PSEUDOMONAS AERUGINOSA BACTEREMIA IN PATIENTS UNDERGOING LIVER TRANSPLANTATION: AN EMERGING PROBLEM

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Pseudomonas aeruginosa bacteremia in patients undergoing liver transplantation: An emerging problem

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In our institution, Pseudomonas aeruginosa bacteremia appeared to occur with increasing frequency in patients undergoing liver transplantation. We thus conducted a prospective study to define risk factors and outcome in these patients. Over a 19-month period 6% of liver transplants were followed by Pseudomonas bacteremia. The mean age was 46 years (range, 24 to 67 years). The interval between transplantation and onset of bacteremia was 3 to 372 days (mean, 80). The incidence of Pseudomonas bacteremia in liver transplants was three times that of other transplants (heart, lung, kidney). Ninety one percent of infections were nosocomial. Polymicrobial bacteremia occurred in 30% of episodes. The portal of entry was respiratory in 30%, abdominal in 35%, and biliary in 13%. Four patients had recurrent Pseudomonas bacteremia: liver abscess (1), biliary obstruction (2), subhepatic abscess (1). Survival at 14 days was 70%. Survival rates were significantly lower for patients with hypotension, on mechanical ventilators, and increasing severity of illness (p < 0.05). Survival was higher when bacteremia occurred within the first 30 days after transplantation compared to after 30 days. A large number (43.4%) of Pseudomonas bacteremias occurred after transplant surgery or biliary tract manipulation, while the patient was receiving a prophylactic regimen of cefotaxime and ampicillin. P. aeruginosa is an important pathogen in the liver transplant recipient; prevention may be possible for a subgroup of patients with the use of prophylactic antibiotics with activity against P. aeruginosa. (SURGERY 1991;109:62-8.)

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PSEUDOMONAS AERUGINOSA is a well-established cause of bacteremia in hospitalized and immunosuppressed patients. At the University of Pittsburgh, *P. aeruginosa* bacteremia has been seen with increasing frequency in patients undergoing orthotopic liver transplantation. During one 9-month period, 25% (13/51) of *Pseudomonas* bacteremias occurring in our hospital occurred in liver transplant recipients compared to 27% (14/51) in the neutropenic patient with underlying malignancy. Significantly fewer *Pseudomonas* bacteremias were seen in kidney (three patients) or heart transplant recipients (one patient) during this same period.

Thus we initiated a prospective study of liver trans-

plant recipients who developed *P. aeruginosa* bacteremia to define the demographics and risk factors to elucidate those factors that might improve survival.

MATERIAL AND METHODS

Study population. All liver transplant recipients with a positive blood culture for *P. aeruginosa* were followed prospectively by an infectious disease physician (J.A.K.) and transplant surgeon (J.W.M.) until the time of death or discharge from hospital. Surviving patients were then followed indefinitely by the surgical investigators (J.W.M., T.E.S.). The study period was 19 months (November 1985 to May 1987). Blood cultures were processed by the BACTEC automated blood culture system (Johnston Laboratories, Towson, Md.). Degree of illness was quantified as follows: temperature >39° C (2 points), mental status [disorientation (1 point), stupor (2 points), or coma (4 points)], hypotension (2 points), mechanical respiratory support (2

points), and cardiac arrest (4 points). Patients were considered 4+ ill if they accumulated ≥4 points within the 72 hours before identification of bacteremia.

Immunosuppression. Cyclosporin A and prednisone dosage schedules were administered as previously reported.[1] On the day of surgery, intravenous cyclosporin A (6 mg/kg/day) was initiated. The serum concentrations were maintained at 500 to 1000 ng/ml (whole blood radioimmunoassay).

Methylprednisolone (Solu-medrol) was given in a 1 gm bolus initially, then a tapering schedule was followed reducing the dose from 200 mg/day to 20 mg/day by the sixth postoperative day. Most patients were maintained on 15 to 25 mg/day of oral prednisone after the first week. If there was evidence of rejection, a 1 gm bolus of methylprednisolone, was administered. The steroid therapy was recycled as above.

