 27). Which component of the normal flora is most important in preserving colonization resistance in humans is unclear on the basis of limited data (3); however, because of their sheer numbers, anaerobic species may be the major contributors. In any event, the newer regimens have been chosen with the intent of sparing the anaerobic flora.

Tables 1 and 2 summarize prospective studies of antimicrobial prophylaxis for nosocomial pneumonia. All of the investigations involved topically applied drugs; those in Table 2 also involved a parenterally administered component. Cefotaxime was the parenterally administered agent, except in one study, in which trimethoprim was used (62). We found no studies in which treatment was given only by the parenteral route. Although in most of the studies patients were randomized to receive prophylaxis or no prophylaxis, a few trials evaluated control and treatment groups in a sequential or alternating fashion (17, 23, 26, 34, 35, 38). Only 8 of 17 trials were placebo controlled (6, 21, 23, 26, 33, 34, 46, 48); the placebo usually consisted of the vehicle for the topical formulation. We examined in Tables 1 and 2 the effect of prophylaxis on the incidence of colonization and infection, the need for antibiotics given therapeutically, and the mortality rate after entry into the study as well as the duration of hospitalization or ICU stay. We used the authors' own criteria for each measurement of outcome; these criteria differed somewhat from study to study. Few authors analyzed the power of their studies to detect a significant difference between control and prophylaxis groups (beta error), and few of the studies seem to have been large enough to detect a significant difference. The study by Gastinne et al. is a notable exception (21).

In all but two of the studies (21, 25) in Tables 1 and 2 from which data are available, there was a reduction in the incidence of colonization and infection in the group given antibiotics prophylactically compared with the incidence in the untreated group; the effects were statistically significant ($P < 0.05$ and usually $P < 0.01$) in all instances in which the P value was stated. We were not able to find any study in which prophylactic regimens with and without a parenterally administered component were compared. However, there was no obvious difference in efficacy between studies involving or not involving a systemically administered drug.

Although most of the studies that involved nonabsorbable orally administered drugs failed to show a clinically significant effect on infection caused by yeast species, there were two studies that did show a benefit (6, 62). Ulrich and associates found fewer infections caused by *Candida* species in the treatment group, which received oral amphotericin B, than in the control group (1 of 48 versus 7 of 52; P = 0.06 with a two-tailed test and $P = 0.04$ with a one-tailed test in our analysis with the chi-square test) (62). Cerra et al. used oral nystatin for their treatment group and found a statistically significant ($P = 0.025$) decrease in the total number of fungal infections (6). However, neither of these studies showed a significant impact of prophylactic antifungal therapy on the incidence of fungal pneumonia as opposed to all fungal infections.

In most studies, there was a decrease in the need for antibiotics given therapeutically. However, most reports did not examine total antibiotic usage, including drugs given prophylactically and therapeutically. In one report (Table 1) in which total antibiotic usage was evaluated, the mean cost for antibiotics was 2.2 times higher in the prophylaxis group (21). In another study (not shown in Tables 1 and 2), there was an increase in the overall amount of antibiotic used as well as the total cost of antibiotics in the treatment group compared with the placebo (control) group (36). A third study of the prevention of nosocomial infections in ICU patients by use of oropharyngeal and enteral colistin, tobramycin, and amphotericin B and parenteral cefotaxime during the first 3 days found that the average cost of prophylactic antibiotics was $500 per patient and that the cost of evaluating and treating secondary infections was higher in the prophylaxis group (25). The effect of prophylaxis on the total amount of antibiotic used is of great importance not only because it affects cost but also because it may be a major determinant of the development of antibiotic resistance.

Because there may be disagreement about the diagnosis of pneumonia and because subjective criteria may lead to biased evaluations, it is of interest to examine the effect of antibiotic prophylaxis on the death rate and the length of hospital stay, outcome measurements that are simple and objective. Although most studies evaluated overall mortality, some provided data on deaths directly attributable to nosocomial pneumonia (4, 17, 25, 26, 33, 58, 62). As indicated in Tables 1 and 2, in only one study, that of Ulrich et al. (62), was there a statistically significant decrease in mortality in the total group of patients given antibiotics prophylactically. Godard and associates found no beneficial effect of oral antimicrobial prophylaxis on survival in patients with ICU stays of less than 7 days, whereas there was a significant decrease in overall mortality in patients staying more than 7 days (23). The mortality of patients with mid-range simple acute physiological scores also was found to be significantly reduced. In the study by Ledingham and colleagues (38), there was a significant decrease in mortality with antibiotic prophylaxis in certain subgroups, including patients with mid-range APACHE-II scores, prolonged hospitalization, and acute trauma. Although Hammond et al. found lower rates of nosocomial infection in patients receiving prophylaxis and with mid-range APACHE-II scores, they did not find reduced mortality rates in this subgroup or in patients with trauma (25). However, in these three studies (23, 25, 38), the subgroups were evaluated by post hoc stratification, a form of retrospective analysis that raises the possibility of a chance occurrence. A recent meta-analysis of clinical studies that compared patients treated with selective decontamination with untreated controls failed to show a clear benefit with regard to mortality (65). Finally, in only one of seven studies that examined the effect of prophylaxis on the length of hospital or ICU stay was a reduction noted

