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Infections Complicating Orthotopic Liver Transplantation

A Study Emphasizing Graft-Related Septicemia

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• In 93 recipients of 102 orthotopic liver homografts, the incidence of bacteremia or fungemia exceeded 70%. The graft itself was usually an entry site for systemic infection after both immunologic and nonimmunologic parenchymal injury, especially if there was defective biliary drainage. The role of the homograft itself as the special infectious risk factor has prompted increased use of defunctionalized jejunal Roux limbs to reduce graft contamination. It has also stimulated very aggressive postoperative diagnostic efforts to rule out remedial mechanical complications of the transplant.

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An increased risk from infection is a well-known price for the chronic immunosuppression that is used for whole organ transplantation in humans. The patterns of infection were worked out more than a decade ago in kidney recipients[1-7] and confirmed more recently.[8-12] It was found that bacterial infections could often be controlled, providing effective antibiotics were available. The greatest risk proved to be from bacteria, fungi, and protozoa of normally low pathogenicity for which highly specific antibiotic treatment could not be offered. If good organ function was achieved without the need for heavy long-term immunosuppression, the patients could return to an essentially normal life without environmental restrictions.[1] Similar observations have been made after cardiac transplantation.[13-16]

The difficulties of infectious disease prevention and management after hepatic transplantation have been even greater than with the aforementioned organs, as has already been emphasized[17-19] and as will be confirmed in this communication. An analysis of the courses of 93 consecutive patients who were treated with liver replacement has shown that most of the added risk is because the hepatic homograft itself is often the site of contamination with and entry by microorganisms from the gastrointestinal tract. Measures to minimize or control the resulting problems will be described.

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SUBJECTS AND METHODS

The 93 patients received their orthotopic liver homografts between March 1, 1963, and November 28, 1974, for a number of indications of which the most common were biliary atresia, primary hepatic malignancy, chronic aggressive hepatitis, and alcoholic cirrhosis. The studies of infectious complications were brought up to date to March 1, 1976, assuring a minimum potential follow up of 15 months for anyone who was still alive at that time.

The 93 patients were given a total of 102 transplants. An infectious disease analysis was carried out for the period of residence of each of the 102 homografts. This set of data from each of the 102 transplants was referred to as a *graft equivalent*. Each of the 93 patients is identified in the Tables by an orthotopic transplant (OT) code number. This system has permitted the following of individual cases in our series from publication to publication.

Twenty-seven of the 93 patients survived for at least one year after operation, with a maximum of more than six years; on March 1, 1976, a total of 16 were still living after 15 to 74 months. These 93 cases were recently restudied, with the objective of defining the single most important cause of failure for allografts lost either by death or retransplantation.[20] A vital element in the final decision was the state of the homograft and the evidence in it of injury from old or new rejection or from other factors.

These principal causes of failure are listed in Table 1, allowing only one entry for each of the lost grafts. The assignment of a single most important cause of failure inevitably required oversimplification, since the terminal events were always complex. However, the simplified analytic approach made it possible to determine the relative role and pattern of infection in each of the four main groups and the numerous subgroups thereby defined in Table 1. The biggest subgroup consisted of 26 complications of

Table 1.—Single Most Important Reasons Why 86 Liver Grafts Were Lost in 77 Patients*

	No. of Examples	Time to Death or Graft Loss, Days/ Orthotopic Transplant Patient No.†
Nonimmunologic homograft damage	**20**	
Ischemic injury	6	7/6, 1/20, 11/24, 2/48, 8/75, 8/85
Hepatic artery thrombosis	3	4/18, 20/38, 1/52b
Tumor recurrences without bile obstruction	3	379/14a, 143/23, 87/45
Viral hepatitis	3	377/29, 623/36, 33/76a
Portal vein clot	1	1/21
Portal vein not reconstructable	1	20/13b
Graft biliary atresia	1	85/52a
Venous outflow of liver blocked	1	7/34
Cause not determined	1	161/66
Immunologic homograft damage	**14**	
Acute rejection‡	6	7/7, 9/31, 31/50, 9/51, 10/71a, 21/86
Septic hepatic infarction	4	133/9, 186/10, 61/11, 105/12
Chromic rejection‡	4	881/13a, 65/16a, 339/16b, 157/65a
Defective biliary drainage	**26**	
Acute fistula	7	23/5, 13/28, 81/47, 27/63, 28/68, 29/69, 34/70
Acute obstruction	3	10/22, 39/25, 20/79
Delayed obstruction	14	2,190/27, 37/30, 61/41, 47/43, 34/44, 73/49, 564/54a, 780/55, 408/58, 62/60, 111/62a, 84/84, 62/87, 47/88
Obstruction by recurrent tumor	2	400/8, 339/15
Deaths not obviously related to homografts	**26**	
Acute operative hemorrhage, hypovolemia, or respiratory distress	4	0/1, 14/71b, 2/76b, 1/80
Neurologic disability	6	6/4, 3/32, 26/39, 32/40, 41/61, 22/72
Systemic infection	16	22/2, 7/3, 57/14b, 35/17, 1,238/19, 76/26, 36/35, 51/37, 22/54b, 64/57, 175/59, 11/62b, 31/65b, 59/67, 15/81, 9/83

*Either by removal at retransplantation (nine examples) or by death of the patient (77 examples). The data for the latter classification and the basis for the conclusions have been reported elsewhere.[20]

†An "a" indicates retransplantation was performed; a "b" means the patient died after retransplantation.