OKT3 (Ortho Pharmaceutical Corp., Raritan, N.J.) (5 cc/day) was given to selected patients in whom rejection was documented by biopsy. In addition it was used as the major means of immunosuppression when patients on cyclosporin A were thought to have developed nephrotoxicity to that drug. In these cases the dosage of cyclosporin A could be lowered without risk of rejection. Three patients received azathioprine because of organ rejection refractory to cyclosporin A, steroids, and OKT3 or compromised renal function as a result of cyclosporin A.

Cefotaxime (1 gm every 6 hours) and ampicillin (1 gm every 6 hours) were administered before operation and from 3 to 7 days after operation as a standard prophylactic regimen for the liver transplant procedure as well as for biliary tract procedures after transplantation. Antibiotics and diet for selective bowel decontamination were not used during the study period.

Statistical methods. Clinical and laboratory data were entered into the Prophet system (Division of Research Resources, National Institutes of Health). Association of survival with clinical parameters and outcome was assessed by the chi-square and Fisher exact tests.

RESULTS

Demographics. During the 19-month study period 363 liver transplant procedures were performed. Twenty-three episodes of *P. aeruginosa* bacteremia occurred in 19 orthotopic liver transplant recipients during this study period (Table I). The mean age of the patients was 46 years (range 24 to 67 years). Fifty two percent (12/23) were graded as 2+ ill, and 48% (11/23) were graded 4+ ill.

The number of days between liver transplantation and onset of *Pseudomonas* bacteremia ranged from 3 to

372 days (mean, 80 days; median 38 days). Five and two patients developed *Pseudomonas* bacteremia within 1 and 2 weeks of transplantation, respectively, (Fig. 1). Sixty one percent (14/23) received a single transplant, whereas 39% (9/23) had received multiple transplants at the time of bacteremia. Two patients died within 7 days after transplant surgery. More *Pseudomonas* bacteremias occurred in patients with Roux-en-Y biliary procedures 65% (15/23) as compared to choledochoholedochostomy (end to end) 35% (8/23).

Ninety one percent (21/23) of the *Pseudomonas* bacteremias were nosocomial. The average length of hospitalization before the positive blood culture was 37 days. Only two patients were neutropenic (white blood cell counts were 1300 and 1700 cells/mm^3) at the onset of bacteremia.

Bacteriology. Polymicrobial bacteremia occurred in 30% (7/23) of episodes; other organisms isolated included *Escherichia coli* (one case), *Streptococcus faecalis* (three cases), *Enterobacter cloacae* (two cases) and *Staphylococcus epidermidis* (one case). In 52% (11/21) of the patients, *Pseudomonas* was also isolated from the sputum; however, only eight of these patients were clinically suspected of having pneumonia.

Four patients had recurrent *Pseudomonas* bacteremia occurring at a range of 17 to 45 days after the first episode. One had a documented liver abscess, two had biliary obstruction and presumed cholangitis, and one had a subhepatic abscess.

Antibiotic therapy. Combination therapy consisting of an antipseudomonal beta-lactam antibiotic plus an aminoglycoside was administered to all patients. (Table I). In two cases the isolates were resistant in vitro to all aminoglycosides, and monotherapy with an antipseudomonal agent was administered. Forty-three percent (10/23) of the episodes were treated with oral rifampin (600 mg/three times a day) in addition to combination β-lactam plus aminoglycoside therapy, as part of an experimental therapeutic protocol for *P. aeruginosa* bacteremia.[2]

Outcome. Seventy percent (16/23) of the cases were alive at 14 days after onset of bacteremia (Table I). Only 26% (5/19, four patients had two episodes) were ultimately discharged from the hospital; however, these discharged patients were all alive 12 months later. Of the four patients who had a repeat episode of *Pseudomonas* bacteremia, 50% (2/4) survived both episodes. Patients with polymicrobial bacteremia had a survival rate similar to those with *P. aeruginosa* bacteremia only (71% [5/7] versus 69% [11/16]).

