

## Nosocomial Infection with Gentamicin-Carbenicillin-Resistant *Pseudomonas aeruginosa*

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*Pseudomonas aeruginosa* resistant to both gentamicin and carbenicillin was isolated with increasing frequency at the Cincinnati Veterans Administration Hospital during the period 1971 to 1974. A comparison of patients from whom *P. aeruginosa* was isolated during this period failed to reveal any significant clinical differences between the patients colonized or infected with resistant organisms and those colonized or infected with susceptible organisms. Overt clinical infection attributable to either organism was rare. The antibiotic-resistant organisms were isolated most frequently from urine. Isolation of the antibiotic-resistant organisms was more frequent from patients who had previously received gentamicin.

Recent reports in both the clinical and microbiological literature have described *Pseudomonas aeruginosa* strains resistant to both carbenicillin and gentamicin (2, 8, 9). Organisms with this resistance pattern have been isolated with increasing frequency at the Cincinnati Veterans Administration Hospital over the past several years. Previous reports from this institution have established that the antibiotic resistance of these strains of *P. aeruginosa* was R-factor mediated and that the responsible R-factor was of the P-2 group (10, 11). It has also been shown that the majority of these antibiotic-resistant organisms belonged to immunotype 7. Furthermore, this R-factor did not influence the organism as to immunotype, pyocin type, or virulence in rats and, although it readily transferred resistance to other *P. aeruginosa*, it did not transfer resistance to *Escherichia coli* or to *Proteus* species (10, 15). Since our clinical impression and reports of others (8) suggested that the resistant organisms rarely caused infection, a study was undertaken to determine the clinical significance of the isolation of resistant organisms as compared with the isolation of susceptible organisms.

### MATERIALS AND METHODS

Susceptibility patterns of *P. aeruginosa* isolates at the Cincinnati Veterans Administration Hospital were determined by a disk diffusion method (1). Isolates obtained during December 1971, March, June, September, and December 1972 and 1973, and

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January and March 1974 were reviewed, and the incidence of gentamicin- and carbenicillin-resistant isolates of *P. aeruginosa* (G<sup>R</sup>C<sup>R</sup>) was determined. Clinical records of patients from whom *P. aeruginosa* was isolated during December 1972, June 1973, and January 1974 were analyzed in depth, with particular reference to the clinical significance of the isolation of *P. aeruginosa* and its role in causing infection. Parameters that were studied included the source of the bacterial isolate, the presence or absence of a urinary tract foreign body and/or urinary tract obstruction, the presence or absence of underlying diseases, and the administration of antibiotics in the 7 days prior to the isolation of *P. aeruginosa*. The number of patients with leukopenia, who were immunosuppressed either by therapy or by virtue of their underlying diseases, was also recorded. The presence of fever, in addition to either chills, leukocytosis, or signs of infection at the anatomical site of isolation (e.g., pyuria and purulent drainage), was considered evidence of infection. The isolation of *P. aeruginosa* without clinical evidence of infection at the site of isolation was considered to represent bacterial colonization. The 3 months used for in-depth analysis were chosen as representative of months of low, intermediate, and high frequency of recovery of isolates of G<sup>R</sup>C<sup>R</sup> organisms. Statistical analysis was performed throughout, using the chi-square test with Yates correction.

### RESULTS

During the 11 months selected for study, *P. aeruginosa* was isolated 564 times from 535 patients. Eighty-five of the patients were infected or colonized with G<sup>R</sup>C<sup>R</sup>, and 450 were infected or colonized with *P. aeruginosa* that was susceptible to both gentamicin and carbenicillin (G<sup>S</sup>C<sup>S</sup>). Figure 1 demonstrates that both the

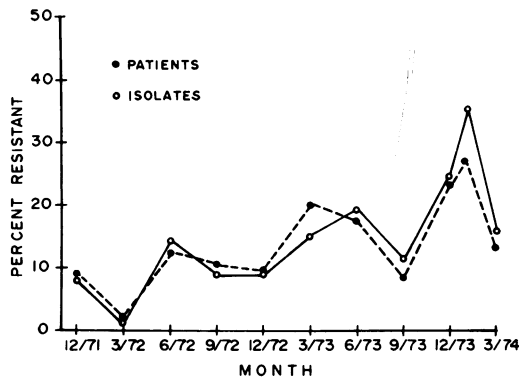


FIG. 1. Increasing incidence of isolation of antibiotic-resistant *P. aeruginosa* between 1971 and 1974. Symbols: ●, percentage of all patients from whom *P. aeruginosa* was isolated in whom the isolate was resistant *in vitro* to gentamicin and carbenicillin; ○, percentage of all *P. aeruginosa* isolates that were resistant *in vitro* to gentamicin and carbenicillin.

