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Antibiotic Treatment and Intestinal Colonization by *Pseudomonas aeruginosa* in Cancer Patients

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To determine whether antibiotic treatment increases the risk of colonization by *Pseudomonas aeruginosa*, we performed a case-control study comparing antibiotic exposure in cancer patients colonized by *P. aeruginosa* and in noncolonized controls. Of 88 patients, 76 had been exposed to at least one antibiotic, but colonization was not statistically associated with exposure to any specific antibiotic treatment, administered orally or parenterally, alone or in combination.

Intestinal colonization by *Pseudomonas aeruginosa* is the major harbinger of systemic infections caused by this microbial species in neutropenic patients with hematological malignancies (14, 15, 17). The risk of systemic infection caused by *P. aeruginosa* is low in patients who are not colonized (17). In contrast, bacteremia may develop in 40 to 70% of patients whose intestinal tracts are colonized by *P. aeruginosa* (13, 16). The mortality associated with *P. aeruginosa* infections in neutropenic patients is high (4) and is higher when initiation of appropriate therapy is delayed (4).

P. aeruginosa is detected in the indigenous intestinal floras of only 10% of normal humans (8), and the intestinal floras of healthy noncolonized subjects resist colonization by exogenous strains of *P. aeruginosa* when the inoculum is lower than 10^6 living organisms (6). Whether the resistance of the intestine to colonization is due mainly to anaerobes and their products (9) remains controversial (3). In normal subjects, ingestion of lower counts of *P. aeruginosa*, such as those found in food (13), can, however, result in colonization after treatment with ampicillin (6). It has also been shown in experimental animal models that resistance to colonization by *P. aeruginosa* can be modified to various extents by erythromycin (1), streptomycin (10), or norfloxacin (11).

Patients with acute leukemia often receive multiple-antibiotic therapy during the neutropenic periods which follow chemotherapy. It could therefore be hypothesized that intestinal colonization by *P. aeruginosa* is more frequent in these patients. One report suggests, however, that in hospitalized patients with prolonged neutropenia, intestinal colonization by *P. aeruginosa* often occurs before antibiotics are used (19). To determine whether antibiotic treatment is associated with an increased risk of colonization by *P. aeruginosa* in cancer patients, we performed a case-control study in a hematology-oncology unit comparing antibiotic exposure in patients colonized by *P. aeruginosa* and in noncolonized matched controls.

We studied retrospectively all the patients hospitalized in an 18-bed hematology-oncology unit between 1 April 1980 and 30 June 1985. During that period, intestinal colonization by *P. aeruginosa* was detected once or twice a week by plating 0.1 ml of a 1:100 dilution of a fecal specimen on Cetrimide agar (Diagnostic Pasteur, Paris, France) incubated for 48 h at 37°C. Urine specimens and oropharyngeal swabs were also obtained for surveillance cultures and plated on Cetrimide agar. At least three blood samples were obtained for culture at the onset of all febrile episodes (over 38°C for 6 h or more). Ten milliliters of blood was incubated in brain heart infusion broth flasks ventilated on arrival in the laboratory and cultured every other day (BCP slide; F. Hoffmann-La Roche, Basel, Switzerland). All isolates of *P. aeruginosa* were identified by conventional techniques, and serotypes were determined with a commercially available antiserum (Diagnostic Pasteur). Susceptibility to carbenicillin, cefsulodin, ceftazidime, gentamicin, and amikacin was determined by disk diffusion technique (Diagnostic Pasteur).

Case patients were defined as patients with one or more stool cultures positive for *P. aeruginosa* and who were hospitalized for at least 10 days before passing the first positive fecal specimen. The surveillance period for a case patient was defined as the time between admission in the hospital and the day when the first fecal specimen positive for *P. aeruginosa* was passed. Two control patients who had not had any stool culture positive for *P. aeruginosa* and who had been hospitalized for a period at least as long as the surveillance period of the case were matched with each case patient on the basis of primary diagnosis, duration of surveillance, and number of surveillance stool cultures performed during the surveillance period. For the control patients, the surveillance period was defined as starting on the day of admission and ending after a number of days equal to that of the surveillance period of the matched case patient. Clinical charts and microbiological data of both case and control patients were reviewed throughout the surveillance periods.

Data were managed and checked by the PIGAS System (18) and analyzed as described previously (5).

In all, 2,936 fecal specimens from 270 patients were analyzed during the study period. *P. aeruginosa* was detected in 85 individual patients. Thirty-one of these patients had been hospitalized at least 10 days before *P. aeruginosa* was detected in their feces (1980, 3 patients; 1981, 5 patients; 1982, 7 patients; 1983, 5 patients; 1984, 11 patients). In 17 patients, the serotype of the colonizing strain was identified. It was type 12 for 4 patients; types 3, 4, 6, and 11 for 3 patients each; and type 10 for 1 patient. Of the 31 isolated strains, 38% were resistant to carbenicillin, 28% to cefsulo-

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TABLE 1. Characteristics of patients colonized by *P. aeruginosa* and of noncolonized matched controls