‡Histopathologically, there were other examples of acute or chronic rejection, but the processes were not thought to be the main reason for the graft or patient loss.

biliary duct reconstruction (Table 1).

The care of liver transplant recipients has been described before in great detail[18] and recently summarized.[19] The usual immunosuppression was with azathioprine, prednisone, and horse antilymphocyte globulin (ALG). If hepatotoxicity of azathioprine was suspected, cyclophosphamide was substituted, since it has an immunosuppressive effect comparable to that of azathioprine. Alternatively, cyclophosphamide was used in a number of cases, with a switch later to azathioprine.

The techniques of biliary duct reconstruction are shown in Fig 1 and 2. The importance of this information in understanding infectious patterns of the liver recipient has been evident for several years.[19-21] In all our early cases, cholecystoduodenostomy (Fig 1, left) or choledochocholedochostomy (Fig 1, right) were used. Cholecystoduodenostomy is no longer employed,[19,20,22] because of the heavy contamination of the liver gastroduodenal contents, because of the high incidence of biliary obstruction at the cystic duct, and because of the excessive risk of duodenal fistula if attempts are made to relieve such biliary obstruction by reoperation. In selected cases, biliary reconstruction is still carried out with choledochocholedochostomy over a T tube (Fig 1, right).

Cholecystojejunostomy is now most frequently used (Fig 2, left), even though it is often necessary to convert from cholecystojejunostomy to choledochojejunostomy some weeks or months after the transplantation because of cystic duct obstruction (Fig 2, right). This secondary procedure has proved to be relatively safe.[20,22]

The causative agents of infections were identified by cultures of blood, sputum, tracheal aspirates, and from recognized sites of infections whenever possible. During operations, the peritoneal cavity, subhepatic space, small bowel contents, and bile frequently were sampled. Bacteria and fungi were isolated and identified in the clinical microbiologic laboratories by standard techniques.

The transplantations were carried out under antibiotic coverage with methicillin sodium, ampicillin sodium, and kanamycin sulfate, which was continued for five to seven days. Cephalothin sodium, carbenicillin disodium, and gentamicin sulfate sometimes were substituted for one of these agents. Antibiotics for treatment of documented infections were selected on the basis of the results in vitro sensitivity testing with antibiotic disks. Emperically selected antibiotics for initial therapy or in the absence of positive cultures often were used.

Suspected or demonstrated fungal infections were treated with amphotericin B or flucytosine or both. Nystatin, administered orally, was given routinely to patients receiving high doses of corticosteroids or antibiotics. In most instances, pulmonary *Pneumocystis carinii* infections were treated on the basis of clinical impression alone and without demonstration of the existence of this infection by biopsy. In a few cases, the correct diagnosis was made at autopsy. Pentamidine and recently a combination of sulfamethoxazole and trimethoprim were used for *Pneumocystis* infections.

RESULTS

High Incidence of Positive Blood Cultures

A striking observation was the frequency of bacteremia and fungemia. This phenomenon will be considered further on for the patients still alive on March 1, 1976. Among the 77 patients who eventually died after receiving a total of 86 grafts, bacteria or fungi (or in 12 instances, both) were grown from cultures of the blood at some time during the residence of 61 of the 86 grafts (Table 2).

The incidence of bacteremia was 59 of 86 (69%) (Table 2). In 29 instances, the patients had bacteremia with more

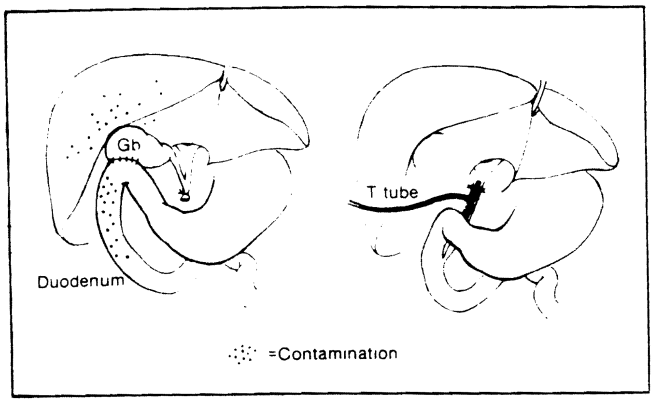


Fig 1.—Techniques of biliary duct reconstruction used in early cases of orthotopic liver transplantation. Left, Cholecystoduodenostomy. No longer used, because of excessive contamination of biliary tract and for other reasons stated in text. Right, Choledochocholedocostomy. Still used in selected cases.

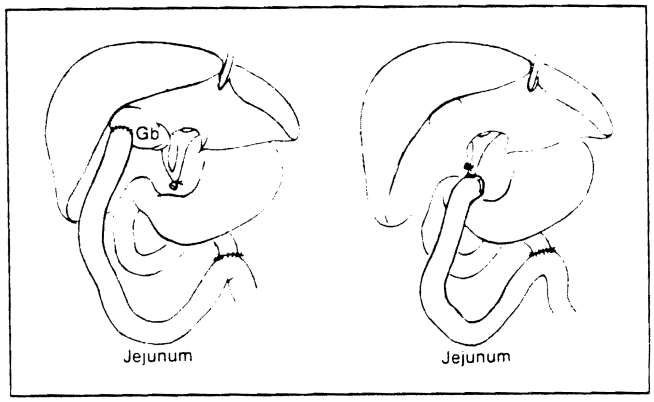


Fig 2.—Use of defunctionalized jejunal limb (Roux-en-Y) for biliary drainage. Objective is to avoid contamination. Left, Cholecystojejunostomy. Right, Choledochojejunostomy. Most commonly, choledochojejunostomy has been secondary procedure that has been made necessary by delayed obstruction of cystic duct after reconstruction shown on left.

than one microorganism simultaneously or sequentially. Frequently, blood cultures were positive for the same microorganism on repeated occasions. However, in compiling the results, a specific microorganism was given credit only once during the time of one graft equivalent.

