Infections in liver transplantation: risk factors and strategies for prevention

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Summary: Infection affects up to 70% of liver transplant recipients and is the second most common complication after rejection and graft dysfunction. Identified risk factors for infection include: previous transplantation; type of biliary anastomosis; transfusion requirements at surgery; surgical complications; duration of operation; duration of postoperative ventilation; serological status of donor and recipient; steroid use and serotherapy for rejection; and pre-and post-transplant antibiotic usage. The majority of symptomatic infections are bacterial and relate to surgery (intra-abdominal, biliary and wound infections), ventilation and intravenous cannulae. Cyto-megalovirus infections occur in 45–100% of recipients but are asymptomatic in the majority. Fungal infections are mostly due to Candida albicans but infections due to Aspergillus spp. occur in approximately 6% and carry a high mortality. There are very few prospective comparative trials of antimicrobial prophylaxis in this patient population. The management of these patients needs to be based on such studies.

Keywords: Liver; fungal infections; risk factors; antimicrobial prophylaxis.

Introduction

Over the past three decades liver transplantation has become established as a routine procedure with a high success rate. More than 500 livers will have been transplanted in the UK in the past year and over 2000 in Europe. Considerable progress has been made in the control of haemostasis, the refinement of surgical techniques and the development of immunosuppression regimens using new and existing agents.

Despite these advances, infection affects up to 70% of recipients and is the second most common complication of the procedure after rejection and graft dysfunction. With infection and rejection closely linked the emphasis needs to be on antimicrobial prophylactic strategies in order to prevent mortality due to serious infection and graft loss. Many liver transplant centres have now reported their experiences enabling the identification of the important risk factors for infection. However, many of the prophylactic regimens in use have evolved from other surgical and immunocompromised host settings and have not been formally examined in the liver transplant patient group. This paper reviews the incidence of the different types of infections, our current understanding of important risk factors and available data on evaluated prophylactic regimens.
Timing of infections post-transplant

Most published series have shown that there is a sequence of infectious complications following transplantation of any solid organ, including the liver. Knowledge of this is helpful in guiding duration of prophylaxis and the use of appropriate investigations and treatment when infection is suspected.

The most frequent infections in the first month post-transplant are those associated with the biliary, vascular and abdominal surgery involved in the transplant procedure. In addition some infections are transmitted with the allograft or were present in the recipient prior to transplantation. Between one and six months post-transplantation the most important organisms causing infections are the herpes group viruses, together with opportunistic organisms such as *Listeria monocytogenes*, *Pneumocystis carinii* and other fungi. Subsequent infectious complications are usually the result of community-acquired organisms. However, a few patients will have chronic viral infections affecting the graft and others who have received the most intensive immunosuppression for rejection, as well as the super-added immunosuppressive problems of herpes virus infection in some cases, will still be at risk of opportunistic infections.

**Bacterial infections**

Bacterial infections occur in 53–70% of transplantation procedures and in some series patients have suffered at least one bacterial infection in the post-transplant period. The commonest types of infection are: intra-abdominal abscess, cholangitis, bacteraemia, wound infection, lower respiratory tract infection and urinary tract infection, with intra-abdominal infection responsible for approximately 30%. The mortality associated with bacterial infection in the first 100 patients transplanted at the Royal Free Hospital was 4% (unpublished data) and this agrees very closely with the mortality data in the literature.

The bacteria isolated from infected patients in the postoperative period have varied in different series. Representative organisms are shown in Table I. Bacteria isolated from the graft perfusion fluid vary in their propensity to cause post-transplantation infection. Positive cultures have been found in 4–40% of cases in renal transplantation but most of these have been with Gram-positive skin bacteria. However, the isolation of the enterobacteriaceae and *Pseudomonas aeruginosa* correlates with vascular infection and postoperative sepsis.

**Fungal infections**

As with most groups of immunocompromised patients there is a high incidence of colonization with yeasts, although the percentage varies according to the number of sites sampled, the frequency of sampling and the
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Table I. Bacterial isolates from infected liver transplant recipients

<table>
<thead>
<tr>
<th>Gram-positive bacteria</th>
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<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Enterococci</td>
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<tr>
<td>Streptococci</td>
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<tr>
<td><em>Listeria monocytogenes</em></td>
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<tr>
<td><em>Nocardia</em> spp.</td>
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<table>
<thead>
<tr>
<th>Gram-negative bacteria</th>
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<tbody>
<tr>
<td>Enterobacteriaceae</td>
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<tr>
<td><em>Pseudomonas</em> spp.</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
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<tr>
<td><em>Legionella</em> spp.</td>
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<th>Anaerobic bacteria</th>
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<tr>
<td><em>Bacteroides</em> spp.</td>
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<tr>
<td><em>Clostridium</em> spp.</td>
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Use of antifungal prophylaxis. Currently 50% of Royal Free Hospital recipients are colonized (unpublished data). However, the incidence of infection varies from 4–50%. More than 50% overall are severe and are responsible for 20–30% of all severe infections. The majority of infections are caused by *Candida* spp. (77–83%) with *Aspergillus* spp. causing up to 23%. *Pneumocystis carinii* pneumonia occurs in 0–11% of liver transplant recipients and is closely linked with cytomegalovirus (CMV) disease. Cryptococcosis has occurred in up to 2%. Cases of mucor mycosis and infection with *Pseudallescheria boydii* have also been described but these seem rare.

