

Association of Infection Caused by *Pseudomonas aeruginosa* Serotype O11 with Intravenous Abuse of Pentazocine Mixed with Tripelethamine

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From July 1979 to June 1983, 25 of 40 intravenous drug addicts with systemic infections had *Pseudomonas aeruginosa* as the etiological agent; by 1982, *P. aeruginosa* had replaced *Staphylococcus aureus* as the most common pathogen. At least 21 of the 25 addicts with *P. aeruginosa* infection abused pentazocine mixed with tripelethamine (commonly known as T's and blues) compared with 6 of 15 addicts infected with other pathogens ($P = 0.006$). Of the 25 *P. aeruginosa* isolates, 23 were of serotype O11. Phenotypic patterns in isolates from addicts and in 22 serotype O11 control isolates from nonaddicts were determined by pyocin and electrophoretic enzyme typing, as well as by susceptibility to heavy metals and antibiotics. Of 25 isolates from addicts, 20 were identical or differed by only one marker, whereas the 22 nonaddict serotype O11 isolates were distributed among 17 distinct phenotypic patterns. We postulate that the emergence of *P. aeruginosa* as the major cause of deep infection in addicts is a consequence of contamination of their paraphernalia during preparation of pentazocine and tripelethamine for self-injection. The phenotypic similarity among isolates from addicts may reflect acquisition from related environmental sources and an unusual ability of certain serotype O11 strains to survive preparation of the drugs or to be invasive.

Deep-seated infections, such as endocarditis, osteomyelitis, and septic arthritis, are well-known complications of intravenous drug abuse. The spectrum of causative organisms has varied geographically and temporally. Thus, for example, clusters of infection with *Serratia* spp., enterococci, group A streptococci, and methicillin-resistant *Staphylococcus aureus* have been reported among drug addicts in San Francisco, Cleveland, New York, and Detroit, respectively (12, 18, 19, 24).

In 1981, we noted a marked increase in the number of deep *Pseudomonas aeruginosa* infections in drug addicts admitted to Michael Reese Hospital, Chicago; over the next 2 years, this organism replaced *Staphylococcus aureus* as the major pathogen. This change prompted us to review the records of all addicts admitted in the last 4 years. We were particularly interested in a possible association between *P. aeruginosa* infection and intravenous abuse of dissolved tablets of pentazocine mixed with tablets of a blue-colored antihistamine, tripelethamine (commonly known as T's and blues), since abuse of this combination had increased recently in Chicago (10). Our review revealed that almost all *P. aeruginosa* recovered from addicts were serotype O11, suggesting the possibility of a common source of infection. To test this hypothesis, we cultured potential sources and examined multiple phenotypic characteristics among isolates of serogroup O11 recovered from addicts and nonaddicts treated at our hospital.

MATERIALS AND METHODS

Patients. Michael Reese Hospital is a 900-bed, acute-care facility serving both private and indigent patients. We reviewed the records of all drug addicts with deep-seated infections admitted from July 1979 through June 1983 and recorded the etiological organism, diagnosis, therapy, outcome, and type of drug addiction.

Cultures of addicts and paraphernalia. Swabs of the throat, rectum, and 10 skin surfaces (e.g., ears, axillae, groin) of three addicts with deep *Pseudomonas* infections were plated on cetrinide agar (Pseudoseal Agar; BBL Microbiology Systems, Cockeysville, Md.) and incubated in Trypticase soy broth (BBL) with 0.03% cetrinide.

Injection paraphernalia (six small containers, eight syringe parts, one needle, two needle shields, three cigarette filters, and nine miscellaneous objects) obtained from one infected addict were cultured. Cigarette filters were immersed in tryptic soy broth, with and without cetrinide, and subcultured onto tryptic soy agar and cetrinide agar. Interiors of syringe barrels and needles were rinsed with tryptic soy broth, which after overnight incubation at 35°C was subcultured onto tryptic soy agar and cetrinide agar. Medicine containers were flushed with sterile water to dissolve residues; portions were cultured in tryptic soy and cetrinide broth and agar. Other items were cultured by inoculating tryptic soy and cetrinide broth and agar with a moistened swab.