Patients with hypotension, on mechanical ventilators, and severe illness as defined by objective criteria, had a

Table I. Twenty-three cases of *Pseudomonas* bacteremia in liver transplant recipients

Patient (episode)	Age	Underlying disease	Antibiotics	OKT3	Portal of entry	No. of trans- plants*	Status of liver at time of +BC	Outcome (14 days)
5 (2)	41	Rejection of prior liver	Imipenem, tobramycin, rifampin	Yes	Biliary	2	Mild rejection/ liver abscess	Lived
6 (1)	29	Chronic active hepatitis	Piperacillin, gentamicin	Yes	Abdominal	2	Portal vein thrombosis	Lived
7	31	Unknown	Piperacillin, tobramycin	Yes	Unknown	1	Mild rejection/ CMV	Lived
9	49	Cirrhosis	Ceftazidime, tobramycin, rifampin	Yes	Biliary	2	Resolving ischemia	Lived
12	45	Crohns' disease	Imipenem, tobramycin, rifampin	Yes	Pneumonia	2	Stable	Lived
16	34	Primary biliary cirrhosis	Imipenem, amikacin, rifampin	Yes	Pneumonia	3	Rejection/CMV hepatitis	Lived
18	62	Cryptogenic cirrosis	Mezlocillin, amikacin	Yes	Pneumonia	2	Stable	Lived
1	27	Hepatoma	Piperacillin, tobramycin	No	Pneumonia	2	Mild rejection	Died
2 (1)	46	Hemophilia, AIDS	Piperacillin, gentamicin	No	Pneumonia	1	Rejection/CMV	Lived
2 (2)	46	AIDS	Imipenem, amikacin	No	Abdominal	1	Rejection/CMV	Died
3	36	Portal vein thrombosis	Imipenem, tobramycin, rifampin	No	Unknown	1	Cholestasis	Died
4	65	Alcoholic cirrhosis	Piperacillin, tobramycin, rifampin	No	Unknown	1	CMV hepatitis	Died
5 (1)	40	Chronic active hepatitis	Piperacillin, tobramycin	No	Biliary	1	Iliac vein thrombosis	Lived
6 (2)	29	Portal vein thrombosis	Piperacillin, tobramycin	No	Abdominal	2	Portal vein thrombosis	Lived
8	24	Sclerosing cholangitis	Imipenem, tobramycin, rifampin	No	Abdominal	1	Rejection	Lived
10	67	Non-A, non-B hepatitis	Piperacillin, tobramycin, rifampin	No	Abdominal	3	Cholestasis	Lived
11	39	Recurrent cholangitis	Imipenem, tobramycin, rifampin	No	Abdominal	3	CMV hepatitis	Lived
13	47	Failure of 1st transplant	Ciprofloxacin	No	Abdominal	1	Abscess	Lived
14	35	Budd-Chiari	Ticarcillin, tobramycin	No	Pneumonia	1	Rejection	Died
15 (1)	59	Cholangiocarcinoma	Cefoperazone, amikacin	No	Pneumonia	1	Recurrent carcinoma	Lived
15 (2)		Cholangiocarcinoma	Piperacillin, tobramycin	No	Unknown	1	Recurrent carcinoma	Lived
17	48	Non-A, non-B hepatitis	Mezlocillin, gentamicin, rifampin	No	Pneumonia	1	Cellular swelling	Died*
19	60	Non-A, non-B hepatitis	Imipenem	No	Unknown	1	Stable	Died

AIDS, Acquired immunodeficiency syndrome; *CMV*, cytomegalovirus; *BC*, blood culture.
*At the time of positive blood culture.

significantly poorer outcome (Table II). Early administration of antipseudomonal agents and the use of rifampin in addition to other antipseudomonal agents were associated with a 70% (7/10) survival at 14 days, which was similar to standard therapy (69%, 9/13).

