Best Practice & Research Clinical Gastroenterology 26 (2012) 61–72

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Gastroenterology

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Risk factors for infection after liver transplantation

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Keywords:
Liver transplantation
Infection
Bacteria
Virus
Fungus
Risk factors
Donor
Recipient
Innate immunity
Toll-like receptors
Complement
Mannan-binding lectin
Ficolin
MBL-associated serine proteases

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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1521-6918
doi:10.1016/j.bpg.2012.01.004

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.

Table 2
Risk factors for infection after liver transplantation.

Transplant factors	*Recipient*
Ischaemia times, ischaemia-reperfusion damage	Underlying condition of the recipient, i.e. malnutrition
Infected preservation fluid	Co-morbidity, e.g. diabetes, obesity, COPD, renal failure and dialysis
Amount of intra-operative blood transfusion	Colonisation with *S. aureus* or resistant organisms
Level and type of immunosuppression (e.g. anti-CD25)	Prolonged hospital stay and catheters before OLT
Additional immunosuppression for rejection	Acute liver failure
Indwelling catheters, deep lines	CMV-status and disease (risk for other infections)
Complications like primary non-function, hepatic artery thrombosis, necrosis, biliary strictures	Presence of hepatitis B or C virus or HIV
Prolonged ICU-stay, dialysis, prolonged ventilation	MELD score >30
Type of biliary drainage (Roux-en-Y, T-tube)	Recipient age
Repeat operations and re-transplantation	Previous immunosuppression (autoimmune hepatitis; re-transplantation)
Antibiotic regimen	Previous infection (esp. airway, urine tract)
Viral prophylaxis and monitoring	Immune status for viruses
Environment (other infected patients, building activity, hygienic measures)	Male recipient receiving male donor liver
	Hygienic measures
	Travelling
Genetic polymorphisms in innate immunity	*Donor*
Lectin pathway of complement activation in donor and donor/recipient mismatch (MBL2, ficolin2, MASP2)	Infection in donor
Toll-like receptors in the recipient	Prolonged ICU-stay
	Quality of the liver graft (e.g. marginal graft)
	Viral status

Level and type of immunosuppression

Immunosuppressive treatment of rejection increases the risk of infection, including CMV reactivation. If possible the level of immunesuppression, especially mycophenolate mofetil or azathioprine, is reduced during CMV primo-infection or CMV-recurrence. During a severe infection or if EBV-DNA becomes detectable, reduction of immunesuppression may be needed in order to control the infection, accepting the risk that later on rejection occurs requiring additional immunesuppression. Sirolimus is associated with less cytomegalovirus infections than calcineurin inhibitors, but can – if used early – lead to wound dehiscence and infection [16,17]. While allowing late introduction of calcineurin inhibitors and thus sparing renal function, anti-thymocyte globulin may increase infection risk [18]. When a steroid-free regimen with anti-CD25 is compared to a regimen with prednisolone without anti-CD25, the infection rate in the regimen with anti-CD25 (basiliximab) is lower in two studies [19,20], similar in two [21,22] and increased in one study [23], with no differences in hepatitis C recurrence.

Recipient factors

A poor condition of the recipient increases the risk for infection: MELD score >30, ICU-stay >48 h prior to transplantation, recipient age, re-transplantation, predicted post-transplant dialysis or probability of reoperation are risk factors for infection (Table 2) [24]. Malnutrition is also a risk factor. Co-morbidity like cystic fibrosis or chronic bronchitis is known to increase the risk for pulmonary infection. Immunosuppression before OLT is a risk factor for infection and mortality, like – especially above the age of 50 years – in autoimmune hepatitis [25]. A prolonged (>1 week) pre-transplant hospital stay, long-term intravenous catheters, and ascites before transplantation were found to be associated with infection after OLT [26]. Obesity and diabetes appear to contribute to the risk of post-OLT wound infections [17]. Gender plays a role in the susceptibility for many, but not all, infections and may be related to the influence of sex hormones and gender differences in innate immunity [27]. As mentioned below, we and others showed that a male recipient of a male liver is at higher risk for bacterial infections than the other combinations of donor and recipient sexes after OLT. If a recipient is colonised

with MRSA or ESBL bacteria or if the recipient is infected with *C. difficile*, isolation measures are important to protect the other (transplant) patients. Environmental factors like building activity in the hospital (risk for *Aspergillus fumigatus*) or inadequate handwashing by personnel can also be risk factors for transferring infections to an OLT recipient. Treatment of *Staphylococcus aureus* colonisation can decrease morbidity after OLT [28,29].