More than 50% of fungal infections originate from the abdominal cavity, with 15–20% of cases involving the lungs and fungaemia or disseminated infection occurring in up to 17%. Although occurring very infrequently, disseminated aspergillosis is the most common cause of focal brain infection in this group of patients and *Cryptococcus neoformans* is the most frequent cause of meningitis.

Severe fungal infections carry a high mortality. Candidal infections are associated with death in 50–77% and invasive aspergillosis is almost universally fatal in this group.

The majority of fungal infections (85–100%) occur in the first two months post-transplant, although *P. carinii* infection tends to be delayed and cryptococcosis may well affect patients in the late transplant period.

**Viral infections**

CMV is the major virus causing morbidity and mortality in this patient group and is responsible for the greatest number of all types of infections.
The incidence of infection varies from 45\textsuperscript{20}–100\%\textsuperscript{21} in different studies, as a consequence of the incidence of seropositivity amongst the recipient population and of the number of seropositive to seronegative transplantations. Overall, 25–30\% of those infected develop disease,\textsuperscript{20,22} although 50–60\% of those at highest risk (seropositive to seronegative transplants) will develop clinical disease.\textsuperscript{23} Only approximately 3\% of those affected will develop CMV pneumonitis\textsuperscript{22} but the incidence of hepatitis is higher than in other transplant groups. CMV retinitis is unusual in these patients. The development of disease is associated with viraemia and in one series 19\% of those with viraemia detected by polymerase chain reaction (PCR) developed disease.\textsuperscript{24} PCR has been shown to detect viraemia a median of five days before the onset of disease, allowing appropriate therapy at an earlier stage than previously.\textsuperscript{25} The direct mortality of CMV disease is difficult to assess as patients often die of other associated disease. However, the mortality associated with pneumonitis appears similar to that seen in other transplant groups with at least 80\% dying in series published prior to the advent of gancyclovir and immunoglobulin therapy.\textsuperscript{3}

In addition to CMV hepatitis, there are a host of other viral causes of post-transplant hepatitis. The most common of these is hepatitis C virus (HCV). The majority of infections with this agent occur as a result of reinfection in patients who have been transplanted for HCV related cirrhosis. PCR techniques have shown that virtually all infected patients suffer reinfection post-transplant. Prior to the screening of blood products and knowledge of donor status primary infections occurred in more than 35\%\textsuperscript{26} but the incidence is now much lower. In one study 95\% of those with pre-transplant infection developed post-transplant hepatitis and the majority were found to be due to HCV. At one year post-transplant 56\% had no histological evidence of chronic liver disease.\textsuperscript{26}

Reinfection with hepatitis B virus (HBV) is almost inevitable unless long-term immunoprophylaxis is used. According to the EUROHEP database the highest recurrence is seen in those who are HBV-DNA positive pre-transplant (83 ± 6\%).\textsuperscript{27}

Epstein-Barr virus reactivation post-transplant is probably under-diagnosed. Whilst post-liver transplant hepatitis and persistent graft dysfunction has been ascribed to the virus in a few cases\textsuperscript{28} the most important complication is post-transplant lymphoproliferative disorder (PTLD). The overall incidence of this condition is approximately 1\%.\textsuperscript{29} In a large series of various solid organ graft recipients viraemia was found in 3-9\%, and 75\% of those with primary viraemia developed PTLD compared with 11\% of secondary viraemia cases.\textsuperscript{29}

Before the advent of acyclovir, herpes simplex virus infections (almost exclusively the consequences of reactivation) were responsible for clinical disease in approximately 50\% of seropositive patients.\textsuperscript{23} Now these infections are much less clinically significant than hcrpcs group infections.
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Other serious infections

Although there would appear to be considerable potential for transmission of *Toxoplasma gondii* via liver transplantation the incidence of toxoplasmosis in the large published series is less than 1%. The incidence of mycobacterial infections is extremely low in the published series. The overall incidence in the transplant population as a whole is 1%, more than 50-fold greater than the incidence in the general population. The occurrence of these and other serious infections is obviously dependent upon the prevalence of infection in the donor and recipient population.

Identified risk factors

Factors associated with the recipient and donor

The serological status of the donor and recipient with respect to the important viral infections previously discussed is probably the most significant factor influencing the frequency of infections post-transplant. In view of the high risk of disease following transplantation from CMV seropositive donor to seronegative recipient, this ought to be avoided, but such a strategy may be influenced by availability of donors and urgency of transplant requirement.

In one study transplantation for primary biliary cirrhosis was shown to be associated with a reduced risk of fungal infection. Urgent transplantation and re-transplantation are associated with an increased risk of fungal infection.