One-hundred percent (7/7) of patients with *Pseudomonas* bacteremia who received OKT3 within 10 days of the onset of the bacteremia survived compared to 56% (9/16) survival for those who did not ($p = 0.057$, Fisher's exact test (Table III). Patients receiving OKT3
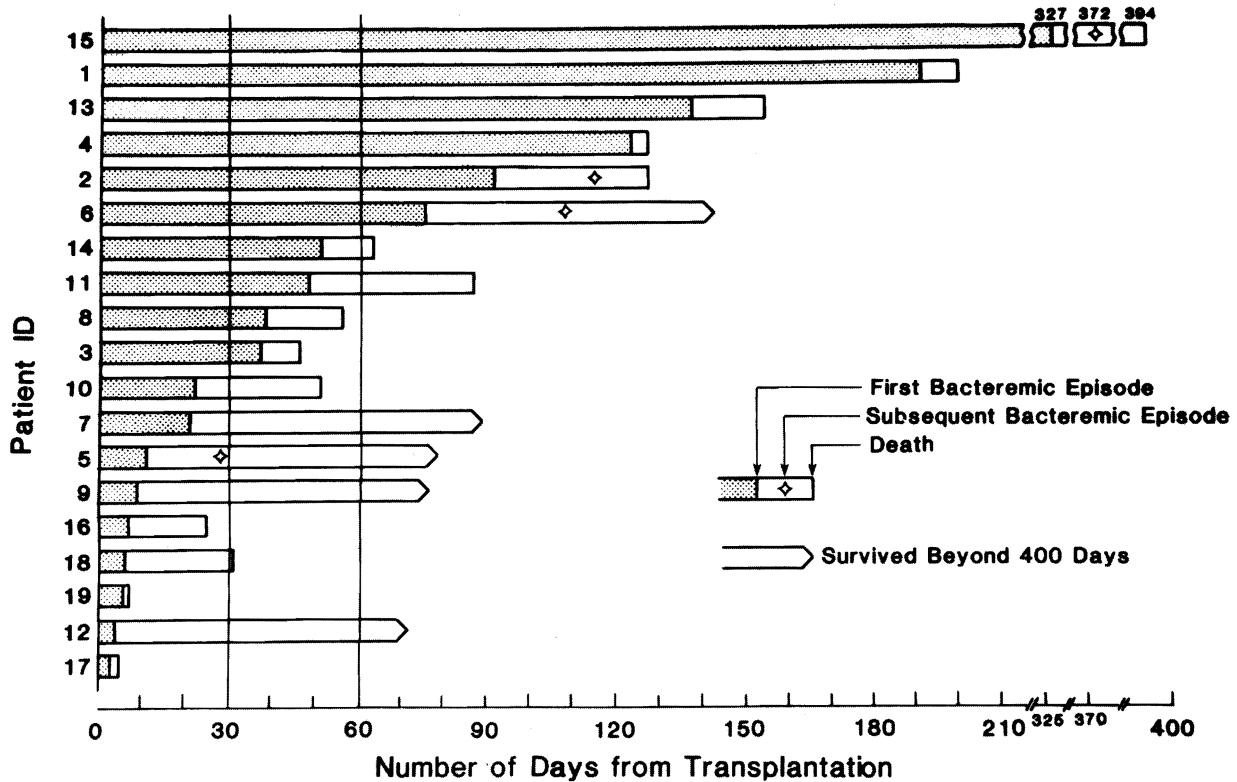
Fig. 1. Twenty-three episodes of bacteremia in 19 liver transplant recipients. Seven patients experienced bacteremia in the immediate postoperative period while receiving cefotaxime and ampicillin for prophylaxis.

were more likely to have onset of bacteremia within 30 days after transplant (86%, 6/7) as compared to greater than 30 days (14%, 1/7).

No statistical difference was found in survival between the type of biliary or arterial anastomosis and outcome (Table IV). Fewer patients survived the episode of *Pseudomonas* bacteremia who were single organ recipients compared to multiple organ recipients. Death occurred at a mean of 12.6 and 22.5 days after positive blood cultures for single transplant and multiple transplant recipients, respectively.

