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Infections in Kidney, Heart, and Liver Transplant Recipients on Cyclosporine

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OUR study involves 216 patients transplanted at the University of Pittsburgh from 1978 to 1983 (Table 1). This includes 64 kidney patients on cyclosporine (CsA), of which 21 were in a randomized trial of CsA, with 17 patients on azathioprine (AZA).[1] Since the latter was a small number, 59 renal patients on AZA from 1978 to 1980 are included for comparison. Except for the immunosuppressive drugs, all renal transplant recipients received comparable management largely from the same surgical team. In addition, from 1981 to 1983, we followed 33 heart and 43 liver transplant recipients who were all on CsA. This drug was first introduced in Pittsburgh in March 1981. A preliminary report of infections in these groups has been published.[2] This article provided additional patients, data, and follow-up material.

MATERIALS AND METHODS

All renal groups were followed for at least 6 months. Heart and liver patients were followed for a minimum of 3 months. The mean duration of follow-up for the latter 2 groups were 277 and 221 days, with a range of 90–400 and 90–594 days. Most patients received intravenous methylprednisolone 1 day prior to surgery. CsA was given according to Starzl et al.[3] On the day of surgery, 17.5 mg/kg/day was given orally, and attempts were made to reduce the dose to 3–10 mg/kg/day. Patients on AZA were begun on 5 mg/kg/day, with maintenance of 2.5 mg/kg/day. All patients on CsA and AZA also received prednisone. Patients on CsA received somewhat less cumulative prednisone than those on AZA.[4] The 3 types of transplant patients on CsA were on similar regimens, except 6 of 33 cardiac recipients also received antithymocyte globulin for rejection. They were not significantly different in terms of episodes of infection.

Infections are defined as clinically significant disease based on clinical and laboratory diagnosis, except in the case of virus infections, where the distinction between infection and symptomatic infection or disease is made.

Throat washings, urine samples, and blood buffy coats were obtained routinely for cytomegalovirus (CMV) and herpes simplex virus (HSV) cultures weekly for the first 8 postoperative weeks, biweekly during the third month, and monthly thereafter. Serum samples were obtained, when possible, from recipients and donors prior to transplantation and from recipients at monthly intervals after transplantation. CMV and Epstein-Barr virus (EBV) serology were performed as previously described.[2]

RESULTS

Table 2 is a summary of infections in all the 1981–1983 groups. Consider first the renal groups. The percent of patients who had at least one infection, as well as mean episodes of infection per patient, was significantly higher in the randomized azathioprine group (88% and 2.18) than in the CsA group (61% and 0.98). None of the infections in the renal groups was associated with deaths, of which there was only one.

The cardiac and liver transplant groups on CsA had more infection than the renal group on CsA immunosuppression. The sites of infections in the kidney, heart, and liver groups varied (Table 3). Most frequent infections for the 3 groups, respectively, were urinary tract, pulmonary and intrathoracic, and abdominal and gastrointestinal infections. Kidney recipients had the lowest frequency of bacteremias. Only the liver group had fungemia. Perhaps more important is the fact that mortality associated with severe infections was significant in the heart and liver groups. Many of the liver group died acutely with many infections. This is reflected in the fact that 50% of all episodes of infection were acquired 1 month after liver transplantation. To reach the same proportion, cardiac patients took 3 months.

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Table 1. Transplant Groups at PUH* Followed for Infections

Time of Transplant	Type Transplant	No. of Patients	Mean Age	Immunosuppression	Duration of Follow-up
1981–1982	Kidney†	64	36	CsA	6 months–1 year
1981–1982	Kidney‡	21	41	CsA	6 months–1 year
1981–1982	Kidney‡	17	41	AZA	6 months–1 year
1978–1980	Kidney	59	33	AZA	6 months–1 year
1981–1983	Heart	33	40	CsA	3 months–1 year
1981–1983	Liver	43	36	CsA	4 months–1 year

*Presbyterian-University Hospital, University of Pittsburgh.

†All kidney patients on CsA.

‡Patients on randomized CsA, AZA trial.

Table 2. Infections and Fatalities in 1981–1983 Transplant Recipients

	Renal Transplant Groups				
Patient Characteristic	Random AZA (n = 17)	Random CsA (n = 21)	All CsA Renal (n = 64)	Cardiac Transpl. (n = 33)	Liver Transpl. (n = 43)
All infections					
Percent Infected*	88%	71%	61%	76%	81%
Total episodes	37	24	63	52	98
Mean episodes†	2.18	1.14	0.98	1.58	2.23
Nonviral infections					
Percent infected	82%	43%	41%	58%	65%
Total episodes	28	13	39	30	70
Mean episodes	1.65	0.62	0.61	0.91	1.63
Infection-associated deaths/total deaths	0/0	0/0	0/1	9/14	17/20

*Percent patients developing one or more infections.