The majority of all bacteria isolated were *Escherichia coli*, *Enterobacter-Klebsiella* or group D *Streptococcus*, all normal inhabitants of the intestinal tract. In contrast, only a few staphylococci, pneumococci, and *Haemophilus influenzae* type B were found in blood cultures.

Candida species, usually *Candida albicans*, were grown in culture from the blood during the residence of 14 grafts (Table 2). In two instances, yeast was the only organism found in the blood, but in the other 12, both bacteria and *Candida* were identified during the same graft residence.

Nonimmunologic Homograft Damage

Twenty patients were judged to have died or lost their grafts because of hepatic damage that did not have an immunologic cause (Tables 1 and 3).

The transplant damage reflected excessive ischemia in six examples (OT 6, 20, 24, 48, 75, and 85) or the inability to satisfactorily reconstruct all the graft vessels in six more (OT 13b, 18, 21, 34, 38, and 52b) (Table 1). The 12 recipients of these livers were all dead within one to 20 days (average, 7.4). They achieved generally poor liver function, with rises in transaminase levels that indicated extensive necrosis. Infectious complications in their heterogenous collection (Table 3) were avoided only in four patients who died after 1, 2, 4, and 7 days (OT 20, 48, 18, and 34). The freedom from infection could have been an artifact whereby death supervened before an infectious diagnosis became possible. However, the other eight patients also died early (OT 6, 13b, 21, 24, 38, 52b, 75, and 85), and, in seven, bacteremia or fungemia appeared. In five of these eight, the same microorganism in the blood were grown from cultures of the liver, bile, or adjacent peritoneum (Fig 3). One patient (OT 85) who had been given a necrotic liver was found, at autopsy eight days later, to have disseminated aspergillosis. This condition may have predated transplantation.

The nonimmunologic graft injury in the other eight patients (OT 14a, 23, 29, 36, 45, 52a, 66, and 76a) was generally late in developing (Table 1) and led to death or retransplantation after 33 to 623 days (average, 236). The most common causes of graft loss were tumor recurrence and hepatitis (three each). During the eight graft equivalents, significant infections were seen, with the single exception of patient OT 14a (Table 3). The combination of positive blood and liver cultures with the same microorganism was not seen.

Moniliasis developed during four of the twenty graft equivalents (Table 4). One of these latter was a patient (OT 36) whose graft failed after almost two years because of recurrent serum hepatitis[23] and who also had systemic candidiasis and nocardiosis (Table 3). Monilial esophagitis was present in three of the four patients.

Immunologic Homograft Damage

On histologic grounds, these 14 livers (Table 1) suffered acute cell-mediated rejection, chronic rejection whereby the dominant finding is vascular damage, and (in four children) a complication termed septic hepatic infarction. With septic hepatic infarction,[15-21] there was thrombosis of the right hepatic artery, areas of consequent gangrene and abscess formation in the liver, and multiple bacteremias that were proved or assumed to be of hepatic origin. Evidence has been presented elsewhere that a combination of immunologic and mechanical factors were responsible for septic hepatic infarction.[15-21]

The incidence of bacteremia in the 14 graft equivalents was 86% (Tables 2 and 4). In eight instances (OT 9, 10, 11, 12, 16b, 31, 51, and 65a), cultures of the same microorganisms were obtained from liver, bile, or adjacent peritoneal fluid (Table 4). Specimens in or around the liver were not obtained in most of the other cases.

Lung or wound infections or both were found in five of the 14 cases.

Table 2.—Microorganisms* Isolated From Blood Cultu

		Aerobic Bacteria						
		Gram-Negative						
	Incidence of Bacteremia	*Escherichia coli*	*Enterobacter-Klebsiella*	*Proteus*	*Citro-bacter*	*Serratia*	*Pseudo-monas*	Miscel-laneous
Nonimmunologic homograft damage (N = 20)	**12**							
Ischemic injury (n = 6)	3	1				1	2	
Hepatic artery thrombosis (n = 3)	2	2	1					
Tumor recurrences without bile obstruction (n = 3)	1		1					
Viral hepatitis (n = 3)	2							
Portal vein clot (n = 1)	1							1
Portal vein not reconstructable (n = 1)	1		1	1				
Graft biliary atresia (n = 1)	1	1						
Venous outflow of liver blocked (n = 1)	0							
Cause not determined (n = 1)	1		1					
Immunologic homograft damage (N = 14)	**12**							
Acute rejection (n = 6)	4	2	2					
Septic hepatic infarction (n = 4)	4	4	3				1	
Chronic rejection (n = 4)	4		1	1				
Defective biliary drainage (N = 26)	**21**							
Acute fistula (n = 7)	5	2	1			1		
Acute obstruction (n = 3)	1	1					1	
Delayed obstruction (n = 14)	13	8	1	3	1	1		1
Obstruction by recurrent tumor (n = 2)	2	2	2				2	
Deaths not obviously related to homografts (N = 26)	**14**							
Acute operative hemorrhage, hypovolemia, or respiratory distress (n = 4)	1		1					
Neurologic disability (n = 6)	4	2	1	1				
Systemic infection (n = 16)	9	3	1				2	

*If a microorganism was grown repeatedly in culture during the residence of a given graft, it was given credit only once.
†The format for analysis by primary reason for graft loss is the same as in Table 1.