Two-liter water samples obtained from hot water taps in 21 locations in Chicago (including two homes of addicts) were cultured by passage through a 0.45- μ m filter (Millipore Corp., Bedford, Mass.), which was then incubated on MacConkey agar. Swabs of bathroom sink drains were also

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obtained at 19 of the 21 locations and cultured onto MacConkey and cetrinide agar.

Strains of *P. aeruginosa*. Isolates recovered from addicts and their paraphernalia were identified by standard methods and then stored at room temperature in either 2% salt agar or a 1/100 dilution of tryptic soy broth. For the present study, 22 of 81 isolates of serotype O11 recovered between July 1982 and January 1983 from patients that were not addicts were selected for analysis as controls.

Susceptibility to antibiotics and heavy metals. Susceptibility of isolates to carbenicillin, gentamicin, tobramycin, and amikacin was determined by the Kirby-Bauer disk method. Susceptibility to chlorhexidine (MIC $\leq 50 \mu\text{g/ml}$) was determined by an agar dilution method (22). High-level antibiotic resistance was sought by growth of a 10^4 - to 10^5 -CFU inoculum deposited in duplicate on Mueller-Hinton agar plates containing streptomycin (0.1 mg/ml), sulfadiazine (5 mg/ml), or tetracycline (0.1 mg/ml) and incubated at 37°C for 18 h (7, 8). Resistance to heavy metals (9, 23) was tested by growth on brain heart infusion agar containing mercuric chloride (10^{-3} M), phenylmercuric nitrate (10^{-4} M), potassium tellurite (10^{-3} M), cadmium nitrate (10^{-3} M), or sodium arsenate (10^{-3} M).

Pyocin typing. Tests for pyocin production were performed by a modification of the method described by Govan and Gillies (5), using their eight indicator strains. Isolates were grown overnight in tryptic soy broth at room temperature. Cotton-tipped applicators were used to smear a 2-cm-wide band of this suspension onto tryptic soy agar, which was incubated overnight at room temperature. After the macroscopic growth was removed, the remaining organisms were exposed to chloroform vapors for 30 min. The eight indicator strains, which had been grown overnight at room temperature in tryptic soy broth with 1% NaNO_3 , were diluted 1:20 and incubated at 37°C for 4 h. These suspensions were applied with a cotton swab perpendicular to the area of original growth and incubated at room temperature overnight. The inhibition of growth of each indicator strain by the test strain was recorded. Tests were performed at least twice; in 6% of the isolates, discordant results were obtained for two of the eight indicator strains.

Serotyping. Tests were performed with *P. aeruginosa* antisera (Difco Laboratories, Detroit, Mich.). The incidence of serotype O11 in isolates collected from nonaddict inpatients between July 1981 and June 1982 and from nonaddict outpatients between September 1982 and May 1983 was compared with that in strains from addicts.

Plasmid analysis. Plasmid isolation was attempted by several methods (1, 4, 7, 8, 14) on isolates from 15 addicts. Lysates of nine serotype O11 isolates from addicts were also examined for the presence of plasmids by George Jacoby, Massachusetts General Hospital, Boston, Mass.

Electrophoretic enzyme typing. The methodology of the electrophoretic enzyme typing approach to epidemiological tracing has been described previously (2, 13a, 20). Aqueous extracts obtained by sonication of cells grown overnight in 100 ml of tryptic soy broth at 37°C were examined by starch-gel electrophoresis to determine the relative electrophoretic mobilities of eight enzymes: esterase, xanthine dehydrogenase, glutamate dehydrogenase, catalase, glutamic oxalacetic transaminase, alcohol dehydrogenase, malate dehydrogenase, and phosphoglucose isomerase. All enzymes but alcohol dehydrogenase, malate dehydrogenase, and phosphoglucose isomerase were polymorphic (Table 1). Each unique profile of electromorphs (allozymes) for the five polymorphic enzymes was recognized as a distinctive elec-