Characteristic	Value for patient group	
	Case	Control
No. of subjects	31	57
Sex (% male)	65	72
Age in yr (% of patients)		
<15	13	30
15–29	39	44
>29	48	26
Presence of neutropenia[a] (% of patients)	71	67
Length (days)	8.5	6.6
SD	5.8	4.1
Fecal culture (no. analyzed)		
Mean	6.4	6.6
Range	1–7	1–9
Counts of *P. aeruginosa* (log CFU/g of feces)		
Mean	5.1	<3.0
SD	1.2	
Oropharynx or urine culture positive for *P. aeruginosa* (no. of patients)	3[b]	1[c]
Bacteremia[d] (no. of patients)		
P. aeruginosa	5	1
Other gram-negative bacilli	1[e]	7[f]
Gram-positive cocci	5[g]	4[h]
Bacteroides sp.	1	1

[a] Fewer than 100 leukocytes per mm^3 of peripheral blood.
[b] Oropharynx, two patients; urine, one patient.
[c] Urine, one patient
[d] Occurring during the hospital stay which included the surveillance period.
[e] *Escherichia coli*, one patient.
[f] *E. coli*, six patients; *Enterobacter cloacae*, one patient.
[g] *Streptococcus* sp., three patients; *Staphylococcus aureus*, one patient; *Staphylococcus epidermidis*, one patient.
[h] *Streptococcus* sp., two patients; *S. aureus*, one patient; *S. epidermidis*, one patient.

din, 0% to ceftazidime, 28% to gentamicin, and 3% to amikacin. Underlying diseases were acute lymphocytic leukemia in 8 case patients, acute nonlymphocytic leukemia in 17 case patients, lymphoma in 5 case patients, and solid tumor in 1 case patient. Two matched controls were identified for 26 of the 31 case patients. For each of the other five case patients, only one control patient was found. Characteristics of case and control groups are given in Table 1. No significant differences were found between cases and controls for any of the characteristics studied.

We found that 86% of our patients (76 of 88) were exposed to at least one antibiotic during the surveillance period. However, we were not able to find any statistically significant difference in exposure to antibiotics between the case patients colonized by *P. aeruginosa* and the noncolonized controls (Table 2).

Our results show that no single or multiple, oral or parenteral, specific or nonspecific antibiotic treatment was a major risk factor for intestinal colonization by *P. aeruginosa* in hospitalized cancer patients. This is in contrast to our previous finding, also obtained by case-control analysis, that intestinal colonization by strains of the family *Enterobacteriaceae* highly resistant to erythromycin (2) or resistant to cefotaxime (12) was significantly associated with previous exposure to the corresponding antibiotic. These contrasting results on the role of previous antibiotic treatment in intestinal colonization by *P. aeruginosa* and by antibiotic-resistant *Enterobacteriaceae* are in full agreement with those

TABLE 2. Antibiotic exposure in patients colonized by *P. aeruginosa* and in matched controls

Treatment	Case patients (n = 31)		Control patients (n = 57)	
	% Exposed	Mean days of exposure (SD)[a]	% Exposed	Mean days of exposure (SD)[a]
Oral				
Polymyxin B	6	3 (NC[b])	2	7 (NC)
Penicillin	10	4.3 (4.0)	7	3 (1.6)
Macrolide	36	15.4 (10.2)	49	15.4 (10.0)
Others		14.5 (19.1)		8.8 (4.8)
Parenteral				
Penicillin	3	3 (NC)	10	4.5 (2.7)
Carboxyureidopenicillins	29	14.4 (12.7)	23	11.0 (9.2)
Narrow-spectrum cephalosporins	3	2 (NC)	4	4 (2.8)
Cefotaxime	65	7.9 (4.8)	58	12.9 (10.0)
Cefsulodin	16	2.4 (1.5)	5	6.7 (4.9)
Other broad-spectrum cephalosporins	3	10 (NC)	3	23 (31)
Aminoglycosides	81	12.9 (10.3)	75	13.6 (10.7)
Vancomycin	39	12.0 (10.9)	30	12.4 (10.8)
Other	23	8.7 (8.2)	5	8.3 (2.1)
Any antibiotic	90	14.2 (10.2)	84	17.3 (11.7)

[a] Calculated from the patients exposed (excluding unexposed patients).
[b] NC, Not calculated (number too small).

obtained in a prospective study (19) on antibiotic-resistant bacteria in surveillance stool cultures of patients with prolonged neutropenia. It has been recently shown that fecal counts of antibiotic-resistant members of the family *Enterobacteriaceae* were sharply lower in subjects receiving sterile food than in those taking a normal diet (7). Therefore, intestinal colonization by antibiotic-resistant strains of *Enterobacteriaceae* apparently results from the combined effects of ingestion of contaminated food and antibiotic exposure, whereas ingestion of contaminated food alone (13) might be sufficient to induce colonization by *P. aeruginosa* in hospitalized patients.

This lack of a significant relationship between intestinal colonization by *P. aeruginosa* and previous antibiotic treatment in hospitalized patients also suggests that care should be taken when transposing to clinical situations experimental data on the effects of antibiotics on colonization resistance obtained in laboratory animal models.

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