Table 3.—Pattern of Infection in 20 Patients Whose Homografts Were Lost†

		Orthotopic Transplant Patient No.								
	No. of Patients	Blood	Liver	Biliary Tract	Peritoneal Cavity	Wound	Lung	Pleura	Heart	Gastroin-testinal Tract
Bacteria										
Escherichia coli	5	38, 52a, 52b, 75	38, 52b, 75	75	38, 75					
Enterobacter-Klebsiella	4	13b, 23, 38	38, 76a		13b, 38	13b				
Proteus	1	13b			13b	13b				
Pseudomonas	2	6, 24				24	6, 24			
Serratia	1		75	75	75					
Group D *Streptococcus*	3	36, 38	38		38	45				
Streptococci, others	0									
Staphylococcus aureus	2	66				36				
Staphylococci, others	0									
Bacteroides	1	13b			13b					
Clostridium	1	36								
Anaerobic diphtheroids	1	76a			76a					
Miscellaneous	2	21								
Fungi										
Candida albicans	4	6, 24, 52a	36			24	36		36	6, 24, 36
Aspergillus species	2				85		45, 85		85	
Miscellaneous	1					45				
Protozoa										
Pneumocystis carinii	1						45			
Nocardia asteroides	1		36				36			
No infection	5*									

*Orthotopic transplant patients 14a, 18, 20, 34, and 48.

uring the Residence of 86 Liver Grafts in 77 Patients*

Gram-Positive								Anaerobic Bacteria			Fungi	
Group D *Streptococcus*	Other Streptococci	Diphtheroids	*Staphylococcus aureus*	*Staphylococcus albus*	*Streptococcus pneumoniae*	*Haemophilus influenzae* B	Miscellaneous	*Bacteroides*	*Clostridium*	Diphtheroids	*Candida albicans*	Other Yeasts
											2	
1												
1									1	1		
	1							1				
											1	
			1									
											2	
1			1				1	1			1	1
1		1		1	1	1	1		1			
								1			2	1
7	1			1	2			3	3	4	1	
1							1	1			1	
2											1	
1	1	1	1	2		1			1	2	1	

Immunologic Damage				
Kidney	Urinary Tract	Central Nervous System	Skin	Other
	36			
	23			
	75			
			66	
				29
36	24	36		36
		85		85
		36	36	

Defective Homograft Drainage

The mechanical defects included three examples of acute duct obstruction, 14 of delayed obstruction, and seven of acute biliary fistula. The consequences were roughly the same under all these circumstances.

The 26 graft equivalents in this group (Table 1) were associated with 21 bacteremias and/or fungemias (Table 5). There was a striking conformity of microorganisms that could be grown from cultures of the blood in comparison to cultures from the liver, bile, perihepatic peritoneum, or wound (Table 5). These microorganisms were usually multiple and almost always of the enteric variety (Table 5).

Metastatic foci of these bacterial infections to organs outside the peritoneal cavity were very rare, as can be seen in Table 5. When organ systems such as the lungs, urinary tract, or gastrointestinal tract became infected, it was of interest that fungi were common.

