Frontiers in Liver Transplantation

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Management of infections pre- and post-liver transplantation: Report of an AISF consensus conference

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Summary

The burden of infectious diseases both before and after liver transplantation is clearly attributable to the dysfunction of defensive mechanisms of the host, both as a result of cirrhosis, as well as the use of immunosuppressive agents.

The present document represents the recommendations of an expert panel commended by the Italian Association for the Study of the Liver (AISF), on the prevention and management of infectious complications excluding hepatitis B, D, C, and HIV in the setting of liver transplantation.

Due to a decreased response to vaccinations in cirrhosis as well as within the first six months after transplantation, the best timing for immunization is likely before transplant and early in the course of disease. Before transplantation, a vaccination panel including inactivated as well as live attenuated vaccines is recommended, while oral polio vaccine, Calmette-Guerin's bacillus, and Smallpox are contraindicated, whereas after transplantation, live attenuated vaccines are contraindicated. Before transplant, screening protocols should be divided into different levels according to the likelihood of infection, in order to reduce costs for the National Health Service. Recommended preoperative and postoperative prophylaxis varies according to the pathologic agent to which it is directed (bacterial *vs. viral vs. fungal).* Timing after transplantation greatly determines the most likely agent involved in post-transplant infections, and specific high-risk categories of patients have been identified that warrant closer surveillance. Clearly, specifically targeted treatment protocols are needed upon diagnosis of infections in both the pre- as well as the post-transplant scenarios, not without considering local microbiology and resistance patterns.

Keywords: Liver transplantation; Cirrhosis; Viral infections; Invasive fungal infections; Bacterial infections.

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Abbreviations: AFB, acid-fast bacilli; Amb, amphotericin B; BAL, bronchoalveolar lavage; CBC, complete blood count; CDC, centres for disease control; CR-BSI, catheter-related blood stream infection; CR-CL, creatinine clearance; CSF, cerebrospinal fluid; CTL, cytotoxic T-lymphocyte; D+/R−, donor positive/recipient negative; EBNA, Epstein Barr virus nuclear antigen; EBV, Epstein-Barr virus; ESKD, end-stage kidney disease; ESBL, extended-spectrum β-lactamase; HSV, herpes simplex virus; HHV8, human herpesvirus 8; ICU, intensive care unit; IGRAs, interferon-gamma release assays; IE, infective endocarditis; INH, isoniazid; KS, Kaposi' sarcoma; L-Amb, liposomal-amphotericin B; LRTI, lower respiratory tract infection; LTR, liver transplant recipient; MDR, multidrug-resistant; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; mTOR, mammalian target of rapamycin; NAT, nucleic acid test; PTLD, post-transplant lymphoproliferative disease; RTI, reproductive tract infection; RSV, respiratory syncytial virus; SDD, selective decontamination of the digestive tract; SOT, solid organ transplant; SS, single strength; SSI, surgical site infection; TDM, target drug monitoring; TEE, transesophageal echocardiography; TMP-SMX, trimethoprim sulfamethoxazole; TST, tuberculosis skin test; TTE, transthoracic echocardiography; UTI, urinary tract infection; VRE, vancomycin resistant enterococci; VZV, varicella zoster virus.

Introduction

Risk of pretransplantation infections

The identification and selection of a candidate for liver transplantation is a complex process that requires a team approach. Both indications and contraindications can change over time, reflecting advances in understanding of and ability to treat certain disease processes [1] including infections. A practical clinical

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approach to the management of patients with cirrhosis during transplant selection [2] includes the evaluation of the infectious risk, aiming to prevent or reduce both the risk of infection-related drop out from the waiting list and the negative impact on the outcome after LT.

Patients with cirrhosis often develop sepsis as a result of the dysfunction of the defensive mechanisms against bacterial, viral or fungal infections [3]. The overall mortality of infected patients is reported to be as high as 38% (odds ratio for death of infected *vs.* non-infected patients of 3.75) [4]. Spontaneous bacterial peritonitis (SBP) represents one of the most common infectious complications reported in patients with cirrhosis while waiting for LT.

Liver transplantation is a major, lengthy and complex surgical procedure performed on severely ill patients. Therefore identification, control, decolonization, and eradication of either bacterial, viral, fungal, or parasitic infections is paramount. A microbial burden that may be kept under control by the host's immune system before transplant may acquire notable relevance after the combination of major surgery and immunosuppression.

Risk of post-transplantation infections

Bacterial infections, especially those involving gram-negative bacteria, represent a major complication in liver transplant recipients, the frequency ranging between 20% and 80% of cases, and they contribute to longer hospital stays and increased hospital costs [5]. Three-fourths of bacterial infectious episodes occur in the first month after transplantation [6]. Most of these infections are endogenous and arise from aerobic gram-negative bacteria (GNB) and yeasts that have colonized the oropharynx, stomach and bowel [7].

The role of selective digestive tract decontamination (SDD) with antibiotics in the prevention of bacterial infections in liver transplant recipients is still a matter of debate [8]. A recent study from Spain did not confirm that fluoroquinolones administered from the time of transplantation have any protective effect against the development of early bacterial infections after liver transplantation [6].

Liver transplant recipients may be at risk for developing mycobacterial infections due to latent tuberculosis (TB). However, once the diagnosis is made and the specific treatment is adopted, patient survival is similar to that of liver transplant recipients without latent TB [9].

Invasive fungal infections (IFI) and Cytomegalovirus (CMV) infection are important causes of morbidity and mortality in liver transplant recipients. A significant reduction in both fungal and CMV infections was demonstrated by adopting prophylactic regimens [10–12].

Aims

The goal of this document is to provide clinical guidelines for the appropriate management of infections in the setting of liver transplantation.

Methods

The promoter of these "Consensus Guidelines" was the Italian association for the Study of the Liver (AISF), which identified a scientific board of Experts in charge of the document preparation. The Consensus was endorsed by the Italian society for Infectious and Tropical Diseases (SIMIT). The scientific board defined the methodology utilized as well as the goals, and acted as developer and reviewer. The methodology chosen involved the following steps:

(a) The promoters and the scientific board selected the main topics of interest: (1) Epidemiology of infections in the transplant setting, (2) Pre-LT infectious work up, (3) Management of infections in the post-LT, (4) Treatment of infections in liver transplantation.
(b) For each topic, a working party was identified by both the promoters and the scientific board, and was composed of a group of at least four experts guided by a chairman. The chairman, together with the promoters and the scientific board, selected the relevant clinical questions regarding both clinical practice and controversial areas. The questions were circulated within the working groups to refine the topics and to avoid duplications. The members of the working parties were identified on the basis of competence, role, expertise and publications/research in the field of infections, end stage liver disease and liver transplantation.
(c) The working groups independently carried out a systematic literature search and review, using Medline/PubMed to support definitions and statements. Each recommendation was graded according to the Centre for Disease Control's (CDC grading system, Supplementary Table 1)
(d) The working groups elaborated the proposed statements, graded according to the selected grading system. They prepared the statements together with the presentation of the literature review for each topic during video-conferences, group meetings, and correspondence before the Consensus Conference
(e) The jury members were by no means involved in the selection, preparation, and discussion of the topics and statements prior to the Consensus Conference.
(f) All the promoters, members of the scientific board, working groups, and jury invited to participate to the Consensus Conference were asked to declare any potential conflict of interests.

A Consensus Meeting was held in Bergamo in 2012. The consensus group consisted of a total of 124 participants (including promoters, scientific board, working groups, jury). The jury was selected among infectious disease specialists, hepatologists, microbiologists, intensive care physicians, surgeons, epidemiologists, patient representatives and ethicists. During the first sessions, the chairman of each group presented the selected topics and the proposed statements for each question. A general discussion was held in order to refine the statements and identify the possible adjustments. At the end of the general session, each group met independently to re-elaborate the final statements to be presented in the final voting session according to the suggestions received. The final general session consisted in the presentation of every single statement by the chairman of each working group, followed by an electronic vote from the jury. The agreement scale consisted of 2 levels of agreement (Agree, Disagree). The results of jury voting are available online as Supplementary data.