percentage of patients with G<sup>RCR</sup> and the percentage of all G<sup>RCR</sup> isolates increased from December 1971 through January 1974. Table 1 lists the medical services of the patients from whom the G<sup>RCR</sup> were isolated; most of these patients were located on the urology and medicine wards. A total of 79% of these organisms were isolated from the urine; in contrast, 40% of the 478 G<sup>SCS</sup> isolates were found in the urine. The increased frequency of isolation of G<sup>RCR</sup> organisms from urine cultures is statistically significant ( $P < 0.001$ ). A total of 7% of G<sup>RCR</sup> and 33% of G<sup>SCS</sup> were recovered from the sputum, which is again a statistically significant difference ( $P < 0.001$ ). The 289 urine cultures represented 51% of the 564 cultures, and 24% of the pseudomonas isolated from urine were of the G<sup>RCR</sup> resistance pattern. In contrast, only 3.5% of the 169 pseudomonas isolated from sputum had the G<sup>RCR</sup> pattern.

A review of the 106 clinical records of patients with *P. aeruginosa* isolates in December 1972, June 1973, and January 1974 revealed 78 patients from whom 115 G<sup>SCS</sup> were isolated and 28 from whom 51 G<sup>RCR</sup> were isolated (Table 2). There was no difference overall in the incidence of serious underlying disease in the two groups. Diabetes mellitus and hepatocellular disease were diagnosed with equal frequency in both groups, but there was significantly more renal disease among patients with G<sup>RCR</sup> ( $P < 0.001$ ). As with the large group of patients described above, G<sup>RCR</sup> was isolated significantly more often from the urine, and G<sup>SCS</sup> was isolated more often from the sputum. The presence of a

TABLE 1. Location of patients with *P. aeruginosa* isolates<sup>a</sup>

Service	Ward	No. of patients with <i>P. aeruginosa</i> isolates	No. of patients with G <sup>RCR</sup> isolates	Total (%)
Surgery	4S	51	9	10.5
Surgery	4N	39	5	5.9
Neurology/neurosurgery	5S	40	4	4.7
Urology	5N	90	19	22.4
Medicine	6S	106	18	21.2
Medicine	6N	88	17	20.0
Other		121	13	15.3

<sup>a</sup> Selected months: December 1971 to March 1974.

TABLE 2. Comparison of clinical findings in 106 patients with *P. aeruginosa* isolates

Clinical finding	Patients with G <sup>SCS</sup> (total = 78)	Patients with G <sup>RCR</sup> (total = 28)	P value <sup>a</sup>
Underlying disease	74	27	NS <sup>b</sup>
Diabetes mellitus	14	7	NS
Hepatocellular disease	4	1	NS
Renal disease	14	15	<0.001
Urinary isolation	32	22	<0.01
Sputum isolation	32	4	<0.05
Infection	9	2	NS
Colonization	31	6	NS
Other infection <sup>c</sup>	38	20	NS
Previous antibiotics	45	21	NS
Previous gentamicin	10	15	<0.001
Previous broad-spectrum antibiotics	25	6	NS

<sup>a</sup> Determined by the chi-square test with Yates correction.

<sup>b</sup> NS, Not statistically significant.

<sup>c</sup> The patient did have clinical infection, but *P. aeruginosa* was not the etiological agent.

urinary tract foreign body or obstruction, however, was no more commonly noted in patients infected or colonized with G<sup>RCR</sup>. There were six patients with clinical conditions that were considered to increase the risk of infection; three had hematological malignancy, one had generalized sarcoidosis, one was receiving prednisone, and one was leukopenic ( $<3,000/\text{mm}^3$ ). Two of the six were considered infected by *P. aeruginosa*, both with G<sup>SCS</sup> organisms. Two patients were colonized by G<sup>SCS</sup> and two were colonized by G<sup>RCR</sup> organisms.

An analysis of the clinical evidence for infection due to *P. aeruginosa* revealed that chills, fever, and leukocytosis occurred no more frequently in patients with G<sup>RCR</sup> than in patients with G<sup>SCS</sup>. When the patients with urinary isolates were considered, the incidence of pyu-

ria did not differ significantly between those with G<sup>R</sup>C<sup>R</sup> (19 of 22) and those with G<sup>S</sup>C<sup>S</sup> (23 of 32) organisms ( $P > 0.05$ ). Other localizing findings indicative of infection (wound drainage, pulmonary infiltrates, or pleural effusion) also occurred with equal frequency in both groups of patients.