Deaths or Graft Losses not Obviously Related to Homografts

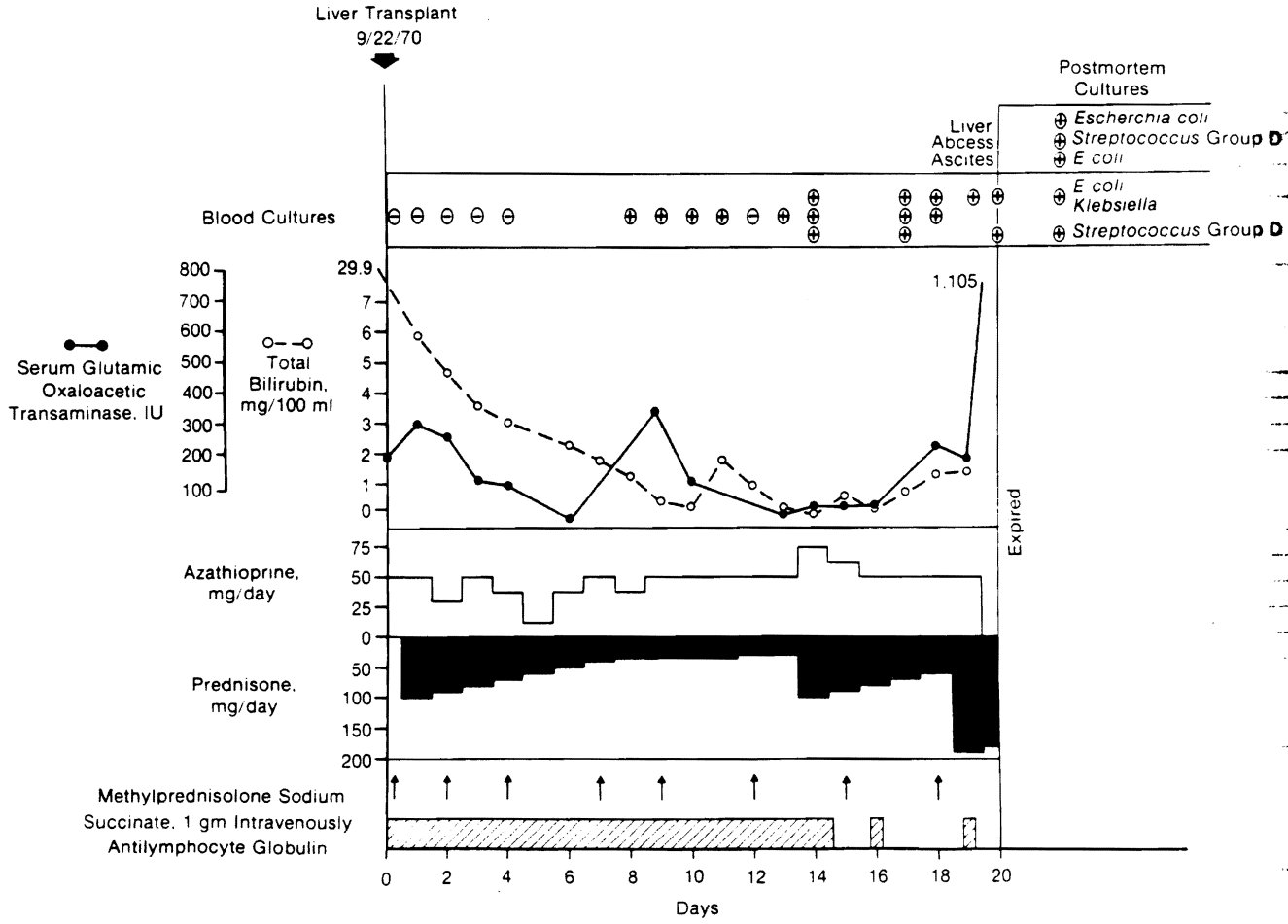
This collection of 26 graft equivalents (Table 6) included 20 primary liver transplants and six retransplants (see Table 1). All the recipients died. Four deaths after one to 14

Table 4.—Pattern of Infection in 14 Patients Whose Homografts Were [illegible]

	No. of Patients	Orthotopic Transplant Patient No.								
		Blood	Liver	Biliary Tract	Peritoneal Cavity	Wound	Lung	Pleura	Heart	Gastrointestinal Tract
Bacteria										
Escherichia coli	6	9, 10, 11, 12, 50, 51	9, 10, 11, 12	12, 51	10	10	10		10	
Enterobacter-Klebsiella	7	9, 10, 12, 16b, 31, 50	10, 12, 16b, 31	12	10, 31	10	10, 31, 86		10	
Proteus	1	13a								
Pseudomonas	2	11				9				
Serratia	0									
Group D *Streptococcus*	5	10, 16b, 65a	10, 16b, 65a			9, 10	86			
Streptococci, others	1	13b								
Staphylococcus aureus	1					86				
Staphylococci, others	2	9, 16a				16a				
Bacteroides	1	9	9		9					
Clostridium	1						86			
Anaerobic diphtheroids	1	86								
Miscellaneous	3	11, 13a, 16b								16b
Fungi										
Candida albicans	6	9, 31, 51	31			10, 16b, 86	31		31	31
Aspergillus species	0									
Miscellaneous	1	11								
Protozoa										
Pneumocystis carinii	1 (?)						16b (?)			
No infection	2*									

*Orthotopic transplant patients 7 and 71a.

Fig 3.—Course of 3-year-old child (OT 38) whose hepatic artery thrombosed, causing partial hepatic necrosis, in spite of which there was good liver function. Graft infection and uncontrollable systemic sepsis supervened. All organisms identified in blood were also grown from cultures of multiple small abscesses in homograft at time of autopsy.



Immunologic Damage				
Kidney	Urinary Tract	Central Nervous System	Skin	Other
		10, 11		
		10		31
		9		

days were caused by bleeding, hypovolemia, or respiratory insufficiency (OT 1, 71b, 76b, and 80). Six adult patients (OT 4, 32, 39, 40, 61, and 72) exhibited crippling and irreversible neurologic disabilities during or just after the transplantation. They died after three to 41 days (average, 22). The other 16 patients were thought to have died primarily from infection.

The patterns of infection in the 26 patients included multiple organs and multiple agents. Gram-negative bacteria and fungi were particularly obvious. Even though manifest problems with the homograft were not diagnosed, bloodstream cultures with the same microorganisms that were found in or around the liver were demonstrated during eight of the graft equivalent periods. Moreover, the peritoneal cavity was infected with bacteria or fungi in 13 of the 26 graft equivalents. A likely explanation for the positive peritoneal cultures was often present and included subphrenic and pericolic abscesses and preexisting bacterial or fungal peritonitis (especially in the retransplant patients).

All but one of the patients died within the first six months (Table 1). The exceptional patient (OT 19) died $3\frac{1}{2}$ years posttransplantation of complications of *Haemophilus* septicemia. Excluding this recipient, whose autopsy has been reported,[7] the average survival of the other 25 was 32.7 days. The pattern of infections in this subgroup of 26 (Table 6) resembled that often found in renal homograft recipients.