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Vaccination and liver transplantation

Pretransplantation

Despite emerging evidence that vaccinations are safe and effective among immunosuppressed patients, most vaccines are still underutilized in these patients. The efficacy, safety, and protocols of several vaccines in this patient population are poorly understood. Timing of vaccination appears to be critical because response to vaccinations is decreased in patients with end-stage organ disease and within the first 6 months after transplantation. In addition, liver transplant candidates might often wait for an unpredictable length of time before a suitable donor is available, and during this interval, all recommended vaccinations as well as boosts should be given. Although vaccination responses in some patients awaiting transplantation are suboptimal, antibody responses are usually even more attenuated when vaccines are administered after transplantation [13–15]. For these reasons, primary immunizations should be given before transplantation, and as early as possible during the course of disease. The vaccination strategy should include vaccination of household contacts and health care workers at transplant centres, unless contraindicated. In the transplant population, however, no conclusive data are available on the use of immune-adjuvants and on the screening for protective titres. Nevertheless, most vaccines appear to be safe in solid-organ transplantation recipients, but live vaccines should be avoided until further studies are available. The risk of rejection following vaccinations appears to date minimal.

The following are the indicated vaccinations for paediatric transplant candidates [16]: Inactivated: Influenza, Hepatitis A and B, Pertussis, Diphtheria, Tetanus, Polio (inactivated), *Haemophilus influenzae*, *Streptococcus pneumoniae* (conjugated or polysaccharide vaccine), and *Neisseria meningitidis*. Live attenuated: Varicella, Measles, Mumps, and Rubella. Rabies vaccine is not routinely administered, and is recommended for exposures, or potential exposures due to vocation or avocation. Smallpox and anthrax vaccinations are not routinely recommended in the pretransplant setting.

In adult liver transplantation candidates, the following vaccinations are indicated [16]: Inactivated: Influenza, Hepatitis A and B, Tetanus, Polio (inactivated), *Streptococcus pneumoniae* (conjugated or polysaccharide vaccine) and Varicella (live attenuated). Other vaccinations are indicated in special circumstances: *Neisseria meningitidis* is recommended in members of the military, travellers to high risk areas, in cases of properdin deficiency, terminal complement component deficiency, and in patients with functional or anatomic asplenia.

Specific contraindications exist for other vaccines, including the oral polio vaccine, Calmette-Guerin's bacillus, and Smallpox.

Post-transplantation

Current data seem to support the assumption that solid-organ recipients will benefit from consistent immunization practices; however, further studies are recommended to improve established protocols in this patient population [17].

In general, the following vaccinations are recommended for paediatric transplant recipients [16]: Inactivated: Influenza, Hepatitis A, Pertussis, Diphtheria, Tetanus, Polio (inactivated), *Haemophilus influenzae*, *Streptococcus pneumoniae* (conjugated or polysaccharide vaccine), and *Neisseria meningitidis*. On the contrary, live attenuated vaccines including Varicella, Measles, Mumps, Rubella, BCG, and smallpox are contraindicated. The Hepatitis B vaccine is poorly immunogenic after transplantation. Serial hepatitis B surface antibody titres should be assessed both before and after transplantation to evaluate the adequacy of the elicited immune response. The following vaccines are recommended for adult transplant recipients [16]: Inactivated: Influenza, Hepatitis A, Tetanus, Polio Polio (inactivated), *Streptococcus pneumonia*. Regarding Hepatitis B virus vaccination after transplantation, it is poorly immunogenic, and accelerated schedules may be yet less immunogenic. Rabies vaccine is recommended only for exposures, or potential exposures due to vocation or avocation. On the contrary, live attenuated vaccines are contraindicated: Varicella, BCG, and Smallpox.

Statements

Pretransplantation

Question 1.a
Is it advisable to define different levels of infectious screening for liver transplant candidates warranting accuracy and reducing costs for the National Health Service and efforts for the patients?

Statement 1.a
The infectious screening in liver transplant recipients should be graduated in different levels, warranting both accuracy and reduction of costs for the National Health Service (III C):

Level 1 → to be performed in all patients candidate to liver transplantation
Level 2 → to be performed only in patients eligible to liver transplantation at the time of listing
Level 3 → to be performed in patients with risk factors or from geographic area endemic for specific infections

Question 1.b
Which are the levels of screening for infections in liver transplantation candidates?

Statement 1.b1

- First level screening to be performed to all patients candidate to liver transplantation (if not available in the previous 3 months) (III C):
  - Human immunodeficiency virus (HIV) 1 and 2 Abs
  - Hepatitis B virus (HBV) serology: HBsAg, HBcAb, HBsAb
    - if HBsAg pos → HBeAg/HBe Ab; HBV-DNA, Hepatitis D virus (HDV) IgG
    - if HBcAb pos → HBV-DNA
  - Hepatitis C virus (HCV) Ab → if positive, HCV-RNA and HCV genotype
  - Hepatitis A virus (HAV) Ab IgG
  - Chest X-ray

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Statement 1.b2

- Second level screening to be performed to all patients eligible to liver transplantation, at listing (III C).
  - *Mycobacterium tuberculosis*: history + Tuberculin skin test (PPD-Mantoux) + Interferon-Gamma Release Assays (IGRAs) (II A)
  - Cytomegalovirus: CMV IgG; CMV-DNA is not recommended before liver transplantation
  - Epstein Barr virus (EBV): EBV VCA IgG and EBNA Ab
  - Human herpes virus 8 (HHV-8) IgG (anti-lytic and anti-latent antibodies)
  - Varicella zoster virus (VZV), Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2) IgG
  - Urine culture
  - Parasitological exam and stool culture (*Strongyloides stercoralis* serology, *Toxoplasma gondii* IgG, *Treponema pallidum* serology - Immune-enzymatic assay with VDRL or RPR if positive -), *Staphylococcus aureus* nasal/axillary swab
  - Dental X-ray or dental scan

Statement 1.b3

Third level screening to be performed to a subset of patients according to the clinical history, comorbidities and to endemic diseases and local epidemiology following ID Consult (III C).

- Vancomycin-resistant *Enterococcus* (VRE) and multidrug-resistant (MDR) Gram (-) *rectal swab*
- Serology for: Histoplasma, Coccidiomycosis, Trypanosome, Schistosoma, Leishmania
- Malaria blood test
- Human T cell lymphotropic viruses (HTLV) 1–2 IgG

Question 1.c

Prophylaxis of tuberculosis infection: Who?

Statement 1.c

Prophylaxis of TB should be considered in all patients candidate to liver transplant with:

- PPD-Mantoux $\geqslant$5 mm after 48–72 h and IGRAs positive (II A)
- Recent close exposure to person with active TB (II A)
- PPD-Mantoux <5 mm and IGRAs positive (II B)
- PPD-Mantoux $\geqslant$10 mm and IGRAs negative (III B)
- In case of indeterminate IGRAs → ID Consult is recommended (III B)

Comment: A systematic review of 7 studies estimated that, compared with the general population, liver transplant recipients have a 18-fold increase in the prevalence of active *Mycobacterium tuberculosis* infection and a 4-fold increase in the case-fatality rate [18] (Supplementary Table 2).

IGRA (Quantiferon TB Gold test or T-spot TB) must be performed, together with PPD, due to the high rate of false negative PPD test in immunodeficient patients [19,20].

Question 1.d

Prophylaxis of tuberculosis infection: Which is the proper schedule?

Statement 1.d

- Recommended treatment scheduled is: Isoniazid 5 mg/kg/d, (max 300 mg/d) + Vit. B6 for 6–9 months (II A)
- In case of chest X-ray evidence of fibrotic lesions and PPD $\geqslant$5 mm, IGRAs positive and no previous TB therapy, treatment should be prolonged up to 9 months (II B)

Comment: In case of isoniazid-resistance or intolerance, rifampicin (10 mg/kg/d, max 600 mg/d, for 4 months) or ethambutol + levofloxacin according to ID consult can be indicated. Except for isoniazid-resistance, no different therapeutic regimens can be recommended, as no better efficacy has been documented and due to the major risk of both toxicity and drug-interactions.