Fig. 1 displays the time course from transplantation to *Pseudomonas* bacteremia to overall death/survival. Grouping the episodes by days from transplantation to onset of bacteremia revealed the following survival rates: day 0 to 30, 50% (5/10); day 30 to 60, 0% (0/4); days greater than 60, 11% (1/9). Survival was more likely if the bacteremia occurred less than 30 days after operation (p = 0.052). Mortality in those patients with bacteremia occurring greater than 60 days after transplantation was multifactorial and related to late complications; for example, acquired immunodeficiency

syndrome (AIDS), recurrent cholangiocarcinoma, cytomegalovirus hepatitis, and chronic rejection.

Sixty percent (6/10) of episodes with onset of bacteremia less than 30 days after transplant were receiving ampicillin and cefotaxime at the time of *Pseudomonas* bacteremia ("superinfection"). Prior treatment with ampicillin and cefotaxime ranged from 3 to 7 days. Twenty percent (2/10) of patients with onset of bacteremia greater than 30 days received ampicillin and cefotaxime as empiric therapy for presumed infection.

Pseudomonas bacteremia was documented in three patients with bile duct colonization. One occurred within 30 days, and two occurred greater than 60 days after transplantation. Two had undergone T-tube cholangiography before bacteremia with one receiving preoperative ampicillin and cefotaxime. The third patient had biliary obstruction from recurrent cholangiocarcinoma. All three patients had a history of previous bile drainage from which *P. aeruginosa* was cultured.

Both cases of neutropenia occurred in patients whose bacteremia occurred greater than 60 days after transplantation; in one case, neutropenia was attributed to

Table II. Impact of clinical factors on survival of liver transplant recipients with *Pseudomonas* bacteremia

	Percentage	No. survived/ total episodes	p value
Fever ≥39° C	100%	3/3	NS
Fever <39° C	65%	13/20	
Nosocomial infection	67%	14/21	NS
Community acquired	100%	2/2	
Portal of entry			
Abdominal/biliary	91%	10/11	NS (0.069)
Other*	50%	6/12	
Hypotensive	14%	1/7	0.0005
Normotensive	94%	15/16	
Possible pneumonia	54%	6/11	NS
No pneumonia	65%	10/12	
Degree illness†			
2+	100%	12/12	0.001
4+	36%	4/11	
Neutropenia	0%	0/2	NS (0.065)
No neutropenia	80%	16/20	
Diabetes mellitus	100%	2/2	NS
No diabetes mellitus	67%	14/21	
Serum creatinine ≤1.5 mg/dl	100%	3/3	NS
Serum creatinine >1.5 mg/dl	63%	12/19	
Respiratory support	46%	6/13	0.007
No respiratory support	100%	10/10	
Hemodialysis	60%	3/5	NS
No hemodialysis	72%	13/18	

NS, Not significant.
*Pneumonia (7), unknown (5).
†See methods.

cytomegalovirus hepatitis, whereas in the other case the cause was unknown.

DISCUSSION

P. aeruginosa is a well-established nosocomial pathogen typically associated with prolonged hospital stay and invasive procedures in severely ill and immunocompromised patients. Although promising new antimicrobial agents are available, *P. aeruginosa* remains a difficult organism to treat; bacteremia caused by this organism carries a mortality rate significantly higher than for other bacterial pathogens.

Bacteremias caused by *P. aeruginosa* have not appeared to be problematic in early studies of infections in liver transplant recipients with only 0 to 9 episodes of *P. aeruginosa* bacteremia documented in four series.[3-6] In our study, 23 episodes of *P. aeruginosa* bacteremia occurred in 19 patients—the largest collection of *P. aeruginosa* bacteremias in orthotopic liver transplant recipients ever reported. An episode of *Pseudomonas* bacteremia followed 6.6% (23/363) of liver transplant procedures. Interestingly, *P. aeruginosa* was second only to *Staphylococcus aureus* as a cause of bacteremia and constituted more than a sixth of all bacteremias. Neutropenia, a well-established risk factor for *Pseudomonas* bacteremia, was not a factor in this series in which only two patients were neutropenic.