TABLE 1. Prospective trials of nonparenteral antimicrobial prophylaxis of nosocomial pneumonia regimens

Study	Study size: no. of treated subjects; no of control subjects [study population][a]	Incidence of colonization	Incidence of infection	Systemic antibiotic use	Mortality	Length of hospital or ICU stay	Development of resistance	Type of prophylactic therapy; placebo
Klastersky et al. (33)	43; 42 (DB, CC) [neurosurgical; tracheostomy; ICU]	Decreased ($P < 0.01$)	Decreased ($P < 0.02$)	Decreased ($P < 0.01$)	Decreased (P value not significant)	No data	Increased (P value not stated)	Endotracheal gentamicin; endotracheal saline
Klick et al. (34)	374; 370 (SC, DB) [medical; surgical; ICU]	Decreased ($P < 0.01$)	Decreased ($P < 0.01$)	No data	No effect	No data	Increased (P value not significant)	Pharyngeal and tracheal polymyxin B; endotracheal saline
Unertl et al. (63)	19; 20 (CC) [neurosurgical; ICU]	Decreased ($P < 0.01$)	Decreased ($P < 0.01$)	Decreased ($P < 0.05$)	No effect	No effect	No effect	Oral, nasal, or nasogastric polymyxin B, gentamicin, and amphotericin B; none
Brun-Buisson et al. (4)	50; 36 (CC) [MICU]	Decreased ($P < 0.05$)	Decreased (P value not stated)	No effect	No effect	No data	Increased ($P = 0.02$)	Oral or nasogastric polymyxin E, neomycin, and nalidixic acid and oropharyngeal povidone-iodine; none
Flaherty et al. (17)	51; 56 (SC) [cardiothoracic; ICU]	Decreased ($P < 0.001$)	Decreased ($P < 0.02$)	Decreased (P value not stated)	No effect	No effect	No effect	Oropharyngeal, oral, or nasogastric polymyxin E, gentamicin, nystatin, H_2 receptor blockers, or antacids; sucralfate
Rodriguez-Roldan et al. (48)	13; 15 (CC, DB) [ICU]	Decreased (P value not stated)	Decreased ($P < 0.001$)	No effect	No effect	No data	No effect	Oropharyngeal and oral or nasogastric polymyxin E, tobramycin or netilimicin, and amphotericin B; nonabsorbable paste
Pugin et al. (46)	25; 27 (CC, DB) [SICU]	Decreased ($P < 0.0001$)	Decreased ($P < 0.0001$)	Decreased ($P = 0.03$)	No effect	No data	No effect	Oropharyngeal and oral polymyxin B, neomycin, and vancomycin; 5% glucose
Godard et al. (23)	97; 84 (CC, SW) [ICU]	No data	Decreased ($P < 0.05$)	No effect	No effect overall[b]	No effect	No effect	Oral colistin and tobramycin[c]; nonabsorbable paste
Cerra et al. (6)	25; 21 (CC, DB) [SICU]	No data	Decreased ($P = 0.025$)	No effect	No effect	Decreased (P value not significant)	No effect	Oral nystatin and norfloxacin; cherry syrup solution
Gastinne et al. (21)	220; 225 (CC, DB) [MICU]	No data	No effect	Decreased (P value not significant)	No effect	No effect	No data	Oropharyngeal, nasal, and nasogastric colistin, tobramycin, and amphotericin B; nonabsorbable paste

[a] CC, concurrent control group (randomized); SC, sequential treatment and control groups; DB, double blind; SW, separate wards for concurrent control and treatment groups (crossover design); MICU, medical intensive care unit; SICU, surgical intensive care unit.
[b] Treated patients who remained in the ICU for more than 7 days had significantly lower mortality rates than controls ($P < 0.05$).
[c] Both control and prophylaxis groups were given amphotericin B orally.