Question 1.e

Prophylaxis of tuberculosis infection: When?

Statement 1.e

- Treatment for TB infection should be started before liver transplant whenever feasible and tolerated (II A)
- The initiation of post- transplant preventive treatment for TB infection should begin as soon as a patient's liver function has stabilized to prevent the development of reactivated diseases (II A)

Comment: A low efficacy of vaccination has been documented and TB vaccination is not recommended in liver transplant candidates. Although it would be optimal to treat TB infection prior to liver transplantation, it is challenging due to potential isoniazid hepatotoxicity.

Mortality rate is higher in liver transplant recipients who developed active TB infection within 5 months post-transplant *vs.* patients who developed active TB infection after 5 months (36% *vs.* 17%, $p = 0.04$) [21–23].

Question 1.f

Is there a role for prophylaxis of fungal and viral infections (excluding HBV) in liver transplantation candidates?

Statement 1.f

Based on current available data prophylaxis of both fungal and viral infections is not recommended in liver transplant candidates (III C).

Comment: IFIs and viral infections are important causes of morbidity and mortality in solid organ transplant recipients [10,24].

Question 1.g

Should surveillance of infections in liver transplant candidates be performed while on the waiting list?

Statement 1.g

During waiting time a periodical surveillance for viral infectious risk may be advisable. HIV 1–2 Ab, CMV Ab (IgG), HSV 1–2 Ab (IgG), VZV Ab (IgG), EBV Ab (EBNA-Ab, VCA IgG-IgM), HHV 8 and Toxoplasma Ab (IgG) should be performed in seronegative recipients every 6 months while on the waiting list (III C).

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Question 1.h
Which is the proper infectious management in patients while on the waiting list?

Statement 1.h
- Any clinical sign of infectious disease in liver transplant patients on the waiting list has to be investigated in order to give the patient an appropriate treatment (III B)
- Any infectious event has to be notified to the liver transplant centre and the *patient might be temporary suspended from the list* until complete resolution, according to a multisciplinary transplant team decision (III B)
- In case of MDR bacteria colonization/infection, eligibility for liver transplantation should be reconsidered by the team, on a case-by-case basis (III B)

Comment: SBP is mainly caused by Enterobacteriaceae. Empirical therapy is based on 3rd generation cephalosporins. Cefotaxime 2 g tid for 5 days is as effective as higher dosages and longer treatments but it is not superior to other cephalosporins. Orally or intravenously administered quinolones have shown the same efficacy as cephalosporins, even though in studies characterized by a low statistical power. SBP treatment with quinolones should be avoided if previous prophylaxis with norfloxacin had been instituted. Aminoglycosides should be avoided for risk of renal toxicity. Patients with bacterial infections other than SBP should be treated according to specific guidelines for single infections (e.g., pneumonia, Skin and Soft Tissue Infections (SSTI), Urinary Tract Infection (UTI) etc. and local epidemiology of bacterial resistance) [25].

Post-transplantation

Question 2.a
Is there a correlation between type of infection and time after liver transplantation?

Statement 2.a
Time after liver transplantation correlates with the type of infection (II A).

Comment: Three time intervals can be identified between liver transplantation and types of infection.

(1) First month after surgery when opportunistic, donor-derived and surgical infections are more prevalent
(2) Between 2–12 months post liver transplantation when opportunistic and community acquired infections are prevalent
(3) More than 12 months after surgery the rate of rare opportunistic infections (TB, Cryptococcus, Rhodococcus, Nocardia, etc.) increases

Comment: Bacterial pathogens are the main causes of infection post liver transplantation. It is important to identify the high-risk populations [26,27].

Question 2.b
Which is the timing of infectious episodes and the appropriate diagnostic work-up following liver transplantation?

Statement 2.b
- Diagnostic work-up in the early post liver transplantation phase includes detection and management of donor-derived, intra-abdominal and wound infections, UTIs, catheter-related bloodstream infections (CR-BSIs) and LRTIs caused by hospital-acquired organisms (I A) (Table 1)
- Defined post-LT time points can be identified (III A):
  - **Early** post-LT infections (<1 month): Surgical complications and prolonged hospitalization/intensive care unit (ICU) are risk factors for abdominal infections due to bacterial and *Candida* spp. (i.e., abscesses, cholangitis, or peritonitis)
  - **Intermediate** period: Opportunistic infections (from 2 to 12 months). Careful medical history (recent travels, contacts with animals, vector exposure, etc.) has to be collected if an opportunistic infection is suspected
  - **Late** post-LT infections (>12 months): Community acquired infections (flu, LRTI, UTIs) often severe and complicated; TB, *Nocardia*, *Rhodococcus*, *Legionella*, etc.

Comment: The diagnostic work-up and therapy (empirical or targeted), should be performed by a multidisciplinary team, including an expert in transplant infectious diseases.

Atypical presentations, poor outcomes and nosocomial anti-microbial-resistant pathogens must be considered [28]. Empiric anti-microbial therapy is usually indicated.

Question 2.c
Are there risk factors for post-LT infections?

Table 1. Features and work-up of most frequent post-transplant infections.

Infection	Features	Workup level I	Workup level II
Abdominal infections	Risks: duration of surgery and re-transplantation	Blood tests (CBC, etc.) Urine and blood cultures	CT scan or US ERCP Liver biopsy
Wound infections	*S. aureus*, streptococci, gram(-) anaerobes; fungi	Gram stain and purulent discharge cultures	US/CT if collection suspected
CR-BSI	*S. aureus*, enterococci, gram(-) (*Pseudomonas spp.*); *Candida spp.*	Blood cultures (CVC and peripheral vein)	Echocardiography
UTI	Gram(-) bacilli, enterococci	Urine and blood cultures	Kidney imaging
LRTI	Gram(-) bacilli, *S. aureus*	Sputum culture and chest X-ray	CT scan, BAL, thoracentesis

BAL, bronchoalveolar lavage; CBC, complete blood count; CR-BSI, Catheter-related bloodstream infections; CT, computed tomography; CVC, central venous catheter; ERCP, Endoscopic retrograde cholangio-pancreatography; UTI, urinary tract infection; LRTI, lower respiratory tract infection; US, ultrasound.

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Statement 2.c
Risk factors have been identified and serve as surveillance criteria. They can be grouped as follows (II B):

- Patient factors
  - Age
  - MELD score >30; DMELD (recipient MELD × donor age) >1600
  - Malnutrition
  - Prolonged hospital stay and catheters before OLT
  - Acute liver failure
  - Previous infections (SBP, sepsis, pneumonia, CMV, UTI)
  - Previous TB
  - >48 h ICU in-patient pre-LT
- Donor factors
  - Prolonged ICU stay of donor
  - Donor infections
  - Marginal graft
- Surgical factors
  - Choledochojejunostomy
  - Prolonged surgery (>12 h)
  - Re-operation, Re-transplantation
  - >15 U transfusions
- Post-LT factors
  - Mechanical ventilation
  - Level and type of immunosuppression (i.e., use of monoclonal and polyclonal antibodies)
  - Primary non-function, hepatic artery thrombosis, portal vein thrombosis, ischaemic cholangitis, biliary strictures and fistulae
  - Post-transplant sclerosing cholangitis

Comment: Several risk factors correlate with the increasing risk of infection. Peritonitis is more frequent in case of high MELD, prolonged surgery, choledocho-jejunostomy, dialysis, bleeding, hepatic artery thrombosis, and hepatic artery stenosis [26,27,29–34].

Question 2.d
How to screen and monitor for donor-derived infections?

Statements 2.d
Aim of infectious disease screening in donors are (AIII):

- Identify infections which may exclude organ and tissue donation
- Establish strategies for prevention of post-transplant infection
- Implement preventive measures (i.e., vaccination or prophylaxis)

Organ donors are screened for infectious risks on the basis of national organ-procurement standards (risk of false positive and false negative) (BIII) [35,36].