TABLE 1. Electromorph profiles for 10 ETs of *P. aeruginosa* represented among 47 isolates from addicts and nonaddicts

ET designation	Anodal mobility value for the following enzymes ^a :				
	EST ^b	XDH	GLUDH	CAT	GOT
a	5	3	2	2	1
b	2	3	2	2	1
c	3	2	2	2	1
d	1	3	2	2	2
e	1	2	2	2	1
f	5	2	2	2	1
g	5	4	2	2	1
h	1	1	2	2	1
i	5	3	1	2	2
j	2	2	1	1	1

^a For each enzyme, electromorphs were numbered in order of decreasing anodal mobility. Abbreviations: EST, esterase; XDH, xanthine dehydrogenase; GLUDH, glutamate dehydrogenase; CAT, catalase; GOT, glutamic transaminase. Monomorphic enzymes: alcohol dehydrogenase, malate dehydrogenase, phosphoglucose isomerase.

^b Electromorph 4 of esterase was represented in isolates of *P. aeruginosa* not included in this study.

trophoretic type (ET), and the 10 ETs represented by the 47 isolates assayed were designated alphabetically in the order in which they were identified in the course of the analysis (Table 1).

Statistics. The chi-square or the Fisher exact test was used for frequency comparisons; the Wilcoxon sign-rank test was used for the analysis of continuous data.

RESULTS

From July 1979 to June 1983, 40 addicts were admitted with deep-seated infections. A total of 25 patients had *P. aeruginosa* infections; 15 patients had other pathogens (9 *S. aureus*, 4 alpha-streptococci, 1 *Candida* spp., 1 *Aspergillus* spp.). The diagnoses for the patients with *P. aeruginosa* infections included osteomyelitis (seven patients), septic arthritis (seven patients), right-sided endocarditis (seven patients), and left-sided endocarditis (four patients). The age range of the patients was 23 to 41 years; 8 patients were female and 17 were male. All patients responded to medical therapy with 4 to 12 weeks of an anti-*Pseudomonas* beta-lactam antibiotic and an aminoglycoside, except the four patients with left-sided endocarditis and three of the seven patients with right-sided endocarditis, who, in addition, required valve replacement or valvulotomy.

Emergence of *P. aeruginosa* as the predominant pathogen. In the period from July 1979 through December 1980, only 2 of 11 deep infections in addicts were due to *P. aeruginosa* (Fig. 1); in 1981, 12 of 15 infections were caused by *P. aeruginosa* and in 1982 to 1983, 11 of 14 infections were attributed to *P. aeruginosa* (for the three periods, $\chi^2 = 12.88$; $P < 0.001$).

Infection with *P. aeruginosa* occurred significantly more often in those addicts who abused pentazocine-tripelenamine ($P = 0.0007$; Table 2).

Phenotypic patterns. Of 25 *P. aeruginosa* isolates from addicts, 23 were serotype O11. The incidence of this serotype was much lower among *P. aeruginosa* isolates recovered from nonaddict inpatients (106 of 511; $P = 2.3 \times 10^{-13}$) or nonaddict outpatients (9 of 100; $P = 9.3 \times 10^{-16}$).

All isolates from addicts and control patients (Table 3) were resistant to sodium arsenate, cadmium nitrate, and chlorhexidine and susceptible to tetracycline (0.1 mg/ml). The reactions to other heavy metals and antibiotics varied and therefore were helpful in differentiating serotype O11