Hepatitis B

In the past hepatitis B virus (HBV) present at OLT almost universally led to recurrence after OLT, often leading to graft failure and recipient death. The long-term administration of anti-HBV immunoglobulins (HBIG) during and after OLT led to a substantial reduction of HBV recurrence, lamivudin further reduced this problem, and the combination allowed OLT to be performed with $<5\%$ recurrence [30,31]. HBV-DNA level at OLT determines the risk of recurrence even with prophylactic treatment [32]. The addition of adefovir dipivoxil to lamivudin allowed late withdrawal of HBIG in many patients [33,34]. More recently, entecavir and tenofovir further reduced HBV recurrence after OLT and also allowed treatment of lamivudin-resistant patients [35,36]. Even entecavir monotherapy was able to prevent HBV recurrence [37]. Recipients of a donor liver with anti-HBV core protein positivity can develop HBV after OLT if they are not immune, therefore such recipients also need HBV prophylaxis [38].

Hepatitis C

Both in the USA and Europe hepatitis C virus (HCV)-related liver disease has become one of the leading OLT indications. If HCV RNA is present at the time of OLT it persists after OLT. In about 60% of patients this leads to more or less severe chronic active hepatitis. These patients can have an accelerated development of cirrhosis. As in HBV, patients transplanted with HCV can also develop cholestasis and rapid liver failure within weeks after OLT. Co-infection of HBV, HCV genotype 1, rejection therapy, recipient age over 49 years, higher donor age, a steatotic or otherwise marginal donor liver and no HCV therapy were risk factors for severe recurrence in different studies [39]. No clear differences in HCV recurrence existed between different induction immunosuppressive therapies [40]. Ideally HCV is treated before OLT, but often this is not tolerated. Addition of telaprevir or boceprevir improves the results of HCV treatment in patients before OLT. Studies with combinations of HCV protease and polymerase inhibitors are underway, even without peg-interferon and ribavirin. HCV recurrence after OLT can be treated with peg-interferon and ribavirin with a sustained overall viral response (SVR) rate of 35%, which is lower than in non-transplant HCV patients. The interleukin-28B TT polymorphism is associated with more severe histological HCV recurrence after OLT [41]. While the outcome of OLT for HCV in African American patients and other races is similar [42], an African American patient with HCV receiving a liver from a Caucasian donor also has a higher risk of severe HCV recurrence [43]. Polymorphisms in Toll-like receptor 3 may influence the development of rejection after OLT, when HCV is present [44]. After OLT use of HCV protease inhibitors can lead to extreme elevations of levels of tacrolimus and ciclosporin, and studies on combination therapy with peg-interferon, ribavirin and a HCV protease inhibitor and regimes without interferon after OLT are awaited [45].

HIV

In the past patients with human immunodeficiency virus (HIV) were excluded from OLT. Nowadays, with the use of highly active anti-retroviral therapy (HAART) HIV replication can be suppressed, and if CD4 lymphocyte counts are normal and no resistance to HAART exists OLT is possible in some patients with end-stage liver disease in HIV. These patients are still more prone to infections after OLT than other recipients and both HAART resistance and drug interactions need a lot of attention. Patients with HIV and HBV can have an excellent outcome after OLT [46]. In a meta-analysis of liver transplant outcomes in HIV-infected patients those with HBV had a better outcome than those without HBV, while patients without detectable HIV-load at OLT did better than those with detectable HIV-load, while in this study presence of HCV was not a predictor of outcome [47]. However, most authors agree

that after OLT especially in HIV-infected patients HCV recurrence can pose a severe problem, with a worse outcome after OLT in HCV-infected HIV-patients than in HIV-patients without HCV [48].