Additional tests are generally recommended for donors traveling, living or originating from endemic areas (BIII):

- HIV antibody
- HBsAg, HBsAb, HBcAb, HCV antibody
- Treponemal and non-Treponemal testing (usually TPHA or TPPA, VDRL or RPR)
- Cytomegalovirus antibody (IgG only)
- EBV antibody
- HSV 1 and HSV 2 antibody (IgG only)
- VZV antibody (IgG only)
- Toxoplasma antibody (IgG only)
- Blood, sputum (BAL), and urine cultures
- Nucleic acid amplification testing (NAAT) for HIV, HCV, HBV in not established infectious risk donors (Supplementary Table 3)

Question 2.e
Is microbiological surveillance useful?

Statement 2.e
Patients should be investigated with microbiological surveillance after transplantation (II A).

Comment: Site-specific colonization study is useful for methicillin resistant *Staphylococcus aureus* (MRSA), Vancomycin resistant enterococci (VRE), extended-spectrum beta-lactamase (ESBL), and carbapenemase-producing GNB. Other surveillance should be adopted according to the donor and recipient pretransplant data. Microbiological surveillance on biliary fluids is not mandatory [29,31,37].

Question 2.f
What are the most relevant criteria for bacterial prophylaxis?

Statement 2.f
- Criteria for prophylaxis have been identified to obtain MRSA decolonization and to prevent VRE and MDR Gram (-) infections (II A): MRSA decolonization is achieved with 2% intranasal mupirocin and chlorexidine baths. VRE and MDR GNB can be prevented by contact isolation

Comment: There is no evidence of the use of SDD (norfloxacine and a paste of polimixine-tobramicine amphotericin-AmB). Vancomycin is not utilized due to the increasing risk of VRE selection [27,31].

Question 2.g
Which are the drugs of choice for bacterial prophylaxis?

Statement 2.g
- Surgical prophylaxis in low risk patients should be performed by cefotaxime and ampicillin or by piperacillin-tazobactam (based on local epidemiology) not exceeding 48 h (II A)
- Cotrimoxazole (TMP-SMX) is the drug of choice for its activity against *Pneumocystis jiroveci*, *Nocardia* spp., *Toxoplasma gondii* and *Listeria* spp. (II A)

Comment: Indication for surgical prophylaxis must be defined according to the local epidemiology [38]. The measurement of efficacy of prophylactic regimens in reducing the rate of post-LT infections is difficult, because no controlled studies have

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compared prophylaxis with no prophylaxis or the efficacy of antimicrobial prophylactic regimens different from cefotaxime and ampicillin. Indeed, a wide variety of antimicrobial combination regimens are utilized among different centres [38]. Traditional prophylactic regimens in liver transplantation have consisted of a third-generation cephalosporin (usually cefotaxime, because of its antistaphylococcal activity) plus ampicillin to cover enterococci. A reasonable alternative is Piperacillin-tazobactam which covers enterobacteriaceae, enterococci and Pseudomonas.

Question 2.h
How should Surgical Infections be managed in the early post-LT?

Statement 2.h
- SSI is a multifactorial event linked to local epidemiology, risk factors and antimicrobial prophylaxis (I)
- Once intra-abdominal infection is suspected the diagnosis is based on radiographic imaging (CT scan or ultrasound) and in the presence of ascites both neutrophil count and culture of ascitic fluid in blood-culture vials is required (I A)
- Treatment of SSI is based on combination of surgical debridement and empiric antimicrobial therapy according to local epidemiology and Gram stain results. Targeted therapy should be based on fluid culture (II A)

Comment: Surgical infections (wound infections, peritonitis, abdominal and hepatic abscesses) can lead to intra-abdominal infections and account for 27–47% of bacterial infections in liver transplant recipient. A prevalence up to 10% has been described in liver transplant recipient: retransplantation, duration of surgery, choledocho-jejunostomy have been identified as risk factors. Gram (-) bacilli and Enterococcus species are frequent. MDR pathogens are frequently found in abscesses [22–24,26,27,39].

Question 2.i
What is the diagnostic management of post-LT CMV infection?

Statement 2.i
The standard for CMV-infection surveillance is weekly or twice a week CMV monitoring (real-time PCR) after the first positive result, for the first three months after transplantation (I A).

- Three months is an adequate period for CMV-reactivation monitoring (I A)
- Serology has no role in post-LT CMV disease diagnosis (II)
- Cultures (blood and urine) are of limited utility for CMV disease management (II)
- CMV pp65 antigenemia (semi-quantitative test) and CMV viral load (NAT) are acceptable options for diagnosis, pre-emptive therapy and monitoring response to therapy (II A)

Comment: 30–60% of solid organ transplant (SOT) recipients are newly infected or reactivate latent CMV infection after transplantation.

In pre-emptive setting of targeted groups of patients, laboratory monitoring of CMV infection is performed by pp65 antigenemia or NAT at regular weekly or twice a week intervals. Lack of standardization across different laboratories is a problem for both tests and centres need to validate their own threshold values. A safe cut-off determined by real-time PCR was demonstrated to range between 100,000 and 300,000 copies/ml of whole blood according to the type of commercial test used. The suggested cut-offs for pre-emptive therapy have been recently validated and are homogeneously and reliably quantified by different methods (both commercial and in-house) and by different laboratories. It is however recommended that each transplant center should work with their clinical laboratories to define the relevant viral load thresholds for their clinical applications. In 2011, the WHO released the first International Reference Standard for the quantification of CMV nucleic acid, and laboratory and commercially developed CMV QNAT assays should now be calibrated to this standard. This may ensure uniformity in viral load reporting, thereby facilitating to define viral thresholds for various clinical applications. In case of persistently positive CMV-DNA antiviral resistance can be screened *in vitro* and treatment switch to foscarnet in case of documented resistance is advisable [40–47].

Definitions for CMV in the transplant setting

- **CMV infection:** evidence of CMV replication regardless of symptoms
- **CMV disease:** CMV infection + symptoms (i.e., viral syndrome with fever, malaise, leuko/thromboctopenia, tissue-invasive disease)
- **Late CMV disease:** according to the length of prophylaxis (3 or 6 months) CMV disease with attributable symptoms, occurring 3 to 6 months post-SOT. May be primary infection (D+/R-) or reactivation/superinfection (R+). May present with atypical symptoms
  - Diagnosis can be missed
  - Patient may not be followed by primary centre or may not be followed as closely
- **Primary infection:** in case of the combination Donor(+)/Recipient(-), over 90% of the recipients develop CMV infection
- In case of **reactivation** of endogenous latent infection, around ~15% of recipients become ill
- **Superinfection:** in case of combination Donor(+)/Recipient(+) but with D(+) reactivation, around ~25% of the recipients become ill

Question 2.l
What is the treatment management of post-LT CMV infections/disease (reactivation, primary infection, reinfection)?

Statement 2.l
- Prevention strategies based on concomitant determination of CMV-DNA and specific T cell responses in the post-transplant period might be useful (II B)

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- "Universal prophylaxis": D+/R−, (3–6 months post-TX): valganciclovir 900 mg/day, oral ganciclovir (3 g/day), or intravenous ganciclovir (5 mg (kg/day)
- "Pre-emptive therapy": the most widely adopted starting criteria for pre-emptive CMV antiviral therapy are [48,49]:
  - In CMV seronegative and/or seropositive: DNAemia ⩾100,000 copies/ml
  - In case of Steroid boluses or ATG/OKT3 therapy for Rejection: any value of DNAemia

- The drug of choice for treatment is ganciclovir (5 mg/kg bid i.v.). Valganciclovir (900 mg bid oral) is an alternative, although it is not approved for this indication in CMV seropositive recipients [48–50] (II A)
- Pre-emptive treatment should be stopped after two consecutive negative CMV viral load performed during treatment) (II A)

Comment: The optimal duration of intravenous or oral treatment after resolution of clinical signs is uncertain. Serial PCR of CMV DNA offers an objective measure of the degree of viraemia and may help to guide the duration of treatment. In all recipients antiviral therapy must be continued until DNAemia clearance. Recurrent episodes of active infection are usually treated with additional courses of ganciclovir starting with DNAemia values ⩾100,000 copies/ml.

Question 2.m
How to diagnose invasive fungal infection (IFI)?