Previous studies have established that combination antibiotic therapy is preferred to monotherapy for *Pseudomonas* bacteremia.[7, 8] In this study survival was only slightly higher for patients who received combination therapy versus monotherapy (70% [14/20] versus 66% [2/3]); however, the sample size was too small for optimal analysis. As expected, patients who were more

Table III. Impact of medical therapies on survival of liver transplant recipients with *Pseudomonas* bacteremia

	Survival		
	Percentage	No. survived/ total episodes	p value
Steroids	73%	16/22	NS
No steroids	0%	0/1	
Steroid bolus	82%	9/11	NS
No bolus	58%	7/12	
Steroid recycle	80%	4/5	NS
No recycle	67%	12/18	
Azathioprine	100%	3/3	
No azathioprine	65%	13/20	NS
OKT3	100%	7/7	NS (0.057)
No OKT3	56%	9/16	
Antipseudomonal agents			
Within 48 hr of positive blood culture	68%	15/22	
Greater than 48 hr	100%	1/1	NS

Table IV. Impact of surgical procedures on outcome survival of liver transplant recipients with *Pseudomonas* bacteremia

	Survival (at 14 days)		
	Percentage	No survival/ total episodes	p value
Arterial procedure			
Arterial conduit	60%	3/5	NS
End-to-end	72%	13/18	
Biliary procedure			
Roux-en-Y	67%	10/15	NS
End-to-end	75%	6/8	
No. of transplants*			
Single	57%	8/14	NS
Multiple	89%	8/9	
Previous biliary surgery	85%	11/13	NS
No previous biliary surgery	50%	5/10	
Stints at OR	83%	5/6	NS
No stints at OR	65%	11/17	

OR, Operating room.
*At time of positive blood culture.

ill as graded by objective criteria at the time of bacteremia had significantly poorer outcome.

The precise cause of death was difficult to ascertain in these patients with multifactorial medical problems. We chose to evaluate death at a fixed end point in time, rather than making a subjective assessment; the assumption was that death within 14 days after the positive blood culture was likely related to *Pseudomonas* bacteremia. The overall mortality rate was 30% (7/23) at day 14. Death at a later date was due to complicated medical conditions including rejection, liver failure, cytomegalovirus hepatitis, AIDS, and recurrent tumor (Table I).

Orthoclone OKT3, a murine monoclonal antibody, which blocks the generation and function of human cytotoxic T cells, has improved both allograft and patient survival.[9] Surprisingly, we found an increased survival for patients who received OKT3 within 10 days of *Pseudomonas* bacteremia. The basis for this finding is unclear.

Ampicillin and cefotaxime have been routinely used in our institution for prophylaxis and empiric treatment of presumed infection in liver transplant recipients, but neither has antipseudomonal activity. These antibiotics may actually promote the emergence of *P. aeruginosa*. In 30.4% (7/23) of the patients, the *Pseudomonas* bac-

teremia could be classified as immediate postoperative "superinfection," since these patients received the prophylactic antibiotics of ampicillin and cefotaxime during surgery and in the postoperative period. In two other patients, bacteremia followed T-tube cholangiography; both of these patients had prior colonization with *P. aeruginosa*, and one received preprocedure ampicillin and cefotaxime. Finally, one patient in whom bacteremia occurred between 30 to 60 days after transplantation was receiving ampicillin and cefotaxime empirically at the time of sepsis.

This study suggests that selection of prophylactic antibiotics before transplant or biliary tract manipulation should include agents with in vitro activity against *P. aeruginosa*; options include piperacillin, imipenem, ceftazidime, and ciprofloxacin. Of the *Pseudomonas* bacteremias reported here 43.3% (10/23) might have been prevented if antipseudomonal antibiotics had been used in the prophylactic regimen. On the other hand, since the administration of more potent antibiotics might lead to emergence of other more resistant organisms, a controlled trial comparing the current prophylactic regimen versus a regimen that includes antipseudomonal agents is likely indicated.

Certainly, antipseudomonal antibiotics should be used for infected patients with known *Pseudomonas* biliary colonization. Finally, empiric antibiotic therapy for presumed bacterial infection in selected liver transplant recipients might also include antipseudomonal agents.

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