Herpes viruses

The donor and recipient immune status for viruses are important risk factors for viral infections. One of the most important viral infections after OLT is cytomegalovirus (CMV) infection: if a donor is IgG anti-CMV positive and the recipient is IgG anti-CMV negative a CMV primo-infection almost universally occurs in the recipient. Since, especially in the acute phase after OLT, this can lead to severe morbidity and even mortality, prophylaxis with valganciclovir is used for this donor positive/recipient negative (D+/R−) CMV-status combination. Most centres use three to six months of valganciclovir prophylaxis in this situation [49], and if the primo-infection then becomes manifest it is milder and the recipient is out of the acute phase after OLT. In renal transplantation less CMV infection and disease occurs if six instead of three months of valganciclovir prophylaxis is given. In the first year after OLT frequent monitoring of CMV-DNA by PCR in blood is indicated. In case CMV-DNA becomes positive after prophylaxis in a D+/R− combination (val)ganciclovir is started preemptively. In general, no prophylaxis with (val)ganciclovir is used in IgG anti-CMV positive recipients [50], although some of these patients may require more intensified CMV-DNA monitoring or prophylaxis.

EBV primo-infection or reactivation in the recipient is possible and can lead to post-transplant lymphoproliferative disease (PTLD) in the OLT recipient. This can range from mononucleosis to frank non-Hodgkin lymphoma. Treatment includes cessation of all immunosuppression except prednisolone, and administration of anti-CD20 in case of a B-cell PTLD. It is advisable to monitor EBV-DNA in the first year post-OLT, and in case of a positive and rising EBV-DNA to at least decrease the immunosuppression. Often EBV-DNA becomes undetectable after decreasing the amount of immunosuppression. The donor/recipient status for EBV, the amount of activated natural killer cells and certain underlying autoimmune disorders were found to increase the risk for PTLD [51].

The degree of immunosuppression and D/R status of IgG to other viruses like HSV 1,2, 6,7,8 and VZV determines the risk of developing disease from these viruses. Especially HSV 1 and 2 and VZV can be treated by (val)aciclovir. Most centres do not use prophylaxis for these viruses, but they use early treatment if required [52–55].

Donor factors

Currently infection of a donor leads to morbidity and mortality in approximately 1% of transplant recipients. Rapid nucleic acid testing for microbial infections in the donor might lead to higher acceptance rates of high-risk donors [56]. Especially with a longer stay of the donor in the hospital the risk to acquire a nosocomial infection increases. Bacterial infections in the donor are often treated with antibiotics in donor and recipient. Some unknown infections in the donor, like dengue or hepatitis E [57], may endanger a transplant recipient. Insufficiently treated or undetected infections in the recipient more often than donor infections lead to sepsis after OLT [58]. The quality of the graft (e.g. steatosis, donor age) relates to graft function, ICU and hospital stay and infectious complications.

Genetic polymorphisms in the innate immune system

Since adaptive immunity is suppressed by the immunosuppressive medication, the recipient becomes dependent on the innate immune system. This includes pattern recognition receptors (PRRs) that recognise pathogen-associated molecular patterns (PAMPs) on microorganisms. The innate immune system can then kill the pathogen directly in a lymphocyte-independent manner or activate adaptive immunity. In several pathways of innate immunity single nucleotide polymorphisms (SNPs) are known. In some other categories of immunosuppressed patients, e.g. bone marrow recipients, some of these polymorphisms were associated with an increased occurrence or severity of infection. This led to the hypothesis that such SNPs might influence the risk and severity of infection after OLT.

Toll-like receptors

Lipopolysaccharide from gram-negative bacteria is mainly recognised by Toll-like receptor 4 (TLR4). However, in a cohort from the Mayo Clinic no significant associations were found between the TLR4 SNPs D299G and T399I and the risk and outcome of gram-negative infections after OLT [59]. Toll-like receptor 2 (TLR2) is the major receptor for gram-positive bacterial cell wall components like peptidoglycan and lipoteichoic acid. The common R753Q SNP in the TLR2 gene results in defective intracellular signalling and impaired cytokine secretion in response to peptidoglycan, lipopeptides, and other known ligands. The mutation has been suggested to increase to risk of bacterial and viral infections and was found to influence the risk for and outcome of cytomegalovirus and hepatitis C infection after OLT [60–62]. The homozygous TLR2 Arg753Gln (R753Q) polymorphism impairs recognition of HCV core and NS3 proteins and was shown to be associated with allograft failure and mortality after OLT for chronic HCV [60,62]. The R753Q polymorphism also paralyses recognition by TLR2-mediated immune signalling in cells exposed to CMV glycoprotein B [61]. Patients homozygous or heterozygous for the TLR2 R753Q SNP had a higher CMV load and more CMV disease than OLT recipients without this SNP [63]. Recently a PCR was developed to detect the N284I and the L412F SNPs in the TLR3 gene that also plays a role in the defence against viruses, and clinical studies in relation to TLR3 polymorphisms are awaited [64].