Statement 2.m
- According to the 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) definitions, there are 3 levels for the diagnosis of IFI: "proven," "probable," and "possible." These criteria may be applied to SOT recipients with the aim of harmonizing clinical and epidemiological research (II A):
  - At least one positive blood culture for *Candida* spp. or other pathogenic fungi
  - A positive culture for a pathogenic fungus from a specimen collected from a normally sterile site
  - A positive culture for a pathogenic fungus from a biopsy specimen (taken across a potentially colonized mucosal surface) plus histopathology confirming fungal elements in tissue with local inflammation
  - Evidence of fungal endophthalmitis based on dilated fundoscopic examination
  - Positive histopathology for fungal elements in a deep tissue biopsy
  - A positive culture for a mould (e.g., *Aspergillus* spp., *Fusarium* spp., *Zygomycete*) from a non-sterile body site together with clinical, histopathologic or radiologic evidence consistent with IFI
  - Positive cryptococcal or histoplasma antigen test and clinical or radiographic evidence consistent with *Cryptococcosis* or *Histoplasmosis*
  - A positive culture or histopathologic evidence of an endemic mycosis (e.g., *Blastomycosis*, *Histoplasmosis* or *Coccidioidomycosis*)
- Invasive diagnostic procedures are required for an accurate, timely diagnosis (II B)
- Diagnostic procedures may be performed by means of imaging techniques and bronco-alveolar lavage (BAL) (II A)
- A proven diagnosis of IFI depends on recovery with microscopic evidence or isolation from cultures of fungal elements from a sterile body site or in diseased tissue (III A)

Comment: Range of IFI incidence after liver transplantation is reported to be wide (4–42%). According to the most recent data based on strict definitions, the incidence is usually reported to be lower (<10% range 2–8%). Among IFI, the majority are sustained by *Candida* species (from 68 to 78.7%) followed by *Aspergillus* species (7.9–11%) and *Cryptococcus neoformans* (6–7.1%) Timing of IFI ranges from early (<3 months) to late (>6 months) period after liver transplantation [27,51–56].

Question 2.n
What are the indications for perioperative prophylaxis for invasive fungal infections (IFI) in post-LTR?

Statement 2.n
- Risk factors for *Candida* and *Aspergillus* infections have been identified (II B) (Table 2)
- According to the number of factors present in the post-LT period, low and high-risk patients are recognised (II B)
- Risk factors are relevant to drive targeted prophylaxis/early or empirical treatment (II B)

Comment: Targeted antifungal prophylaxis (the use of an antifungal agent in a subgroup of transplanted recipients at higher risk for the presence of predisposing conditions and/or risk factors for *Candida* and for *Candida* and *Aspergillus*) represents the ideal treatment strategy. Different therapeutic strategies are to be considered for the risk of *Candida* and *Aspergillus* [10,27,51,57–63]. Antifungal prophylaxis is suggested only for high-risk patients (fluconazole 400 mg/kg daily or liposomal AmB (L-AmB) 3–5 mg/kg daily up to 4 weeks. or until resolution of symptoms). All of the azole-derivative antifungal agents decrease the metabolism of calcineurin inhibitors and Sirolimus resulting in modest to profound increases in serum concentration and AUC. The interaction of fluconazole with calcineurin inhibitors is both dose- and drug-dependent. At modest doses (100–200 mg/day) of fluconazole used for nonsystemic candidiasis, effects on CsA are minor, while moderate to significant increases are seen with Tacrolimus. At doses of fluconazole required for systemic fungal infection (e.g., 400 mg for cryptococcosis or candidemia), dose reduction of immunosuppressants is required. The new echinocandin antifungal agents provide alternatives to the use of azole derivatives [62,63,61].

Question 2.o
What is the management of invasive fungal infections in liver transplant recipient?

Statement 2.o
- In invasive candidiasis (IC) fluconazole or an echinocandin are recommended as initial therapy (II B)
- In invasive aspergillosis voriconazole is the drug of choice (I A)

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Table 2. Risk factors for post-transplantation fungal infections.

Risk factors for *Candida*	Risk factors for *Aspergillus*
Renal replacement therapy Surgical factors • Prolonged operation time (>11 hr) • Second surgical intervention within 5 days • Choledochojejunostomy anastomosis • >40 units of blood products during surgery	Dialysis Surgical factors • Retransplantation
Microbial factors • Early fungal colonization (within 3 days) • Documented colonization (nasal, pharyngeal or rectal)	Microbial factors • CMV infection • Prior colonization
Acute liver failure	Acute liver failure

CMV, cytomegalovirus.

– Limitations in liver transplant recipient are interference with immune-suppressants and liver toxicity. L-AmB is considered an alternative therapy (III B) (Table 3)

Question 2.p
What is the management of MDR Infections in liver transplant recipients?

Statement 2.p
– Careful screening and antibiotic selection for multidrug resistant pathogens (MDR) pre- and post-transplant is mandatory and the identification of MDR requires experienced microbiology laboratories (III A)
– An expert opinion in antimicrobial treatment of multidrug resistant organism is mandatory for the choice of the right drug regimen (III A)
– **In case of Vancomycin resistant enterococci (VRE) (III A):**
  • Transthoracic echocardiography (TTE), Transesophageal echocardiography (TEE) and biliary tract infections workup are indicated when multiple positive blood cultures are identified
  • Wounds debridement, abscesses drainage, and foreign bodies removal are recommended
  • Limit broad spectrum antimicrobials use is indicated

– **Methicillin resistant *S. aureus* (MRSA) (III A)**
  • Monitoring of MRSA colonization must be adopted
  • Isolation and decontamination is suggested

– **Multi drug resistant (MDR) Gram (-) extended spectrum beta-lactamase (ESBL) (III A)**
  • The identification requires experienced microbiology laboratories
  • Limited options for therapy – adjust according to individual susceptibility testing

Comment: MRSA, VRE, ESBL and carbapenem-resistant gram-negative bacilli (KPC, NDM-1) are increasing worldwide [31,39,64–87] (Table 4).

Question 2.q
What is the diagnostic work-up in liver transplant recipients with lower-tract respiratory infections?

Statement 2.q
– Nasopharyngeal swab for respiratory viruses PCR or antigens, viral PCRs on blood, fungal and acid-fast bacilli (AFB) blood cultures, sputum culture and chest X-ray must be performed (I A)
– More sensitive diagnostic tools, i.e., thoracic CT scan, BAL, and thoracentesis in case of pleural effusion should always be considered (III A)

Comment: Leukocytosis, new infiltrate on chest film, and hypoxemia is reported as the typical triad in post-LT lung infections [88]. Various causes, including opportunistic (*P. jiroveci*, atypical mycobacteria, viruses), rare pathogens (i.e., metapneumovirus, Rhodococcus equi, etc.), and highly resistant germs (MRSA, *Pseudomonas*, *Stenotrophomonas*, *Bulkholderia*, carbapenem-resistant Gram (-)) should be considered. Fever, increased sputum, dyspnoea and/or low oxygen saturation are common [88]. *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis, according to the international guidelines, is recommended for 6–12 months post-transplant (Tables 5 and 6).

Question 2.r
What is the management of tuberculosis in liver transplant recipients?

Statement 2.r
– **In latent TB:**
  • Obtain TST (BII), medical history and chest X-ray (II A)
  • IGRAs not optimal in high immunosuppression and cirrhosis (II D)
  • Exclude active TB (III B)
  • Treatment: isoniazid 300 mg/day + Vitamin B6 for 6–9 months (I B) waiting for stable liver function (III B)
  • Rifampicin (RMP) + pyrazinamide (PZN) not recommended due to toxicity (II C). If isoniazid (INH) intolerance, strict f/u and rifampicin 600/day p.o. for 4 months (III B)

– **In active TB:**
  • Efforts to obtain an isolated organism for sensitivity testing should be made (III A)
  • Avoid rifampicin due to difficulty in maintaining adequate levels of immunosuppression and risk of organ rejection (III B)
  • Prolonged treatment (12–18 months) recommended in rifampicin-sparing regimens and extrapulmonary TB (III B)

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Table 3. Treatment of fungal infections in liver transplant recipients.