Infections in Patients Still Alive

The 16 patients alive on March 1, 1976, fifteen months to more than six years after liver transplantation, had not been free of infection (Table 7). Ten of the 16 have had bacteremias, and only five have been spared major infections.

Five of the 16 survivors had biliary duct complications. The obstructed or improperly draining liver became a focus of infection, which was reflected in identical cultures of the bile and blood. Secondary bile duct reconstruction made the situation manageable (Fig 4).

COMMENT

The weakening of immune reactivity by commonly employed combinations of immunosuppressive agents has been described in great detail by many authors, usually from observations in kidney recipients.[1-13] The best known consequence is a diminution of reactions subserved by cell-mediated immunity, but an impaired humoral antibody responsiveness has also been well demonstrated. In spite of these changes, it is often feasible with the careful use of drugs to achieve a balance whereby renal homografts may survive with normal function for many years without excessively jeopardizing the host from infection. Failure to obtain a good result in kidney recipients usually implies either poor homograft function, a need for excessive chronic immunosuppression to maintain graft function, or both.[4,6,13] In heart recipients, the transplant itself does not often serve as a source for systemic infection,[14-16] although the homograft kidney or ureter may be a common portal.[5]

Since survival of kidney, heart, and liver grafts depends on essentially identical immunosuppressive techniques, it is not surprising that the infections after the transplantation of all three organs have similarities. Common features include a high risk from pneumonitis, a tendency for localized sepsis to quickly become multifocal, and the frequent etiologic role of Gram-negative bacteria, fungi, and other less common microorganisms of normally low pathogenicity.

However, the purpose of this communication is to determine what *extra* conditions existed in recipients treated by liver transplantation to account for the previously described[17-19,26] enormous risk from infection borne by these patients. The first step was to identify in failed cases the single most important triggering event in the downhill courses. The resulting analysis of hepatic cases was recently reported[20] and served as the framework on which the otherwise bewildering array of infections could be viewed for the present study.

The liver itself proved to be the special infectious risk factor, consistent with earlier experimental studies of Brettschneider et al[27] and Alican and Hardy.[28] In the analysis of the 93 recipients, damage to the liver emerged as the principal factor of failure in almost three fourths of the cases. Although the nature of the liver injury varied widely, the effects on infection were similar. Early in the course, ischemia, partial or complete hepatic devascularization, biliary obstruction, and rejection were frequently

Table 5.—Pattern of Infections in 26 Patients Whose Homografts Implicated Genesis of Sy

	No. of Patients	Orthotopic Transplant Patient No.						
		Blood	Liver	Biliary Tract	Peritoneal Cavity	Wound	Lung	Heart
Bacteria								
Escherichia coli	18	5, 8, 15, 30, 41, 43, 44, 47, 54a, 58, 60, 69, 79, 84	30, 41, 43, 44, 54a, 69	5, 30, 41, 43, 44, 47, 49, 54a, 69, 79	25, 43, 44, 47, 49, 58, 68, 69, 79, 84, 87	5, 49, 58, 68, 79, 87		
Enterobacter-Klebsiella	15	8, 15, 27, 28, 43, 47, 58	8, 43	25, 27, 28, 43, 47, 49, 60, 68, 87	22, 25, 43, 47, 49, 58, 68, 87	25, 27, 28, 62a, 68, 79		
Proteus	4	43, 58		43, 58	47	87		
Pseudomonas	5	8, 15, 79		49	79	8, 49, 79		
Serratia	2	87		27	87	27	87	
Group D *Streptococcus*	11	15, 27, 41, 43, 54a, 87	41, 43, 69	41, 43, 58, 69	43, 47, 68, 69, 87	27, 62a, 68	87	
Streptococci, others	6	27, 30	30	27	25, 49, 87	27, 62a, 87		
Bacteroides	8	8, 27, 43, 47, 49, 54a	54a	43, 54a, 58	43, 47, 68			
Clostridium	6	44, 49, 60		58	44, 47			
Anaerobic diphtheroids	3	54a, 55, 84						
Miscellaneous	7	27, 88	54a	49	47	27		
Fungi								
Candida albicans	15	8, 30, 70		43, 58, 63, 68, 70	25, 41, 43, 63, 68, 70, 79, 87	8, 25, 41, 49, 54a, 58, 62a, 63, 68, 70, 79, 87	5, 25	5
Aspergillus species	3		41, 79	79			79, 88	79
Miscellaneous	4	47	47		22	27, 62a		
Protozoa								
Pneumocystis carinii	3					27 (?), 49, 55		

Table 6.—Pattern of Infection in 26 Patients* Whose Homografts Did Not Seem Implicated in the Ge

	No. of Patients	Orthotopic Transplant Patient No.							
		Blood	Liver	Biliary Tract	Peritoneal Cavity	Wound	Lung	Pleura	Heart
Bacteria									
Escherichia coli	7	14b, 37, 39, 57, 72	39		3, 37, 39, 57, 59	59	39	39	
Enterobacter-Klebsiella	6	65b, 72, 76b			62b, 65b, 76b	59	3, 62b	62b	
Proteus	3	40			40		2, 40		
Pseudomonas	4	14b, 17			3		2, 3, 17		
Group D *Streptococcus*	3	54b, 61, 72			61				
Streptococci, others	2	14b			57				
Diphtheroids	1	14b							
Staphylococcus aureus	1	57							
Staphylococci, others	2	14b, 59			59				
Haemophilus influenzae B	1	19							
Clostridium	1	19							
Anaerobic diphtheroids	1	67							
Miscellaneous	3	59			72				17
Fungi									
Candida albicans	10	40, 83		59	17, 39, 40, 81, 83	14b, 54b, 59, 65b	40, 83		83
Aspergillus species	3		19				19, 71b, 81	71b, 81	81
Miscellaneous	1			62b		62b			
Viruses									
Herpes simplex	5						26, 39, 67, 81		26, 67
Cytomegalovirus	8		61	61			3, 26, 35, 37, 40, 65b, 83		26
Miscellaneous	1						26		26
Protozoa									
Pneumocystis carinii	5						19, 37 (?), 54b (?), 57, 61		
Toxoplasma gondii	1						17	17	
No infection	4†								