Factors associated with surgery

Duration of surgery and transfusion requirements have been shown to influence the risk of both bacterial and fungal infections. Improvements in the management of intraoperative coagulopathy have meant that most patients now receive only a few units of blood in contrast with the frequent need for the replacement of total blood volume many times over which was the norm just 10 years ago.

The type of biliary drainage also exerts an effect on the risk of bacterial and fungal infection. The technique of direct duct-to-duct anastomosis without the use of a splint has lead to a reduction from 37.5 to 2.6% in the incidence of cholangitis at the Royal Free Hospital (unpublished data).

The effects of immunosuppression

Steroid use, both pre- and post-transplant (particularly boluses given during the first two months) is an independent risk factor influencing the incidence of fungal infections. Recognition of this fact has led to a reduction in steroid dosage in more recently employed regimens. Whilst steroid usage has not been shown to have a significant effect on viral infections, the introduction of cytotoxic agents such as azathioprine correlated with the
increase in CMV infections seen, and the use of anti-lymphocyte globulin, anti-thymocyte globulin, OKT3 monoclonal antibody and the number of episodes of acute rejection treated are all associated with an increased risk of fungal and viral infections.\textsuperscript{3,10,19,23} Although the treatment of acute rejection episodes is necessary, this emphasizes the need for accurate diagnosis of rejection and underlines the fact that transplant immunosuppressive regimens cannot yet be considered optimal. Recent studies of the new agent tacrolimus (FK506) have shown a reduction in the number of CMV infections,\textsuperscript{30,31} cases of invasive aspergillosis,\textsuperscript{32} and bacterial infections,\textsuperscript{33} in comparison with patients treated with cyclosporin. This effect is probably due to a reduction in the total steroid dosage and serotherapy used for rejection episodes, and the number of rejection episodes encountered.\textsuperscript{31,33}

Other risk factors
The use of antibiotics pre-and post-transplant have been shown to correlate with the incidence of fungal infections.\textsuperscript{10} It is also likely that excessive usage will select out more resistant organisms which may subsequently cause infection in the recipient (or others on the unit) and so, for these reasons, the duration of therapy should be kept to a minimum, particularly when employing empirical therapy with subsequent lack of clinical or microbiological evidence of infection.

Other factors associated with an increased risk of infection include reintubation (usually for serious surgical complication or pneumonia) and vascular complications.

Prophylaxis and other preventative measures
There have been no large prospective randomized studies to examine the optimal antimicrobial prophylaxis required for the surgical procedure itself. Whilst choice of agents and duration of administration may be responsible for the differences in organisms isolated and numbers of the various types of infections seen in the literature, no firm conclusions can be drawn. Some centres have used selective decontamination of the digestive tract (SDD) with gentamicin, polymyxin E and nystatin and demonstrated a reduction in the number of infections in those in whom SDD effectively eliminated aerobic faecal flora.\textsuperscript{34-36} Certainly these centres appear to experience a low incidence of fungal infections. However, there is evidence that administration needs to begin a week or more before surgery to have optimal effect which makes this approach difficult to deliver.\textsuperscript{34,37} Proof of efficacy still awaits prospective comparative controlled trials.

Apart from the SDD studies there have been few publications on attempts to prevent fungal infections in this group of patients. Although fluconazole
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shows some promise there are no large comparative trials of azole prophylaxis. The outcome of the current multicentre UK fluconazole prophylactic study is awaited with interest.

Several randomized comparative studies have demonstrated the superior efficacy of early (the first 14 days or until discharge) post-transplant gancyclovir, with or without gammaglobulin in presenting CMV symptomatic infection when compared with various doses of acyclovir. Symptomatic infection was reduced to 5–9%. Acyclovir in high dose appears to be effective in comparison with no antiviral prophylaxis. Once the optimal dosage and duration of gancyclovir prophylaxis have been established we are likely to see a significant impact on the overall incidence of post-transplant infections.

Although colony stimulating factors have found their use in the treatment of neutropenic patients they are now being investigated in the non-neutropenic population, both for prevention of infection and for treatment. A preliminary study from Chicago where granulocyte colony stimulating factor was given to 34 consecutive liver transplant recipients for the first 10 days post-transplant is of some interest. As expected, there was a significant increase in the peak absolute neutrophil count when compared with the previous 49 consecutive untreated patients (20.5 × 10^9L^-1 vs. 9.3 × 10^9L^-1), but there was also a significant reduction in the length of intensive care unit stay, the number of patients developing adult respiratory distress syndrome and the number of infections per patient. This approach certainly seems worthy of further investigation.

Conclusions

Having identified the important risk factors for post-liver transplant infections there is a need to examine the impact of various preventative strategies in carefully controlled studies. There is currently a dearth of prospective comparative trials of antimicrobial prophylaxis in liver transplant recipients, although it is encouraging to see some important studies reaching publication, particularly with respect to CMV infection which has such a major impact on these patients. Although the indications are that some preventative strategies are bearing fruit, the management of infections in these patients needs to be based upon soundly conducted clinical research.

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