Candidiasis and aspergillosis	
Site of infection	
Invasive candidiasis	Invasive aspergillosis
Empirical treatment if IC suspected*. • Echinocandin preferred in haemodinamically unstable or previous azole exposure (**BIII**); • L-AmB is an alternative (**III C**)	**Empirical treatment** only if high risk factors + microbiological/clinical criteria. L-AmB preferred if toxicity risks, azole exposure (**III C**)
Targeted treatment • Fluconazole 800 mg (loading: 12 mg/kg) then 400 mg daily (**BII**) or an echinocandin • Caspofungin (loading 70 mg, then 50 mg day) or micafungin (100 mg day) or anidulafungin (loading 200 mg, then 100 mg day) (**AII**) ± stepdown to fluconazole after 3-5 days if susceptibility confirmed (**II A**)	**Targeted treatment** • Voriconazole (loading 6 mg/kg bid then 4 mg/kg bid) (**I A**); OS if ClCr <50 ml/min (**III B**) or • L-AmB (3-5 mg/kd day) (**I A**) • Caspofungin (**BII**) and posaconazole as alternative/salvage (**III C**)

Cryptococcosis	
Site of infection	
Meningoencephalitis/disseminated disease	Pulmonary
Induction (2 weeks) • L-AmB 3-4 mg/(kg day) plus flucytosine 100 mg/(kg day) (**I B**) or • L-AMB 3-4 mg/(kg day) (**II B**) or • AmB lipid complex 5 mg/(kg day) (**III C**)	Fluconazole 400 mg/day for 6-12 months (**II C**) Disseminated disease must be excluded in all patients (**III A**) Asymptomatic forms require treatment in SOT (**III B**) *Diffuse pulmonary infiltrates and acute respiratory failure treated as meningoencephalitis
Consolidation (8 weeks) • Fluconazole 400-800 mg/day (**II B**)	
Maintenance (6-12 months)** • Fluconazole 200 mg/day (**II B**)	

*Useful monitoring of cryptococcal antigen titres.

**(1) Persistent fever (38 °C) despite broad spectrum therapy for 96 h and (2) no other known cause of fever plus (3) Candida colonization for the same species from at least 2 non-contiguous (including non-sterile) sites and/or (4) the presence of specific risk factors and/or, (5) clinical-radiological suspicion of IC and/or detection of –D glucan in serum.

AmB, amphotericin B; IC, invasive candidiasis; L-AMB, liposomal-amphotericin B; SOT, solid organ transplantation; TDM, targeted-drug monitoring.

- Alternative regimens: isoniazid + ethambutol + pyrazinamide or use of quinolones (moxifloxacin, levofloxacin) (II C)
- In HIV-infected liver transplant recipient avoidance of rifamycins + addition of a quinolone are recommended (III B)
- Consultation with a TB specialist is mandatory [89,90] (III A)

Comment: Latent tuberculosis is not a contraindication to liver transplantation but requires pre or post-transplant treatment according to the clinical conditions and the international guidelines.

Both latent (anergy – skin test negativity) and active TB are difficult to diagnose. There is no wide literature-based consensus on TB infection management, and most clinical practice is based upon experts' opinion [91–93]. It is recommended that the approach to the treatment of TB in solid organ transplant recipients is similar to immunocompetent hosts. However, the following important issues specific to solid organ transplant recipients should be highlighted: (a) rifamycin-containing regimen is strongly preferred for both severe and localized non-severe TB due to the potent sterilizing activity of such regimens and the importance of preventing the emergence of resistance; (b) the rifamycins (especially rifampicin) reduce serum concentrations of tacrolimus, cyclosporine, rapamycin (sirolimus), and everolimus via induction of the cytochrome p450 isoenzyme CYP3A4, and this bears the risk of inducing rejection. Therefore, dose of the CNI or rapamycin should be increased accordingly and serum concentrations regularly monitored.

Question 2.s

What is the management of the most common food-borne diseases in liver transplant recipients?

Statement 2.s

- Most foodborne diseases are self-limited and require only supportive care while in immunocompromised patients an antibiotics treatment is often required (III B) (Table 7)
- Prevention is essential in reducing the cases of foodborne illness. Education of patients and their caregivers is crucial (I B)

Comment: Salmonellosis, listeriosis, and parasitic diseases may cause severe infections in liver transplant recipients [94–96].

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Table 4. Management of drug resistant pathogens.

Vancomycin-resistant Enterococci (VRE)		
Treatment options	Pros	Cons
Linezolid (**III B**)	Oral formulation, reaches high bile concentrations in bile	Possible resistance, long term toxicity, bactero-static
Daptomycin (**III B**)	Once daily administration, synergism with RMP and other antimicrobials	Lack of data
Quinopristin/dalfopristin (**II C**)	Active on *E. faecium*	Not to be used against *E. faecalis*, requires CVC placement
Tygecycline (**II C**)	Reaches high concentrations in bile	Bactero-static, not to be used in ICU/bacteraemia/ lung infections

Multidrug resistant Gram(-) (MDR)	
Treatment	Notes
Carbapenems (**II A**)	Not to be used against carbapenemase-producing bacteria
IV Colistin (**II B**)	Lack of data, associations/aerosol, renal toxicity
Tygecycline (**II C**)	Not to be used in UTI, bacteremia or high-density infections

Methicillin-resistant *Staphylococcus aureus* (MRSA)	
Treatment	Notes
Vancomycin (**I B**)	Not to be used if MIC ≥2 μg/ml, monitoring of levels warranted
Daptomycin (**II B**)	Not to be used in pneumonia cases
Linezolid (**II B**)	Bactero-static (reduced effect in bacteremia/infective endocarditis)
Telavancin (**III C**)	Not to be used in kidney failure, limited data available

CMV, cytomegalovirus; CVC, central venous catheter; D+, donor positive; ESKD, end-stage kidney disease; ICU, intensive care unit; LTR, liver transplant recipient; LTX, liver transplantation; MIC, minimal inhibitory concentration; RMP, rifampicin; TX, transplantation.

Table 5. Likely respiratory pathogens in solid organ transplant recipients based upon the presenting chest X-ray radiographic pattern.

Diffuse interstitial-alveolar	Lobar-segmental	Reticulonodular	Discrete nodule
• CMV • Influenza • RSV • Adenovirus • *P. jiroveci*	• Bacterial • *Legionella* • *Rhodococcus equi* • *Cryptococcus* • RSV Influenzae	• *Nocardia* • *M. tuberculosis* • Non-tuberculous mycobacteria • *P. jiroveci* • Histoplasmosis • *Cryptococcus*	• *Aspergillus* • Other mycelia • *M. tuberculosis* • *Nocardia* • PTLD (EBV) • *Cryptococcus* • Histoplasmosis

EBV, Epstein-Barr virus; CMV, cytomegalovirus; M tuberculosis, *Mycobacterium tuberculosis*; *P jiroveci*, *Pneumocystis jiroveci*; PTLD, post-transplant lymphoproliferative disease; RSV, respiratory syncytial virus.

Question 2.t

What is the management of EBV, and HHV8 infections in liver transplant recipients?

Statement 2.t

- **Epstein Barr virus (EBV) infection**
  - Monitoring regularly EBV-DNA in the same laboratory in D+/R− (III A)
  - Monitoring of EBV-specific CTL activity is also helpful (II B)
  - Diagnosis is made by tissue examination (II A)
  - EBV-DNA (PCR) and EBV-specific CTL activity correlate with risk (II A) but inter-laboratory variability must be taken into account (III A)

- **HHV-8 Infection**
  - HHV-8 viral load monitoring useful in D+/R− in endemic areas (II A)
  - Diagnosis and KS monitoring preferred by NAT (II A)
  - In recipients with positive HHV8 serology or receiving an organ from a positive HHV8 serology donor the monitoring of HHV8-DNA post-transplant is strongly recommended (III B) (Supplementary Table 5)
  - Management of KS:
    - Minimization of immunosuppression and switch to an mTOR inhibitor (either sirolimus or everolimus) (II A)
    - Lesions removal is required (II A) [97–100]

Comment:

Epstein Barr virus (EBV) infection: EBV is responsible for the majority of PTLD. Recognized risk factors are: young age, D+/R−, CMV positivity, T cell depleting therapies.