*All died.
†Orthotopic transplant patients 1, 4, 32, and 80.

nfection by Defective Biliary Drainage

Gastrointestinal Tract	Kidney	Urinary Tract	Central Nervous System
		28	
5, 25		5	
79	79		79

or Perpetuation of Systemic Sepsis

Gastrointestinal Tract	Kidney	Urinary Tract	Central Nervous System	Skin	Other
		57			
		19, 40			
83	65b	39, 40, 61, 65b, 83			
	81		81		
		62b		81	81
39, 61, 81					
	26			26, 61, 67	
					26
				26	
		17	17		17

accompanied by systemic infections, and these often included bacteremias, especially of the Gram-negative variety.

At a later time, febrile and other manifestations of systemic infection accompanied by Gram-negative bacteremia proved in the overwhelming majority of cases to be related to defective bile duct reconstruction, most commonly partial obstruction. Failure to promptly alleviate either biliary obstruction or bile fistula formation resulted in eventual patient death with or without other foci of infection in distant sites. Both with the early delayed complications, it became possible in a large number of cases eventually to compare positive blood cultures with cultures of bile, liver tissue, or fluid collected from or around the liver. The conformity of the blood cultures to the various cultures found in and around the liver was striking, particularly when duct obstruction was present.

From this information, steps have been taken to improve infectious disease care. We have been performing biliary reconstruction for the last $2\frac{1}{2}$ years with a Roux-en-Y technique that is known[20,22] to protect the liver from contamination by placing it outside the upper gastrointestinal tract (Fig 1, left). An acceptable alternative that retains the intact sphincter of Oddi is choledochocholedocostomy (Fig 1, right).

Even with such improvements of biliary reconstruction, there must be close surveillance afterward for obstructions, bile fistulas, abscesses, or other complications that are focused in the right upper quadrant. Because bacteremias are so often the first signal of such evolving disasters, a single-minded determination is necessary to clearly explain their causation, particularly if positive blood cultures persist in multiple samples Transhepatic cholangiography has been the single most important diagnostic test. Additional diagnostic tests that may rule out other causes of liver injury that could contribute to systemic infection include needle or open biopsies, scans using isotopes that measure recituloendothelial or parenchymal function, and serial liver function tests.

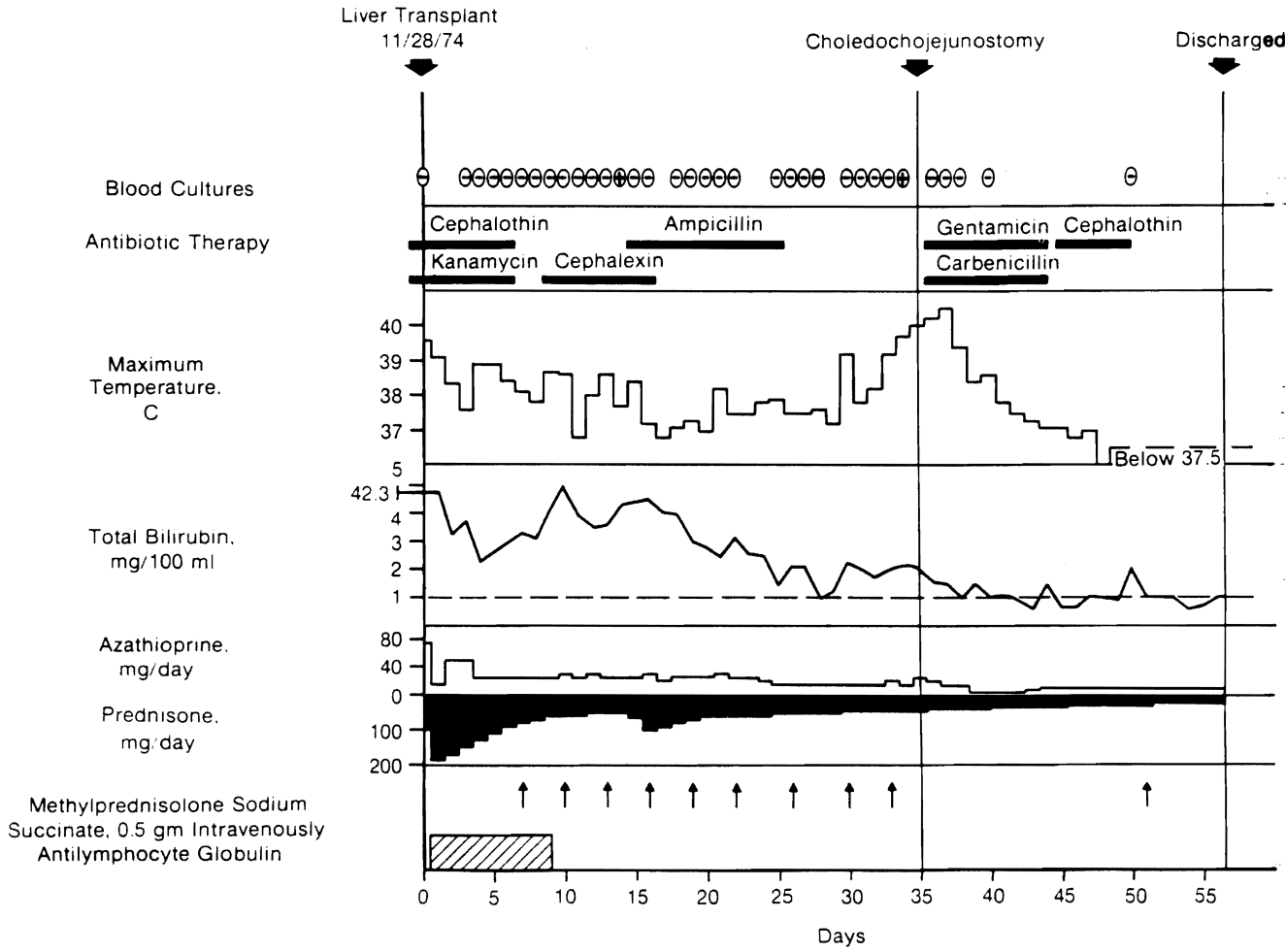
When an infection is found in or around the liver, curative treatment (usually surgical) must be instituted. Revision of biliary drainage is an especially important possibility. Imperfections of biliary construction that previously were always lethal have been successfully repaired in increasing numbers despite the fact that these corrective procedures have been carried out in the presence of positive bile, subhepatic, or liver cultures.[20,22] Success depends on carefully chosen antibiotic coverage.