TABLE 2. Prospective trials of parenteral antimicrobial prophylaxis of nosocomial pneumonia[a]

Study	Study size: no. of treated subjects; no. of control subjects [study population][b]	Incidence of colonization	Incidence of infection	Systemic antibiotic use[c]	Mortality	Length of hospital or ICU stay	Development of resistance	Type of prophylactic therapy; placebo
Ledingham et al. (38)	163; 161 (SC) [MICU, SICU, trauma]	Decreased (*P* value not stated)	Decreased ($P = 0.006$)	Decreased *P* value not stated	No effect	No data	No effect	Topical, oral, and nasogastric polymyxin E, tobramycin, and amphotericin B; none
Tetteroo et al. (58)	56; 58 (CC) [SICU; postesophageal resection]	Decreased ($P < 0.01$)	Decreased ($P < 0.05$)	Decreased ($P = 0.013$)	No effect	No effect	No effect	Topical, oral, and nasogastric polymyxin E, tobramycin, and amphotericin B; none
Aerdts et al. (1)	17; 39 (CC)[d] [ICU]	Decreased ($P < 0.001$)	Decreased (*P* value not stated)	Decreased ($P < 0.001$)	No data	No data	No effect	Oral and nasogastric norfloxacin, polymyxin E, and amphotericin B; none
Konrad et al. (35)	82; 83 (SC) [SICU]	Decreased ($P < 0.001$)	Decreased ($P < 0.01$)	No data	No data	No data	Increased ($P < 0.05$)	Oropharyngeal and nasogastric polymyxin E, tobramycin, and amphotericin B; none
Hartenauer et al. (26)	99; 101 (CC, SW) [SICU]	Decreased ($P < 0.001$)	Decreased ($P < 0.001$)	No data	No effect	No data	No effect	Oropharyngeal and nasogastric or oral polymyxin E, tobramycin, and amphotericin B; nonabsorbable paste[e]
Ulrich et al. (62)	48; 52 (CC) [ICU]	Decreased (*P* value not stated)	Decreased ($P < 0.01$)	No effect	Decreased ($P < 0.02$)	No data	No effect	Oropharyngeal and nasogastric polymyxin E, norfloxacin, and amphotericin B; none
Hammond et al. (25)	114; 125 (DB, CC) [ICU]	Decreased (*P* value not stated)	No effect	No data	No effect	No effect	Increased ($P < 0.005$)	Oropharyngeal and oral or nasogastric colistin, tobramycin, and amphotericin B; nonabsorbable paste[e]

[a] All regimens included parenteral cefotaxime for the first 3 to 5 days, with the exception of the study by Ulrich et al., which used systemic trimethoprim (the route of administration was not stated).
[b] CC, concurrent control group (randomized); SC, sequential prophylaxis and control groups; SW, separate wards for concurrent control and treatment groups (crossover design); MICU, medical intensive care unit; SICU, surgical intensive care unit; DB, double blind.
[c] Does not include cefotaxime.
[d] Two control groups were pooled for the purpose of analysis.
[e] Both control and prophylaxis groups were given parenteral cefotaxime.

(6). Thus, in terms of the effect on mortality and hospital stay, which some might call "the bottom line," the evidence fails to show a beneficial effect of prophylaxis.

ANTIMICROBIAL RESISTANCE

The most obvious risk of the widespread application of antimicrobial prophylaxis, as was shown in the early studies noted above (16, 32–34), is the development of antimicrobial resistance. Although the development of resistance was searched for in all but one of the studies summarized in Tables 1 and 2, an increase was noted in only 5 of the 17 studies (4, 33–35). Thus, Klastersky and associates noted an increase in the number of gentamicin-resistant strains in patients given gentamicin prophylaxis (33), while Klick et al. found a slight increase in tracheal colonization with polymyxin B-resistant *Serratia* and *Proteus* species during cycles of prophylaxis with polymyxin B (34). Konrad and colleagues found a significant increase in the number of cefotaxime- and oxacillin-resistant staphylococci as well as cefotaxime-resistant members of the family *Enterobacteriaceae* during prophylaxis with cefotaxime (35). Hammond and associates also found a significant increase in colonization with methicillin-resistant *S. aureus* in their treatment group (25). One of the most impressive increases was in the study by Brun-Buisson et al. (4) (Table 1), in which topical polymyxin E, neomycin, and nalidixic acid as well as povidone-iodine was given to control an outbreak of infection by multiply-resistant members of the family *Enterobacteriaceae*. There was a marked reduction in colonization and infections caused by these species, but there was overgrowth in the fecal flora of species resistant to the decontamination regimen.

The emergence of resistance has also been noted in other studies, which are not shown in Tables 1 and 2 because they did not involve controlled comparisons. For example, Stoutenbeek et al., who administered a nonabsorbable paste of polymyxin E, tobramycin, and amphotericin B to the oropharynx and intestinal tract in combination with parenteral cefotaxime, found an excess of cefotaxime-resistant organisms in wound infections but not in pneumonia in treated patients (55, 57). However, in other studies by the same group (54, 56), there was no increase in the numbers of resistant organisms in patients given several agents for the prevention of nosocomial pneumonia. Recently, Nau et al. reported an increase in the prevalence of multiply-resistant staphylococci and gentamicin-resistant isolates of *Pseudomonas* species cultured from tracheal aspirates of intubated patients in units in which there was routine use of a prophylactic regimen of topical polymyxin E, gentamicin, and amphotericin B supplemented with parenteral cefuroxime (41). A recent review of the development of resistance during antimicrobial prophylaxis of nosocomial pneumonia described additional alarming data suggesting that selective decontamination is resulting in a steady increase in the rate of isolation of resistant organisms (10). The broad historic experience with this kind of problem in combination with the growing number of reports describing the development of resistance should lead to concern about the routine use of such methods for the prevention of hospital-acquired pneumonia.