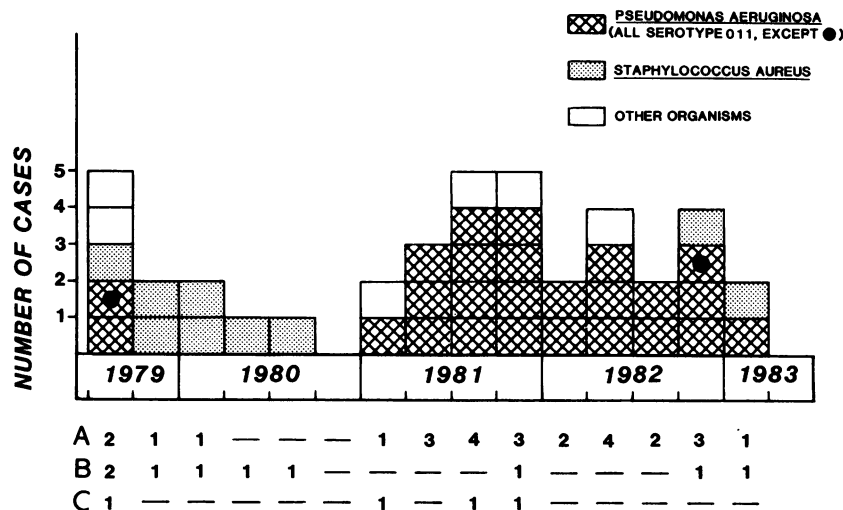


FIG. 1. Deep infections in addicts and type of drug abused by quarter from July 1979 to June 1983. Type of drug abused is shown below chart: A, pentazocine-tripelenamine; B, cocaine or heroin; C, unknown.

strains. Pyocin typing divided the O11 serotype into only two subgroups, whereas multiple enzyme electrophoresis revealed a total of 10 electrophoretic types (Table 1). Plasmids could not be demonstrated in any of the 15 serotype O11 isolates examined from addicts.

Based on the typing methods used, 13 of 25 isolates from addicts shared phenotypic pattern 1 (Table 3). This pattern occurred throughout the 4-year period. Seven other isolates from addicts differed from this common pattern by only one marker. In contrast, the 22 serotype O11 strains from nonaddicts were distributed among 17 different phenotypic patterns; 15 of 22 isolates from nonaddicts but only 5 of 25 isolates from addicts differed from the common addict pattern by two or more markers ($P = 0.001$).

Levels of phenotypic heterogeneity among serotype O11 isolates from addicts and nonaddicts were quantitatively compared by calculating diversity indices for each of the 11 phenotypic characters (Table 3). For each character, diversity was expressed as $1 - \sum x_i^2$, where x_i is the frequency of the i th character state (13). In all 11 characters, diversity was greater among the serotype O11 strains from nonaddicts than among those from addicts; mean values of diversity were 0.0941 for addicts and 0.3805 for nonaddicts (by the Wilcoxon sign-rank test; $T_S = 0$; $P < 0.001$).

Environmental and body surface cultures. Culture of a medicine bottle used for suspending drugs before injection

yielded isolates of *P. aeruginosa* serotype O11 that had the same common phenotype (pattern 1) that was recovered from the patient who had used the medicine bottle and from most other addicts. None of the other paraphernalia cultures; hot water samples; or body surface, throat, or rectal cultures from addict patients grew *P. aeruginosa*.

DISCUSSION

This report documents the recent emergence of *P. aeruginosa* as the major pathogen in deep infections among intravenous drug abusers seen at Michael Reese Hospital and demonstrates the association of *P. aeruginosa*, particularly serotype O11, with pentazocine-tripelenamine abuse. This is probably part of a city-wide and perhaps wider geographical trend. We examined isolates from four addicts admitted to Billings Hospitals, Chicago, located a few miles south of Michael Reese Hospital, and found that all were serotype O11; three isolates shared the common phenotype pattern 1 exhibited by most of our strains from addicts. Of the *P. aeruginosa* isolates obtained from addicts at Cook County Hospital, which serves Chicago's west side, 75% have been serotype O11 (K. R. Rajashekaraiyah, L. Bhatia, T. Rice, J. Kowalski, D. McCulley, and C. Kallick. Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami, Fla., abstr. no. 367, 1982). The experience in Chicago differs somewhat from that reported in Detroit, where *P. aeruginosa* became an important cause of endocarditis in addicts but *S. aureus* remained the most common pathogen (17). Nevertheless, 82% of *P. aeruginosa* isolates obtained from addicts in Detroit were immunotypes 1 and 2 (16), which correspond with serotypes O6 and O11, respectively; more recently, most isolates (9 of 10 tested) have been serotype O11 (M. Zervos, personal communication).