HHV-8 Infection: Kaposi sarcoma (KS) and other proliferative diseases are frequently associated. This condition presents geographic variability (5–20% prevalence in Mediterranean area) [97,101].

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Table 6. *Pneumocystis jiroveci* pneumonia: Prophylaxis and therapy.

Prophylaxis		
Primary	Alternative	Comments
• TMP-SMX, SS or DS once/day or • DS three times/week	• Dapsone, 50-100 mg/day or • Pentamidine aerosol, 300 mg inhaled monthly via Respirgard II® nebulizer or • Atovaquone, 1500 mg/day	• **Duration**: 6-12 months post-transplant. Consider prophylaxis during and after treatment of acute rejection (duration 6 wk) • **Additional benefit** of TMP-SMX: most *Toxoplasma* and *Nocardia* infections can be prevented (as are some GI infections, UTI, and RTI • **Dapsone**: check G6PD deficiency in risk population

Therapy		
Hospitalized patient, PaO_2 <70 mmHg (<10 kPa)		
Primary	Alternative	Comments
TMP-SMX 15 mg/kg/day of TMP component IV divided in three doses + prednisone (if PaO_2 <70 mmHg) for 21 days	Primaquine 15-30 mg PO q24h + clindamycin 600 mg IV q8h x 21 days or Pentamidine 4 mg/kg/day x 21 days + prednisone (see comments)	Based on data from HIV patients: consider concomitant use of corticosteroids if PaO_2 <70 mmHg: prednisone (start before TMP-SMX) 40 mg PO BID for 5 days, then 40 mg PO q24h for 5 days, then 20 mg PO q24h for 11 days) Less evidence of efficacy with alternative therapy Secondary prophylaxis recommended

BID, bis in die; DS, double strength; GI, gastrointestinal; HIV, Human immunodeficiency virus; IV, intravenous; PaO_2, partial pressure of arterial oxygen; PO, per os; RTI, reproductive tract infection; SS, single strength; TMP-SMX, trimethoprim sulfamethoxazole.

Table 7. Blood-borne infections after liver transplantation.

Pathogen	Features	Risk factors	Management
Salmonella spp	• High risk of bacteremia (2-14%)	• Antirejection treatment • Recurrent (latent) infections	• Fluoroquinolones or III generation cephalosporin • Surgery (vascular prosthesis infection) (**II B**)
Listeria spp	• Within 2 months from LT (TMP/SMX prophylaxis may reduce the risk)	• Acute rejection, CMV disease, DM	• Ampicillin ± gentamycin or TMP-SMX • Surgery if brain abscess (**II B**)
Parasites *Cryptosporidium spp*	• Low response rates to treatment. • Prophylaxis with TMP/SMZ for 6 months recommended	• Contaminated water • D+/R- • Undercooked meat	• Azithromycin, paromomycin (**II C**) • pyrimethamine/sulfadiazine (**I B**)

CMV, cytomegalovirus; D+/R−, donor positive/recipient negative; DM, diabetes mellitus; LT, liver transplantation; TMP-SMX, trimethoprim sulfamethoxazole.

Question 2.u
What is the management of CNS infections in liver transplant recipients?

Statement 2.u
- Specific diagnostic tools for CNS infection in liver transplantation have been identified (I A) (Supplementary Table 6)
- Prompt administration of therapy on suspicion of the diagnosis without definitive proof is needed to control infection (III A)

Comment: the following time points for CNS infections can be identified in the post–LT period (Supplementary Tables 7 and 8):

- **Early** post-LT: 40% of CNS infections in liver transplant recipient (donor-derived, complication of surgery or ICU)
- **1–6 months** Post liver transplantation: Aspergillus, Listeria, Nocardia, Candida dissemination, HHV6
- **Late** post-LT: subacute-chronic meningitis (rare) due to *Cryptococcus*, *Coccidioidomycosis*, *Histoplasmosis*, progressive multifocal leukoencephalopathy (PML, due to JC virus), EBV associated B-cell lymphoproliferative disease

Question 2.v
What is the treatment management of Nocardiosis in liver transplant recipients?

Statement 2.v
- Specific organ-related therapeutic regimens for Nocardiosis in liver transplantation recipients have been identified (II B /III B) (Table 8).

Comment: Rates of Nocardiosis in liver transplant recipient varies between 0.7% and 3.5%. Nocardiosis is unlikely earlier than 1 month post-liver transplantation (can exceptionally be seen in

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Table 8. Organ-related therapeutic regimens for nocardiosis in LT recipients.

Regimens
Pulmonary; stable TMP-SMX 15 mg/(kg day in 3-4 divided doses) (**II B**) for 6-12 months
Critical, disseminated, CNS Imipenem (500 mg q 6) + TMP-SMX (**BII**) or amikacin (10-15 mg/kg day) (**III C**) for 9-12 months (**III B**)
Alternative Meropenem 1-2 g q8h (**III B**) Linezolid 600 mg q12h (**III C**)
Recommendations
• Antimicrobial association preferred in the seriously ill (**III C**) • Susceptibility tests recommended for alternative regimens (**III B**) • IV >3 wk in the seriously ill (**III B**) • Drainage of brain abscesses and MRI follow-up for relapses (**III B**)

CNS, central nervous system; IV, intravenous; MRI, magnetic resonance imaging; TMPSMX, trimethoprim sulfamethoxazole.

cases of extremely high immunosuppression). The infection typically occurs via respiratory entry (i.e., inhalation of contaminated dust) with blood dissemination in 18–40% of cases with granulomatous pulmonary forms and frequently multiple abscesses (cerebral abscesses). The identified risk factors are: high dose steroids, CMV disease, and severe hypogammaglobulinemia. Antimicrobial susceptibility varies with species. Delayed onset of Nocardiosis can be observed because of TMP/SMZ prophylaxis. Cephalosporins and minocycline can be used after initial therapy, however with variable outcomes [102].

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2013.12.021.