Lectin pathway of complement activation

The lectin pathway of complement activation is an evolutionary conserved defence against microorganisms [65]. It includes mannan-binding lectin (MBL), ficolin-2 (FCN2) and MBL-associated serine protease 2 (MASP2). These proteins are almost exclusively liver-derived and crucial effectors of the innate immune system in the defence against pathogens. Lectins are humoural PRRs that recognise carbohydrate-motifs on microorganisms and elicit innate immunity. These lectins cooperate with phagocytes and other humoural factors, including complement [66,67]. Polymorphisms in the lectin pathway determine its functional activity and are quite common. Mannan-binding lectin (MBL) and ficolin-2 (FCN2) both can activate the MBL-associated serine protease 2 (MASP2) [68]. FCN2 has similarities in structure and function to MBL and its preferential binding target is *N*-acetyl-glucosamine, a constituent of bacterial peptidoglycans and a major component of their cell wall [69,70]. Activated MASP activates the complement cascade and leads to opsonisation of microorganisms for phagocytosis or leads to formation of a complement membrane-attack complex (Fig. 1), which leads to 'holes' in the bacterial wall resulting in death of the pathogen [71–73]. It had been shown that SNPs in the exon1 region of the MBL gene (MBL2) interfere with the oligomerization of the protein and polymorphisms in the promoter regions alter the rate of synthesis of the protein, leading to changes in avidity and protein level of MBL respectively, resulting in MBL deficiency [74–76]. Ficolin-2 (FCN2) SNPs in the carbohydrate-recognition domain encoding region are associated with decreased (FCN2-B) or increased (FCN2-C) ligand binding of ficolin-2 compared to wild-type ficolin-2 (FCN2-A) [77].

MBL deficiency is associated with more and more severe infections in HIV infection, bone marrow transplantation, pancreatic and renal transplantation, but not in several other conditions, such as pneumococcal infections in randomly included patients, and it may confer protection against tuberculosis [78–80]. However, MBL deficient patients receiving a pancreas–kidney transplantation had better outcomes because of some protection against ischaemia-reperfusion injury and rejection [81]. Two polymorphisms in the MASP2 gene lead to a functional defect in the protease [82]. One SNP leads to the inability to activate complement [83,84], the other SNP is located in the control protein domain2 of MASP2, which is important in stabilising the structure of the serine protease domain [85], and is essential for cleavage of complement C4 [86]. Since MBL, ficolin-2 and MASP2 are almost exclusively produced by the liver their impact in OLT is of particular importance [87]. Our group recently showed that polymorphisms in the lectin pathway of complement activation are important risk factors for bacterial infection post-OLT. Transplantation of a MBL deficient donor liver into a MBL sufficient recipient results in rapid decrease in MBL blood levels, while the functionally important MBL2 SNP in the donor that resulted in low blood levels was also associated with bacterial infections after OLT [88]. This finding was then confirmed by others [89,90]. Since the ficolin pathway may compensate for

