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Risk factors for infection after liver transplantation

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A B S T R A C T

Infection is a common cause of morbidity and mortality after liver transplantation. Risk factors relate to transplantation factors, donor and recipient factors. Transplant factors include ischaemia-reperfusion damage, amount of intra-operative blood transfusion, level and type of immunosuppression, rejection, and complications, prolonged intensive care stay with dialysis or ventilation, type of biliary drainage, repeat operations, re-transplantation, antibiotics, antiviral regimen, and environment. Donor risk factors include infection, prolonged intensive care stay, quality of the donor liver (e.g. steatosis), and viral status. For the recipient the most important are MELD score >30, malnutrition, renal failure, acute liver failure, presence of infection or colonisation, and immune status for viruses like cytomegalovirus. In recent years it has become clear that genetic polymorphisms in innate immunity, especially the lectin pathway of complement activation and in Toll-like receptors importantly contribute to the infection risk after liver transplantation. Therefore, the risk for infections after liver transplantation is a multifactorial problem and all factors need attention to reduce this risk.

Introduction

Orthotopic liver transplantation (OLT) has become a routine operation. One- and five-year patient survival is around 90% and 80%, respectively. A major cause of mortality and morbidity after OLT is infection, which occurs in up to 80% of the patients. Bacterial infections are most frequent (70%),

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followed by viral (20%) and fungal infections (8%) [1–3]. Clinical symptoms can be blurred or absent due to immunosuppression, often leading to delayed diagnosis. Both donor and recipient factors as well as aspects related to the transplant operation contribute to the risk of infection after OLT. Recently genetic polymorphisms in the innate immune system, from both donor and recipient, have been identified as important risk factors for infection after OLT. The known risk factors for infection after OLT will be discussed.

Transplant factors

The timing of infections after OLT is shown in Table 1 [3–5], divided in early, intermediate (immune suppression related) and late infections. Factors directly related to the OLT procedure contributing to the risk of infection can be either surgical technical issues, but can also be preservation-related or graft-related factors (Table 2). The rate of contaminated preservation fluid varies among centres and regions [6]. Peri-operative antibiotics will usually treat this, but culture-guided therapy sometimes is required [7]. Particularly the amount of intra-operative blood transfusion is related to the risk of infection immediately after OLT, both from the abdomen and other sources [2,8]. Initial poor graft function carries an increased infection risk. Partial hepatic necrosis, e.g. due to hepatic artery thrombosis, can lead to abscesses and bile duct injury with bacterial cholangitis. Abdominal fluid collections can become infected after OLT and need meticulous attention with imaging and diagnostic punctures. Both anastomotic and non-anastomotic biliary strictures (NAS) increase the risk of cholangitis. These are frequent complications and NAS more frequently occurs after non-heart-beating (NHB) donation (=DCD: deceased from cardiac death) [9]. Longer ischaemia times and genetic factors contribute to the risk of NAS, and thus indirectly contribute to the risk of infection after OLT [10]. Biliary leakage can lead to infected biloma, and this is seen more often with the use of a T-tube and bile duct ischaemia, whether or not due to hepatic artery stenosis or thrombosis [11]. The risk of surgical site infection is increased in the case of choledocho-jejunostomy [12]. In addition, indwelling catheters, invasive interventions, and prolonged dialysis or ventilation increase the risk of bacterial infection [3]. The antibiotic regimen around OLT has impact on the infection risk. Recent studies recommend oral selective digestive decontamination (SDD) during stay in the ICU [13,14]. Studies on SDD in OLT show a decrease in gram-negative bacterial infection, with an increased risk for gram-positive infection and resistance and a questionable net effect [15]. Extensive use of antibiotics poses the patient at risk for *Clostridium difficile* or fungal infection. Fungal prophylaxis decreases this latter risk but appears to be only justified in high-risk patients [3]. Risk factors for invasive candidiasis apart from heavy immunesuppression are prolonged or repeat operations and re-transplantation, high transfusion requirement, previous Candida colonisation or renal failure after OLT, and a choledocho-jejunostomy. For *Aspergillus* species the risk factors are similar plus fulminant hepatic failure, CMV disease and a prolonged ICU-stay [3].

Table 1
Timing of different infections after liver transplantation [3,4].

First month
Surgical site, abdomen (infected ascites, abscesses, cholangitis), blood stream, urinary system, respiratory tract, *Clostridium difficile colitis*, herpes, *Candida*.
Between one and six months after OLT
Opportunistic infections, often related to over-immunosuppression (e.g. after rejection): a.o.
CMV (especially D+/R− serostatus), EBV, HSV 6 and 7, *Aspergillus* species, *Pneumocystis jirovecii*, *Nocardia*, tuberculosis, endemic mycoses, toxoplasma gonddi.
Bacterial cholangitis in case of biliary strictures.
Hepatitis C virus recurrence.
More than six months after OLT
Community-acquired, especially airway and urine tract in addition to opportunistic infections like varicella-zoster.
Bacterial cholangitis in case of biliary strictures.
Hepatitis C virus recurrence.
More infections in case of graft dysfunction, biliary strictures or recurrent rejection.