CONCLUSIONS

Antimicrobial prophylaxis appears to have beneficial effects in reducing the incidence of nosocomial pneumonia in critically ill patients, although questions of observer bias in the diagnosis of pneumonia continue to pose a problem. The use of bronchoscopic techniques for the diagnosis of ventilator-associated pneumonia might help resolve this problem (7), although the utility of bronchoscopy in diagnosing nosocomial pneumonia remains controversial. Double-blind, placebo-controlled trials would seem to be the best solution. However, the use of an inactive vehicle for topical application as a placebo could theoretically predispose patients to infection by acting as foreign or occlusive material or by serving as a vector for the introduction of exogenous pathogens. A compromise would be for the control group to receive no topical agent, while the diagnosis of pneumonia would be made by a blinded observer. The results of studies in which a systemically administered antibiotic was added to a topical regimen do not appear to be superior to those of studies involving a topical regimen alone, but direct comparisons within the same study are not available. There is no evidence in most studies that prophylaxis decreases the mortality rate of patients in the ICU, shortens the length of hospital stay, or decreases the total amount of antibiotics needed. In fact, in three studies, the total amount of antibiotics, including drugs given for prophylaxis and treatment, was higher with routine prophylaxis; this fact could be important in the development of antimicrobial resistance. Although the development of antimicrobial resistance has so far been reported only episodically, experience shows us that this issue must be of major concern. Whereas the beneficial effects of antimicrobial prophylaxis, if any, would likely be seen immediately, effects on antimicrobial resistance would be expected to appear only with time.

Weighing the risks and benefits of antimicrobial prophylaxis to prevent pneumonia in critically ill patients, we conclude that routine clinical use of this practice should be discouraged but that further study is warranted; careful attention should be paid to the impact on mortality, hospital stay, the total amount of antibiotics used, and the emergence of antibiotic-resistant organisms. In addition, future studies should carry out a cost-benefit analysis, i.e., the savings that arise from the prevention of nosocomial pneumonia as opposed to the cost of the prophylactic treatment. Units in which antimicrobial prophylaxis is being used should be encouraged to report their experience with the development of resistant organisms. Pending clinical trials of efficacy, a simple measure that may be helpful is to encourage the use of the semirecumbent position, for patients able to tolerate it, rather than the supine position.

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ADDENDUM IN PROOF

Since this manuscript was accepted for publication, several relevant articles have appeared. One deals with the source of organisms causing nosocomial pneumonia, another is concerned with the efficacy of prophylaxis, and two relate to the development of antimicrobial resistance. Serial cultures of gastric aspirates taken during a trial of selective decontamination of the nasopharynx demonstrated a correlation between the organisms causing nosocomial pneumonia and those found in pharyngeal but not gastric cultures (A. E. Martinez-Pellus, J. Ruiz, J. Garcia, M. T. San Miguel, G. Seller, M. Bru, and C. Palazon, Intensive Care Med. **18**:218–221, 1992). Prophylaxis using oropharyngeal applications of gentamicin, polymyxin B, and nystatin and intravenous cefotaxime produced a significant reduction in the

incidence of bacteremia and pulmonary infections in treated versus control patients; treated patients also had a shorter stay in the hospital and intensive care unit and a lower mortality, but these differences were not statistically significant (F. R. Cockerill III, S. R. Muller, J. P. Anhalt, H. M. Marsh, M. B. Farnell, P. Mucha, D. J. Gillespie, D. M. Ilstrup, J. J. Larson-Keller, and R. L. Thompson, Ann. Intern. Med. **117**:545–553, 1992). Among 61 patients treated with oropharyngeal applications of tobramycin, colistin, and amphotericin B, 8 developed pneumonia caused by *Enterococcus faecalis* (M. J. Bonten, F. H. van Tiel, S. van der Geest, E. E. Stobberingh, and C. A. Gaillard, N. Engl. J. Med. **328**:209–210, 1993). A study of patients treated with intragastric instillations of gentamicin, polymyxin E, and amphotericin B found substantial increases of gentamicin resistance among gram-negative bacilli and staphylococci in gastric samples during the study (B. Misset, M. D. Kitzis, P. Mahe, G. Conscience, F. W. Goldstein, A. Fourrier, and J. Carlet, Infect. Control Hosp. Epidemiol. **14**:62–64, 1993).

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