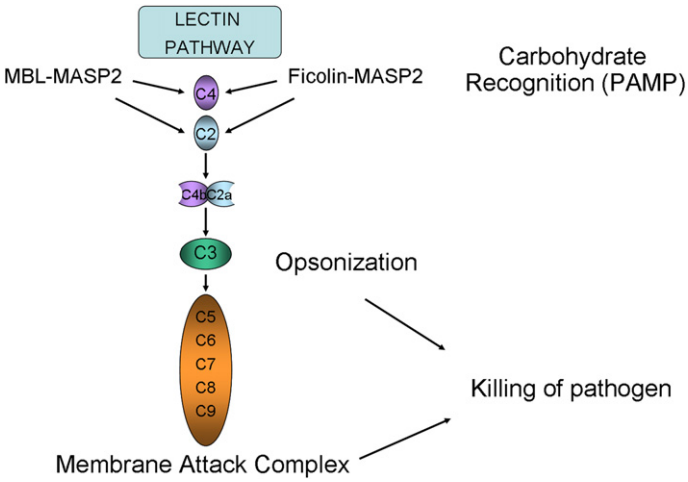

Fig. 1. The lectin pathway is activated when either mannose-binding lectin (MBL) or ficolin-2 binds to carbohydrate structures or PAMPs which are present on a large number of pathogens. Upon binding, the associated serine protease MASP2 is responsible for activation of the complement cascade. This will lead to opsonization for phagocytosis and the formation of a membrane-attack complex, both resulting in the killing of the pathogen. Modified from: Dommett et al. Mannose-binding lectin in innate immunity: past, present and future. Tissue Antigens (2006) 68: 193–209.

deficiency in the MBL pathway (both activate MASP), high-resolution melting assays were developed to include all known functional SNPs in the lectin pathway of complement activation, including MBL2, FCN2 and MASP2 [91]. Recipients receiving a donor liver with mutations in all three components, i.e. MBL2 (XA/O or O/O), FCN2+6359T, and MASP2+371A, had a cumulative risk of bacterial infection of 75% as compared to only 18% with wild-type donor livers, an observation confirmed in a second cohort. In addition a genetic (mis)match between donor and recipient conferred a two-fold higher infection risk for each separate gene. The more SNPs leading to a deficient phenotype (with low MBL level and low-binding ficolin levels in the recipient), the higher the risk for bacterial infection (Fig. 2). This was

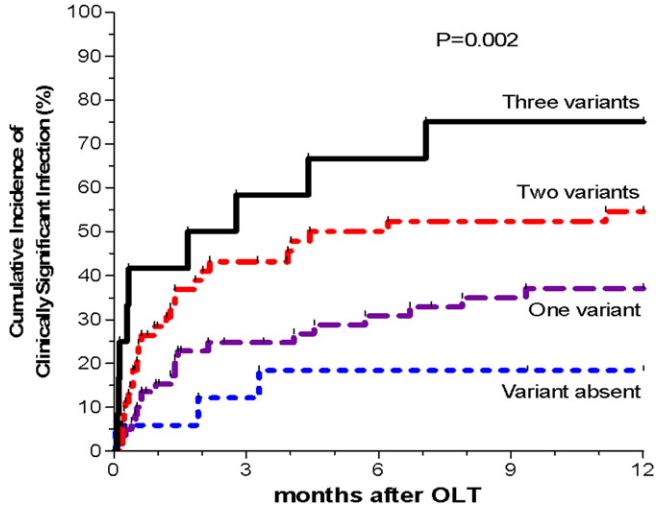

Fig. 2. Cumulative incidence of clinically significant infection after orthotopic liver transplantation, according to donor lectin pathway intergenic haplotype. Ref. [92].

a stepwise increase in the risk with the lectin pathway gene profile of the donor and the donor–recipient (mis)match profile independent from other risk factors gender and antibiotic schedule. In addition, patients with the indicated lectin pathway gene polymorphisms and infection had a six-fold higher mortality, of which 80% was infection-related [92].