Unlike *S. aureus*, which probably comes from the addict's own flora, *P. aeruginosa* and other pathogenic gram-negative bacilli probably derive from the addict's environment (21). The absence of *P. aeruginosa* on the body surfaces of our addict patients, together with its recovery from injection paraphernalia, in our experience and that of others (15) is consistent with this view. Methods employed by our patients to prepare pentazocine-tripelenamine for injection provided ample opportunity for contamination by *P. aerugi-*

TABLE 2. Association of deep *P. aeruginosa* infection with pentazocine-tripelenamine abuse^a

Drugs abused	No. of patients with the following infecting organisms:	
	<i>P. aeruginosa</i>	Other ^b
Pentazocine-tripelenamine	21	6
Cocaine or heroin	1	8

^a $P = 0.0007$; level of significance when the four addicts with unknown habits (three with *Pseudomonas* infection and one with non-*Pseudomonas* infection) are excluded. Even if addicts with unknown habits are included "against" the trend (add three to last value in the "*P. aeruginosa*" column and one to first value in "Other" column), the association is still significant ($P = 0.02$).

^b For specific organisms, see the text.

TABLE 3. Phenotypes of *P. aeruginosa* isolates from addicts and nonaddicts

Phenotype	No. of patients that were:		O serotype	Pyocin type ^a	ET ^b	Reaction to:								
	Addicts (n = 25)	Nonaddicts (n = 22)				Heavy metals ^c			Antibiotics ^d					
						Hg	Pm	Te	Sm	Su	Ge	To	Am	Cb
1	13		11	10	a	+	-	-	-	-	-	-	-	-
2	3	1	11	10	d	+	-	-	-	-	-	-	-	-
3	1		11	10	b	+	-	-	-	-	-	-	-	-
4	1	1	11	4	a	+	-	-	-	-	-	-	-	-
5	2	3	11	10	a	-	-	-	-	-	-	-	-	-
6	1		11	4	a	+	-	+	-	-	-	-	-	-
7	1		11	10	d	+	-	+	-	-	-	-	-	-
8	1		11	4	c	-	-	-	-	-	-	-	-	-
9	1		2, 5, 16	4	h	+	-	-	-	-	-	-	-	-
10	1		3	ND ^e	j	ND	ND	ND	ND	ND	-	-	-	-
11		2	11	10	a	+	-	+	-	-	-	-	-	-
12		1	11	10	a	+	+	-	-	+	-	-	-	-
13		1	11	10 or 4	c	-	-	-	-	-	-	-	-	-
14		1	11	10 or 4	f	-	-	-	-	-	-	-	-	-
15		1	11	10	a	+	-	-	-	-	+	+	-	+
16		1	11	4	g	-	-	-	-	-	-	-	-	-
17		1	11	10	a	-	-	-	+	+	-	-	-	-
18		2	11	10	a	+	-	+	+	+	-	-	-	-
19		1	11	10	a	+	-	-	+	-	+	+	-	-
20		2	11	10	e	+	-	+	+	-	+	+	-	+
21		1	11	10 or 4	a	+	-	-	+	+	+	+	-	-
22		1	11	4	a	+	-	+	+	+	-	-	-	-
23		1	11	10	i	+	-	-	-	+	+	-	+	+
24		1	11	4	d	+	-	+	+	-	+	+	-	+

^a Pyocin types 10 and 4 are listed when both patterns were obtained in two or more attempts to type a strain (see text).

^b See Table 1.

^c Symbols: +, resistant; -, susceptible; Hg, mercuric chloride; Pm, phenylmercuric nitrate; Te, potassium tellurite.