†Total number of episodes divided by number of patients.

Table 3. Site of Infections According to Type of Transplant Patient on Cyclosporine

	Frequent Sites of Infection				
Type of Transplant	Site	Percent of All Infections	Bacteremias	Fungemia	Infection-Associated Deaths
Kidney	Urinary tract	41%	5%	0%	0%
Heart	Pulmonary and intrathoracic	38%	24%	0%	27%
Liver	Abdominal and gastrointestinal	35%	30%	16%	40%

Table 4. Organisms Causing Infections in 1981–1983 Transplant Recipients

	Renal Transplant Groups				
Organism	Random AZA (n = 17)	Random CsA (n = 21)	All CsA Renal (n = 64)	Cardiac Transpl. (n = 33)	Liver Transpl. (n = 43)
Gram-negative aerobes	18 (53)*	10 (39)	37 (34)	13 (33)	36 (49)
All gram-positive	11 (53)	7 (29)	13 (17)	10 (24)	29 (58)
Staphylococcus	7 (41)	1 (5)	4 (6)	4 (12)	12 (23)
Fungus	0 (0)	1 (5)	1 (2)	1 (3)	22 (44)
Other	12 (71)	13 (48)	30 (36)	27 (58)	23 (47)
Total	46 (88%)	13 (86%)	81 (67%)	51 (79%)	110 (88%)

*Number of isolates (percent patients infected by isolate).

Table 5. Effect of Azathioprine and Cyclosporine on Infections in Renal Transplant Recipients

Group	Bacteremias	Staph Bacteremia	Lung Infection	Lung Staph	Pneumocystis
Random AZA	5/17 (29%)	2/17 (12%)	5/17 (29%)	3/17 (18%)	
1978–1980 AZA	11/59 (19%)	5/59 (9%)	23/59 (39%)	5/59 (8%)	6/179 (3%)*
CsA	3/64 (5%)	0/64 (0%)	5/64 (8%)	0/64 (0%)	14/156 (9%)*

*Based on data for all renal transplantation 1978–1982.

Table 4 presents organisms responsible for infections in the 1981–1983 transplant groups. The following are notable. (1) Gram-negative aerobes were significant pathogens in all groups. (2) Gram-positive infections, particularly staphylococcal infections, were more common in the randomized AZA group than all other groups on CsA. (3) Severe fungus infections were a serious problem only in the liver transplant patients. Forty-four percent of liver patients had serious fungal infections and 16% were fungemic. The most common agent was Candida, which caused serious infections in 15 patients. Of these, 3 had disseminated disease, 6 had fungemia, 7 had abdominal, and 3 had lung and chest infections. Four patients had aspergillosis, in whom one produced dissemination and 3 produced pneumonia or chest infections. There was one severe Mucor wound infection and one cryptococcal meningitis. (4) Symptomatic viral infections, included here under "other," were a problem in cardiac transplant patients and are discussed below.

Renal patients on AZA had more infections that were more severe and were predominately Staphylococcal (Table 5). This statement is substantiated by including data from the 1978–1980 AZA group, whose incidence of infection was similar to the small randomized AZA group of 1981–1983.[2] The two AZA groups had 29% and 39% pneumonias, as opposed to 8% for the CsA group. Staphylococcal penumonias and bacteremias were also more common in patients on AZA. In contrast, the incidence of non-life-threatening urinary tract infections were almost identical: 41%, 39%, and 42% (not shown in table). Pneumocystis pneumonia, however, may be a special problem in renal patients on CsA. Our total Pittsburgh incidence rates for the AZA and CsA groups prior to the institution of trimethoprim-sulfa prophylaxis in September 1982 were 3.4% and 9.0%, respectively, which are significantly different. This problem is discussed by Hardy et al. elsewhere in this issue.

Virus infections, particularly of the herpesvirus group (CMV, HSV, VZV, and EBV) are frequent occurrences after organ transplantation.[5] In previous experience, the degree and type of immunosuppression has been critical in determining the morbidity. In renal transplant recipients, antithymocyte globulin has been associated with more symptomatic infection.[6] Primary infections, i.e., those