The relationship between cytomegalovirus (CMV) and MBL in solid organ transplantation had been studied mainly in kidney transplantation [78,93,94], and only in a small number of patients after OLT [95]. We investigated the complete MBL–ficolin–MASP gene profile in relation to CMV infection after OLT. It became clear that polymorphisms in the lectin pathway of complement activation also increase the risk of CMV disease. Combined analysis of variant MBL2 (XA/O or O/O) and wild-type FCN2 (FCN2-A) polymorphisms in the donor liver showed an independently associated increased risk of CMV infection for either and both genotypes. This effect was especially strong in IgG anti-CMV donor negative/recipient positive (D−/R+) patients. Moreover, a genetic donor–recipient mismatch for MBL2 and FCN2 increased the CMV risk independently, also combined, and also particularly in CMV D−/R+ patients. For MBL the highest risk for CMV infection was in MBL sufficient recipients of a MBL deficient donor liver. In addition, a FCN2-C (high-affinity) donor liver reduced the chance for CMV infection in a FCN2-A recipient as opposed to the other FCNs genotype combinations. Again, there was a stepwise increase in CMV infection risk with the gene profile of the donor and the combined MBL2 and FCN2 donor-recipient mismatch profile, independent from donor–recipient CMV serostatus, also at increasing CMV (re)infection cut-off values of CMV positivity [96]. These data indicate that a link exists between several components of the lectin pathway of complement activation and the initial immune response to bacteria and CMV after OLT. The association of MBL2 SNPs with CMV and with bacterial infections was similar after OLT. However, with bacterial infections an association with FCN2-B and with MASP2 SNPs was found, while for CMV infection FCN2-C was important and no relation with MASP2 was found [96]. This illustrates differences in innate immune defence against bacterial and viral (CMV) pathogens after OLT [92,96]. CMV regulates immunomodulatory genes, that also change innate immunity in favour of CMV survival, e.g. inhibition of NF-κB leading to decreased cytotoxicity, and inhibition of dendritic cells and their functionality [97–99]. This might also explain why CMV infection or reactivation increases the susceptibility to bacterial and pneumocystis infection. Complement activation is potentially detrimental to the host and is kept in place by inhibitors. CMV is able to upregulate the expression of host-encoded (surface) complement inhibitors [100], and counteracts complement activation by incorporation of host cell-derived complement regulatory proteins CD55 and CD59 [101]. As mentioned, TLR2 Arg753Gln gene polymorphism is associated with CMV replication after OLT [63]. MBL is able to interact with TLR2 in the phagosome to initiate pro-inflammatory signalling [102], and therefore SNPs in both may affect this signalling and changed immunity against CMV after OLT. A subsequent mechanism by which MBL could be involved in immunity against CMV is that the intracellular interaction of its isoform L-MBL with CMV glycoproteins may disrupt CMV virion assembly or formation, restricting CMV replication [103].

A possible clinical application of our findings could be to screen for recipient and donor MBL2, FCN2 and MASP2 risk alleles. Subsequently one could intensify the antibiotic strategy or antiviral prophylaxis and more closely monitor high-risk patients. It is unknown if supplementation of recombinant MBL or ficolin will decrease the infection risk post-OLT. It has been shown that recovery of opsonic activity lags behind recovery of MBL serum levels [104]. A study with recombinant MBL in OLT was terminated by the sponsor, as yet for unclear reasons.

It has become clear that certain innate genetic profiles of donor and recipient are important risk factors for infections after OLT [105]. Indeed, as shown, they seem more important than some clinical or environmental factors. Other disturbances in innate immunity may also play a role. This may include changes in – for instance – other Toll-like receptors, Nod-receptors, or RIG-1 like receptors [106]. Recognition of PAMPs by PRRs triggers a cascade of downstream signalling leading to an array of antimicrobial immune responses by cytokines, chemokines and type I interferons, and these responses may also be changed due to polymorphisms in some recipients [106]. Crosstalk between innate and adaptive immunity may also be affected. More investigation into this area is urgently needed. If the genetic make-up of donor and recipient is known this may lead to more personalised prophylaxis around OLT.

Practice points

- Many transplantation-related, recipient and donor factors are involved in the risk for infection after liver transplantation.
- Genetic polymorphisms in innate immunity, e.g. in recipient toll-like receptors, and in both the donor and recipient lectin pathway of complement activation have an important impact on the infection risk in the liver transplant recipient.

Research agenda

- The influence of polymorphisms in the innate immune system on the infection risk after liver transplantation needs to be further elucidated
- Prospective controlled studies are needed to investigate the role of intensified monitoring and anti-microbial prophylaxis in recipients at high-risk for infectious complications.

Conflicts of interest

The authors have no conflicts of interest.

Acknowledgements

The work was supported by MD Clinical Research Trainee (AGIKO) ZonMw (The Netherlands Organisation for Health Research and Development) grant 40-00703-98-10578, the Dutch Digestive Foundation (W007-18) and the Foundation Prof. A.A.H. Kassenaar Fund from the Leiden University Medical Center.

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