^d Symbols: +, resistant; -, susceptible; Sm, streptomycin; Su, sulfadiazine; Ge, gentamicin; To, tobramycin; Am, amikacin; Cb, carbenicillin.

^e ND, Not done.

nosa, which has a propensity for moist environments. In one common method of drug preparation, drug tablets are placed in a match book; crushed by chewing; suspended in warm tap water, toilet water, or saliva in a small unsterile container; filtered through a piece of cotton or a cigarette filter; and injected with a syringe and needle which are often shared by others. Importantly, and in contrast to the preparation of heroin, pentazocine-tripelenamine is usually not boiled ("cooked"), leading perhaps to a greater chance for survival of contaminating bacteria.

Because 23 of 25 *P. aeruginosa* isolates from our addicts were serotype O11, a serotype found in only 9% of isolates from nonaddict outpatients, we initially suspected a "common source" outbreak. Additional support for this was gained by the similarity of multiple phenotypic markers among addict isolates (Table 3). In contrast, the control group of serotype O11 strains from nonaddicts was much more heterogeneous, with 22 isolates distributed among 17 different phenotypic patterns. Potential common sources of strains include injection paraphernalia (since addicts often share equipment while gathering in "shooting galleries"), the drug tablets, and tap water. The paraphernalia seems unlikely as a common source of infection since it would not explain the wide geographical occurrence of serotype O11. Intrinsic contamination of drug tablets could account for the distribution. Our cultures of confiscated tablets did not show *P. aeruginosa* isolates (data not shown); however, contamination could have been at a very low frequency or in a brand(s) of tripelenamine not yet sampled. Similarly, our cultures of tap water (including samples from homes of addicts) did not yield *P. aeruginosa*. Although *P. aeruginosa*

has been recovered from some potable water supplies, serotype O11 does not seem to predominate (6).

The phenotypic similarity in the isolates from addicts could also reflect a special ability of serotype O11 strains to survive in the environment. For example, in studies in our laboratory, it has been shown that a slurry of pentazocine-tripelenamine, prepared as if for injection, supports the growth of serotype O11 isolates from addicts but rapidly inhibits many other *P. aeruginosa* strains (K. B. Botsford, R. A. Weinstein, C. Nathan, and S. A. Kabins, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 24th, Washington, D.C., abstr. no. 331, 1984). The serotype O11 isolates may also have a propensity to be invasive or cause deep infections or both. These possibilities are being assessed by serum susceptibility tests, as well as in the rabbit model of endocarditis.

The fact that serotype O11 strains have caused most reported outbreaks of whirlpool-related folliculitis (6) further attests to the unusual epidemic potential, and perhaps hot water tolerance, of this serotype. Moreover, in a study of hospital outbreaks of *P. aeruginosa* in 13 different states, serotype O11 was more common in epidemic strains than in endemic strains and caused 53% of 17 single-strain outbreaks (3). We do not know whether serotype O11 strains in the whirlpool and nosocomial outbreaks share the other characteristics of our strains.

The use of multiple phenotypic markers for *P. aeruginosa* helped differentiate strains that shared the O11 serotype. In particular, electrophoretic typing allowed us to compare the allotypes of several metabolic enzymes, providing an indirect comparison of a portion of the genotype of each

strain. This technique, previously used with eucaryotes (11) and *Escherichia coli* (2, 20), adds another dimension to the epidemiological typing of isolates and warrants further study. Since plasmids were not found in the first 15 strains from addicts tested, we did not pursue this marker, which has been helpful in some epidemiological studies.

In summary, we documented the recent emergence of *P. aeruginosa* as the major pathogen causing deep infections in drug addicts in Chicago. Infection with *P. aeruginosa* was correlated with abuse of pentazocine-tripelenamine, which may have become contaminated when addicts prepared the drugs for self-administration. The striking phenotypic similarity among the *P. aeruginosa* serotype O11 isolates from these addicts, as compared with those from nonaddicts, may reflect acquisition from related environmental sources and an unusual ability for these strains to survive during the drug administration or to cause deep infections.

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