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Infections After Liver Transplantation: Risk Factors and Prevention

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LIVER transplantation (OLT) has now emerged as the treatment of choice for many patients with end-stage liver disease, and the number of centers performing OLT has grown tremendously over the last 5 years. Standardization of surgical techniques and the routine use of veno-venous bypass combined with improvements in organ preservation and immunosuppression have resulted in better overall patient survival. Despite these improvements, infections continue to dominate the early postoperative period in many patients and account for high morbidity and most deaths.

RISK FACTORS

Impeccable surgical technique remains the most important initial factor in preventing early infectious complications. The urgency of transplantation, surgical history, prolonged operative time, and excessive blood loss are well-documented risk factors. Technical complications requiring reoperation often increase bacterial and fungal infection rates. The need for retransplantation because of severe graft dysfunction and rejection or aggressive treatment of rejection in itself is a major influence on the subsequent development of sepsis in the perioperative period.

REVIEW OF RECENT STUDIES

Reports of infections from centers experienced in performing OLT over the last 5 years are summarized in Table 1.[1-5] Overall rates of infection varied from 50% to 83%, with mortality ranging from 4.6% to 26%. The improvements noted during this interval are multifactorial and reflect changes in technique and type of immunosuppression and overall better perioperative care of patients during this time. The high mortality in the early Pittsburgh series (26%) has been reduced to 4.6% with the introduction of a new immunosuppressive agent (FK 506), despite a relatively short follow-up period. Immunosuppression protocols, which included cyclosporine (CyA) and steroids, were used in the other studies. With the exception of the Mayo Clinic, most centers did not use selective bowel decontamination. In all series, the highest rates of bacterial infection were seen in patients with such risk factors as rejection, reoperation, and the need for retransplantation, and occurred almost exclusively in the first 2 months.

Table 1. Incidence of Infections and Mortality Over the Last 5 Years Reported From Liver Transplantation Centers

Center	Date	Number of Patients	Infection Rate (%)	Mortality (%)
Univ. of Pittsburgh	3/88	101	83	26
Univ. of California (LA)	3/88	35	66	14
Univ. of Minnesota	12/88	93	—	8.6
Mayo Clinic*	5/89	53	75	7.6
Univ. of Pittsburgh	8/90	110	50	4.6

*With selective bowel decontamination.

SELECTIVE BOWEL DECONTAMINATION

Most infections developing in immunocompromised patients arise from endogenous aerobic bacteria. The theoretic concept supporting the use of selective bowel decontamination (SBD) relies on the elimination of gram-negative aerobic colonizers ("resistance colonization") with preservation of the anaerobic flora. The activity of anaerobes in controlling local flora appears to protect patients against potential pathogens by limiting their growth in the gut and ultimately decreasing serious endogenously derived infections. Centers engaged in trials of routine use of SBD in leukemic and critically ill surgical populations report a decrease in rates of such infections, but mortality and ICU stays are not decreased. Despite many reports on this topic, controversy exists regarding the routine use of SBD. Concern has been expressed about the emergence of resistant organisms and about patients' compliance. The literature on SBD in patients undergoing OLT is sparse. This has been championed by the group at the Mayo Clinic, where routine SBD is given to all patients from the time an active donor search begins and continued through the first 3 postoperative weeks. Gram-negative infections are virtually eliminated during this period, with gram-positive organisms dominating those infections that develop during treatment. Rapid colonization with a similar spectrum of pretreatment organisms is seen once SBD is stopped and does not appear to influence morbidity. The Mayo Clinic data suggest that SBD does reduce perioperative gram-negative infection and should probably be used in patients undergoing OLT. The issues that require clarification include the timing of SBD, the selection of patients, the length of treatment, and the agents to be used. European centers use a combination of tobramycin and amphotericin, whereas the Mayo Clinic uses a gentamicin, nystatin, and polymyxin B regimen. The additional expense of the drugs used in Europe may well become a major influence against their ultimate choice in the United States. The persistence of significant numbers of gram-

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positive infections will require separate future consideration.

IMMUNOSUPPRESSION

Immunosuppression clearly plays a major role in decreasing host resistance to infection. The use of multiple drug regimens along with antilymphocytic and antithymocytic agents results in high infectious morbidity. The avoidance of heavy steroid pulses and recycles results in lowered rates of serious infections. Our recent experience with FK 506 is particularly promising, for in many cases, steroids can be withdrawn completely and the single agent FK 506 preserves good graft function. The infectious complication rate of the CyA era was reduced from 83% to 50%. Overall mortality was reduced from 25% to 4.6%, reflecting the lower rates of retransplantation, reoperation, and rejection associated with FK 506.

LONG-TERM PROPHYLAXIS

Major changes have also taken place in the use of long-term prophylaxis to prevent the development of opportunistic infections in these immunocompromised hosts. Protozoal infections, mainly *Pneumocystis carinii*, have been virtually eliminated in our patients by the daily administration of Bactrim for prolonged periods. Low-dose acyclovir has significantly decreased herpetic infections. Cytomegalovirus (CMV) infection, however, continues to be a major challenge. Among all transplantation patients, CMV appears with highest frequency in patients undergoing OLT. The development of symptomatic CMV is associated with certain well-established risk factors that include serologic status of the recipient-donor pairs, degree of immunosuppression, and the use of antilymphocyte therapy in managing steroid-resistant rejection. A recent randomized double-blind trial comparing high-dose acyclovir with placebo in a group of patients undergoing renal transplantation reports a significant decrease in rates of symptomatic CMV. Preliminary data in our patients given FK 506 under a similar protocol have not supported the findings in the Minnesota study. Episodes of CMV occur as frequently as they did in patients treated with CyA but have been associated with fewer deaths. The recent and successful addition of DHPG therapy to the management of symptomatic CMV infection has shown promise in reducing morbidity. Prophylactic treatment trials should be undertaken.

FUTURE DIRECTIONS

Future improvements in OLT will be directed toward decreasing the morbidity associated with this major procedure. Control of infection will continue to play a dominant role. The deliberate interruption of host defense mechanisms by immunosuppressive therapy is a necessary evil that requires novel approaches to infection prophylaxis. Prospective trials of SBD and improvements in antifungal and antiviral protocols are needed to minimize the constant threat of uncontrolled infection in these patients.

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