Eleven patients were thought to be infected solely with *P. aeruginosa*, as evidenced by (i) the recovery of the organism from blood or a closed body cavity or (ii) the fact that *P. aeruginosa* was the only isolate in association with clinical signs of infection, and clinical improvement occurred after the institution of appropriate chemotherapy. Nine were infected with G<sup>S</sup>C<sup>S</sup>; two were infected with G<sup>R</sup>C<sup>R</sup>. This difference is not statistically significant. Only one of the 106 patients had *P. aeruginosa* bacteremia, and the isolate was susceptible to gentamicin and carbenicillin. An additional 58 patients (38 with G<sup>S</sup>C<sup>S</sup> and 20 with G<sup>R</sup>C<sup>R</sup>) had evidence of infection, but culture revealed multiple organisms, and a clinical response was attained with antibiotic therapy not specifically chosen to treat *P. aeruginosa* infection. The remaining 37 patients were considered colonized by *P. aeruginosa* since the isolation of the organism was not associated with signs of infection and antibiotic therapy was not instituted. There was no difference in the percentage of patients colonized by either G<sup>R</sup>C<sup>R</sup> or G<sup>S</sup>C<sup>S</sup>.

An analysis of the role of antibiotics in leading to infection or colonization revealed that 45 of 78 patients in the G<sup>S</sup>C<sup>S</sup> group and 21 of 28 patients in the G<sup>R</sup>C<sup>R</sup> group received antibiotics during the week before the isolation of the *P. aeruginosa*. This was not a significant difference ( $P > 0.1$ ). However, when the prior administration of gentamicin (either alone or in combination with other antimicrobials) was considered, a significant difference was found. Ten patients in the G<sup>S</sup>C<sup>S</sup> group of 78 and 15 patients in the G<sup>R</sup>C<sup>R</sup> group of 28 had received gentamicin ( $P < 0.001$ ). None of the patients whose charts were reviewed in detail had received carbenicillin prior to the isolation of *P. aeruginosa*.

## DISCUSSION

The widespread distribution of *P. aeruginosa* in a hospital environment is well recognized (3), and its potential to cause infection has been emphasized. Earlier reports of *P. aeruginosa* infections, however, dealt with infection occurring in patients with impaired defense mechanisms. Such patients included those with extensive burns, leukemia, Hodgkin's disease and other lymphomas, and patients with widespread

solid tumors who were receiving toxic antineoplastic agents (12, 14). Although reports in the recent literature have acknowledged the role of *P. aeruginosa* in nosocomial infections in general (4, 5), few have examined the extent of infection or colonization with antibiotic-susceptible or antibiotic-resistant *P. aeruginosa* in a general hospital, where only an occasional patient is immunosuppressed (7, 13). The 106 patients in this report did have underlying diseases, most frequently atherosclerotic heart disease, chronic pulmonary disease, and cerebrovascular or other neurological diseases. A few patients were in the postoperative period after abdominal surgery, and others had sustained second- and third-degree burns, but none had greater than 20% of the total body surface area involved. Only six patients could be considered immunosuppressed.

Despite an abundance of *P. aeruginosa* in the hospital environment (3), it can only rarely be directly incriminated as a cause of infection. One study of gentamicin- and carbenicillin-resistant strains of *P. aeruginosa* suggested that the antibiotic-resistant strains were less pathogenic than the antibiotic-susceptible strains (8). However, our investigation and another recent study (13) were unable to demonstrate either increased or decreased pathogenicity of the antibiotic-resistant strains.

When the records of 106 patients from whom *P. aeruginosa* had been isolated were reviewed, the only factor that significantly predisposed to the isolation of a gentamicin-carbenicillin-resistant strain was whether the patient had received parenteral gentamicin therapy during the 7-day period prior to the bacterial isolation. A higher percentage of the resistant isolates were recovered from the urinary tract, and a higher percentage of antibiotic-susceptible organisms were recovered from the respiratory tract. This probably does not represent any inherent difference between the two strains, but reflects the empiric administration of gentamicin in urinary tract infection. Possibly, the increasing prevalence of gentamicin-carbenicillin-resistant strains of *P. aeruginosa* during the study period is the result of the increasing usage of gentamicin (gentamicin usage at Cincinnati Veterans Administration Hospital doubled between 1971 and 1974) and the well-recognized phenomenon of antibiotic selection of hospital-acquired microbial flora (6).

There was no difference in the percentage of patients judged to be clinically infected by G<sup>R</sup>C<sup>R</sup> or G<sup>S</sup>C<sup>S</sup> pseudomonas. Both resistant and susceptible organisms were the sole cause of infection in 10% of the patients from whom pseudomonas was isolated. This finding corre-

lates with another clinical report (13) and with animal studies that revealed no difference in mortality in animals infected with G<sup>R</sup>C<sup>R</sup> versus G<sup>S</sup>C<sup>S</sup> organisms (15).

In summary, from 1971 to 1974 increasing numbers of *P. aeruginosa* resistant gentamicin and carbenicillin were isolated from patients at the Cincinnati Veterans Administration Hospital. The majority of the resistant organisms were isolated from the urinary tract, and the majority of patients from whom such organisms were isolated had received gentamicin alone or in combination with other antibiotics in the 7-day period prior to isolation. *P. aeruginosa*, both with and without the R-factor-mediated G<sup>R</sup>C<sup>R</sup> resistance pattern, rarely caused infection in this general hospital population.

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