Although it seems established that the liver homograft itself accounts for many of the infections after hepatic transplantation, it does not explain them all. Many of the recipients whose lethal infections seemed to be independent of the liver were generally those with the most advanced disease, possibly so far along that transplantation was no longer warranted. Some had bacteremia or fungemia at the time of transplantation, several others were receiving second grafts, and six suffered severe postoperative neurologic impairment that may have been

Table 7.—Infections in 16 Patients Who Were Alive March 1, 1976, From 15 Months to 6[illegible]

Orthotopic Transplant Patient No.	Reoperation for Biliary Complication	Infections of		
		Blood	Biliary Tract	Peritoneal Cavity
33	No			
42	No	*P aeruginosa*		
46	No	Anaerobic diphtheroids		
53	No	Anaerobic diphtheroids; *E coli*		
56	Yes	*E coli*	*E coli; P aeruginosa; Klebsiella*	
64	No			
73	No			
74	No	*S aureus*		
77	Yes	*E coli*	*Klebsiella*	
78	No			
82	No			
89	No	Diphtheroids; Gram-positive rods; Gram-positive cocci		
90	Yes	*Serratia*; group D streptococci	*Serratia*; group D streptococci	
91	Yes	*Klebsiella*; group D streptococci; *Clostridium; Bacteroides*		*Klebsiella*; group D streptococci; *Bacteroides; Herellea; P aeruginosa*
92	Yes	*E coli*	*Klebsiella*	
93	No			

Fig 4.—First two months after liver replacement in patient OT 92 (11-year-old boy). Positive blood cultures with *Escherichia coli* caused suspicion of partial obstruction, which was confirmed with transhepatic cholangiography. Despite apparently effective treatment with ampicillin sodium, fever persisted until partial obstruction relieved at reoperation. Eventually, bile shown to be infected with *Klebsiella* as well as *E coli*. Preoperative antibiotic therapy not effective against *Klebsiella*.



Liver Transplantation
Other Infections
Urinary tract infection (*Escherichia coli, Proteus, Pseudomonas aeruginosa*); pneumocystosis, herpes zoster
Necrotizing cellulitis (*P aeruginosa, Staphylococcus aureus*); pneumocystosis; disseminated herpes zoster; gluteal abscesses; serum hepatitis
None
Urinary tract infection (*Klebsiella, E coli*)
None
Pneumocystosis (?)
None
Vulvitis; laryngitis (influenza B virus); pneumocystosis (?); pneumonitis (*Candida albicans* [?]); subcutaneous abscesses (*S aureus*)
Herpes zoster; serum hepatitis
Nocardiosis (lung, prostate); pulmonary aspergillosis (?)
Sinusitis
None
Pleuritis (*Serratia*, group D streptococci); serum hepatitis
Urinary tract infection (*E coli*)
None
Pneumocystosis

derivative from central nervous system changes caused by the preexisting liver failure. More discriminating selection of candidates or earlier transplantation will be necessary in the future in order to avoid such circumstances. Greater care to avoid overimmunosuppression will be necessary as well, since, in our experience, rejection has not been a major feature of most of the homografts examined at autopsy.

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Nonproprietary Names and Trademarks of Drugs

Azathioprine—*Imuran*.
Ampicillin sodium—*Alpen-N, Amcill-S, Omnipen-N, Principen/N, Totacillin-N*.
Cephalothin sodium—*Keflin*.
Gentamicin sulfate—*Garamycin*.
Amphotericin B—*Fungizone*.
Flucytosine—*Ancobon*.

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