Table 6. Herpesvirus Infections in 1981–1983 Transplant Recipients

	Renal Transplant Groups														
	Random AZA (n = 17)			Random CsA (n = 20)			All CsA Renal (n = 60)			Cardiac Transpl. (n = 29)			Liver Transpl. (n = 27)		
Virus	No.	(%)	Symptomatic	No.	(%)	Symptomatic	No.	(%)	Symptomatic	No.	(%)	Symptomatic	No.	(%)	Symptomatic
All CMV	13	(76)	1	15	(75)	1	46	(77)	5	27	(93)	10*	21	(57)	12
CMV viremia	5	(26)	1	8	(40)	1	20	(33)	5	18	(62)	10*	15	(41)	10
Herpes simplex	9	(53)	6	8	(40)	6	26	(43)	14	16	(55)	8	19	(51)	9
Herpes zoster	0	(0)	0	1	(5)	1	2	(3)	2	3	(10)	3	2	(5)	2
Total symptomatic			7(41)†			7(35)			19(32)			17(59)*			18(49)

*Significantly different from other CsA groups (χ^2 test), $p < 0.05$.

†Number patients symptomatic (% of group).

Table 7. Primary and Reactivation CMV Infections in 1981–1983 Transplant Recipients

Pretransplant Serologic Status	Renal Transplant Groups: Random AZA (n = 17) I/T	(%)*	Sy†	Random CsA (n = 20) I/T	(%)	Sy	All CsA Renal (n = 60) I/T	(%)	Sy	Cardiac Transpl. (n = 25) I/T	(%)	Sy	Liver Transpl. (n = 18) I/T	(%)	Sy
Positive	10/13	(77)	1	15/17	(88)	1	42/51	(82)	4	15/15	(100)	5	7/10	(70)	2
Negative	3/4	(75)	0	0/3	(0)		4/9	(44)	1	9/10	(90)	5	5/8	(62)	2
Total Infected	13/17	(76)	1	15/20	(75)	1	46/60	(77)	5	24/25	(96)	10	12/18	(66)	4

*I/T (%), infected/total evaluable (%).

†Sy, symptomatic patients.

occurring in seronegative recipients, have been found to be more symptomatic.[7]

Herpesvirus infections in our transplant groups are presented in Table 6. The first row describes all CMV infections diagnosed by isolating the virus from routine throat, urine, or blood buffy coat specimens. The majority of patients became infected, and the rates are indistinguishable from results from previous series of patients, most of whom were on AZA. As a group of agents, herpesviruses and gram-negative aerobes are the most frequent causes of symptomatic infections.

The incidence of CMV viremia varied from 26% to 62%. All patients who had symptomatic CMV infection were viremic, but there were also many viremic patients who were not symptomatic. The percent of patients with symptomatic disease due to CMV and herpesviruses in general was significantly higher in the cardiac group. They also had more viremia due to CMV.

Of the patients with symptomatic CMV infection, there were three cases of CMV pneumonitis in the renal group on CsA. In a separate communication (Hardy et al., this issue), the relationships of CMV infection to Pneumocystis pneumonia is discussed. Five of the ten symptomatic cases in the cardiac group were associated with CMV in the lung. One was found in association with pneumocystis in a lung biopsy and four were found at autopsy. There were 12 symptomatic cases in the liver group, including one case of interstitial pneumonia and three instances of disseminated disease found at autopsy.

Primary and reactivation CMV infections are listed in Table 7. Except for a suggestion in the case of cardiac transplant recipients that primary infection in previously seronegative subjects resulted in more symptomatic infection than reactivation infection, the numbers are too small to incriminate primary more than reactivation infections in symptomatic disease.

Rates for EBV infection are shown in Table 8. Cardiac transplant recipients had more infection, and only they had probable symptomatic disease due to EBV (see Dummer et al., this issue). However, our total experience is still relatively small.

SUMMARY AND CONCLUSIONS

Renal patients on CsA had fewer bacteremias, pneumonias, and gram-positive staphylococcal infections than renal patients on

Table 8. Epstein-Barr Virus Infections in 1981–1983 Transplant Recipients

Pretransplant IgG-VCA	Renal Transplant Groups: Random AZA	Random CsA	All CsA Renal	Cardiac Transpl.	Liver Transpl.
Negative	0/0	0/1	1/3	3/3	0/1
Positive	2/17	3/19	5/34	8/21	1/13
Total infected	2/17	3/20	6/37	11/24*	1/14
Percent	12%	15%	16%	46%	7%

*Significantly different from all other groups on CsA, $p < 0.01$. Five were symptomatic; two had primary infections, one had EBV lymphoma.

AZA. Patients on CsA may be at risk for pneumocystis.

Severity and site of infection is largely determined by type of transplantation. Heart and liver transplant recipients had serious chest and abdominal infections.

Serious fungal infections occurred largely in liver transplant recipients.

Almost every patient was infected with CMV; 8%–34% developed symptomatic disease. This was always associated with viremia.

Heart transplant recipients developed more CMV viremia and more EBV infection. They also had more symptomatic disease from all herpesviruses.

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