References

[1] Fox AN, Brown Jr RS. Is the patient a candidate for liver transplantation? Clin Liver Dis 2012;16:435–448.
[2] Koffron A, Stein JA. Liver transplantation: indications, pretransplant evaluation, surgery, and posttransplant complications. Med Clin North Am 2008;92:861–888.
[3] Navasa M, Rodes J. Bacterial infections in cirrhosis. Liver Int 2004;24:277–280.
[4] Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010;139:1246–1256, [1256 e1241–e1245].
[5] Rubin RH. The direct and indirect effects of infection in liver transplantation: pathogenesis, impact, and clinical management. Curr Clin Top Infect Dis 2002;22:125–154.
[6] San Juan R, Aguado JM, Lumbreras C, Diaz-Pedroche C, Lopez-Medrano F, Lizasoain M, et al. Incidence, clinical characteristics and risk factors of late infection in solid organ transplant recipients: data from the RESITRA study group. Am J Transplant 2007;7:964–971.
[7] van Saene HK, Zandstra DF. Selective decontamination of the digestive tract: rationale behind evidence-based use in liver transplantation. Liver Transpl 2004;10:828–833.
[8] de Jonge E, Schultz MJ, Spanjaard L, Bossuyt PM, Vroom MB, Dankert J, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. Lancet 2003;362:1011–1016.
[9] Yehia BR, Blumberg EA. Mycobacterium tuberculosis infection in liver transplantation. Liver Transpl 2010;16:1129–1135.
[10] Playford EG, Webster AC, Sorrell TC, Craig JC. Systematic review and meta-analysis of antifungal agents for preventing fungal infections in liver transplant recipients. Eur J Clin Microbiol Infect Dis 2006;25:549–561.
[11] Saliba F, Delvart V, Ichai P, Kassis N, Botterel F, Mihaila L, et al. Outcomes associated with amphotericin B lipid complex (ABLC) prophylaxis in high-risk liver transplant patients. Med Mycol 2013;51(2):155–163.
[12] Kalil AC, Mindru C, Botha JF, Grant WJ, Mercer DF, Olivera MA, et al. Risk of cytomegalovirus disease in high-risk liver transplant recipients on valganciclovir prophylaxis: a systematic review and meta-analysis. Liver Transpl 2012;18:1440–1447.
[13] Hibberd PL, Rubin RH. Approach to immunization in the immunosuppressed host. Infect Dis Clin North Am 1990;4:123–142.
[14] Molrine DC, Hibberd PL. Vaccines for transplant recipients. Infect Dis Clin North Am 2001;15:273–305, [xii].
[15] Gangappa S, Kokko KE, Carlson LM, Gourley T, Newell KA, Pearson TC, et al. Immune responsiveness and protective immunity after transplantation. Transpl Int 2008;21:293–303.
[16] Guidelines for vaccination of solid organ transplant candidates and recipients. Am J Transplant 2004;4:160–163.
[17] Duchini A, Goss JA, Karpen S, Pockros PJ. Vaccinations for adult solid-organ transplant recipients: current recommendations and protocols. Clin Microbiol Rev 2003;16:357–364.
[18] Holty JE, Sista RR. Mycobacterium tuberculosis infection in transplant recipients: early diagnosis and treatment of resistant tuberculosis. Curr Opin Org Transpl 2009;14:613–618.
[19] Kim SH, Lee SO, Park IA, Park SJ, Choi SH, Kim YS, et al. Diagnostic usefulness of a T cell-based assay for latent tuberculosis infection in kidney transplant candidates before transplantation. Transpl Infect Dis 2010;12:113–119.
[20] Manuel O, Humar A, Preiksaitis J, Doucette K, Shokoples S, Peleg AY, et al. Comparison of quantiferon-TB gold with tuberculin skin test for detecting latent tuberculosis infection prior to liver transplantation. Am J Transplant 2007;7:2797–2801.
[21] Holty JE, Gould MK, Meinke L, Keeffe EB, Ruoss SJ. Tuberculosis in liver transplant recipients: a systematic review and meta-analysis of individual patient data. Liver Transpl 2009;15:894–906.
[22] Jahng AW, Tran T, Bui L, Joyner JL. Safety of treatment of latent tuberculosis infection in compensated cirrhotic patients during transplant candidacy period. Transplantation 2007;83:1557–1562.
[23] Singh N, Wagener MM, Gayowski T. Safety and efficacy of isoniazid chemoprophylaxis administered during liver transplant candidacy for the prevention of posttransplant tuberculosis. Transplantation 2002;74:892–895.
[24] Playford EG, Webster AC, Sorell TC, Craig JC. Antifungal agents for preventing fungal infections in solid organ transplant recipients. Cochrane Database Syst Rev 2006;25(1):CD004920.
[25] Fagiuoli S, Colli A, Bruno R, Burra P, Craxi A, Gaeta GB, et al. Management of infections in cirrhotic patients: Report of a Consensus Conference. Digestive Liver Dis 2013.
[26] Huprikar S. Update in infectious diseases in liver transplant recipients. Clin Liver Dis 2007;11:337–354.

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[27] Romero FA, Razonable RR. Infections in liver transplant recipients. World J Hepatol 2011;3:83–92.
[28] Blair JE, Kusne S. Bacterial, mycobacterial, and protozoal infections after liver transplantation – part I. Liver Transpl 2005;11:1452–1459.
[29] Snydman DR. Posttransplant microbiological surveillance. Clin Infect Dis 2001;33:S22–S25.
[30] Sun HY, Cacciarelli TV, Singh N. Identifying a targeted population at high risk for infections after liver transplantation in the MELD era. Clin Transplant 2011;25:420–425.
[31] Russell DL, Flood A, Zaroda TE, Acosta C, Riley MM, Busuttil RW, et al. Outcomes of colonization with MRSA and VRE among liver transplant candidates and recipients. Am J Transplant 2008;8:1737–1743.
[32] van Hoek B, de Rooij BJ, Verspaget HW. Risk factors for infection after liver transplantation. Best Pract Res Clin Gastroenterol 2012;26:61–72.
[33] Fishman JA, Issa NC. Infection in organ transplantation: risk factors and evolving patterns of infection. Infect Dis Clin North Am 2010;24:273–283.
[34] Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007;357:2601–2614.
[35] Grossi PA, Fishman JA. Practice ASTIDCo. Donor-derived infections in solid organ transplant recipients. Am J Transplant 2009;9:S19–S26.
[36] Ison MG, Grossi P. Practice ASTIDCo. Donor-derived infections in solid organ transplantation. Am J Transplant 2013;13:22–30.
[37] Rodriguez-Hernandez MJ, Ruiz-Perez-Pipaon M, Canas E, Bernal C, Gavilan F. Strongyloides stercoralis hyperinfection transmitted by liver allograft in a transplant recipient. Am J Transplant 2009;9:2637–2640.
[38] Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195–283.
[39] Asensio A, Ramos A, Cuervas-Mons V, Cordero E, Sanchez-Turrion V, Blanes M, et al. Effect of antibiotic prophylaxis on the risk of surgical site infection in orthotopic liver transplant. Liver Transpl 2008;14:799–805.
[40] Gerna G, Baldanti F, Torsellini M, Minoli L, Vigano M, Oggionnis T, et al. Evaluation of cytomegalovirus DNAaemia *vs.* pp65-antigenaemia cutoff for guiding preemptive therapy in transplant recipients: a randomized study. Antivir Ther 2007;12:63–72.
[41] Gerna G, Lilleri D, Chiesa A, Zelini P, Furione M, Comolli G, et al. Virologic and immunologic monitoring of cytomegalovirus to guide preemptive therapy in solid-organ transplantation. Am J Transplant 2011;11:2463–2471.
[42] Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Snydman DR, et al. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation 2010;89:779–795.
[43] Len O, Gavalda J, Blanes M, Montejo M, San Juan R, Moreno A, et al. Donor infection and transmission to the recipient of a solid allograft. Am J Transplant 2008;8:2420–2425.
[44] Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis 2002;34:1094–1097.
[45] Lilleri D, Lazzarotto T, Ghisetti V, Ravanini P, Capobianchi MR, Baldanti F, et al. Multicenter quality control study for human cytomegalovirus DNAemia quantification. New Microbiol 2009;32:245–253.
[46] Grossi P, Kusne S, Rinaldo C, St George K, Magnone M, Rakela J, et al. Guidance of ganciclovir therapy with pp65 antigenemia in cytomegalovirus-free recipients of livers from seropositive donors. Transplantation 1996;61:1659–1660.
[47] Fryer JF, Heath AB, Anderson R, Minor PD. Collaborative study to evaluate the proposed 1st WHO International Standard for human cytomegalovirus (HCMV) for nucleic acid amplification (NAT)-based assays. WHO ECBS, Report; 2010. p. WHO/BS/10.2138.
[48] Kusne S, Shapiro R, Fung J. Prevention and treatment of cytomegalovirus infection in organ transplant recipients. Transpl Infect Dis 1999;1:187–203.
[49] Paya C, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B, et al. Efficacy and safety of valganciclovir *vs.* oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 2004;4:611–620.
[50] Asberg A, Humar A, Rollag H, Jardine AG, Mouas H, Pescovitz MD, et al. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 2007;7:2106–2113.
[51] Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis 2010;50:1101–1111.
[52] San-Juan R, Aguado JM, Lumbreras C, Fortun J, Len O, Munoz P, et al. Universal prophylaxis with fluconazole for the prevention of early invasive fungal infection in low-risk liver transplant recipients. Transplantation 2011;92:346–350.
[53] Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis 2006;42:1417–1427.
[54] Clancy CJ, Jaber RA, Leather HL, Wingard JR, Staley B, Wheat LJ, et al. Bronchoalveolar lavage galactomannan in diagnosis of invasive pulmonary aspergillosis among solid-organ transplant recipients. J Clin Microbiol 2007;45:1759–1765.
[55] Senn L, Robinson JO, Schmidt S, Knaup M, Asahi N, Satomura S, et al. 1,3-Beta-D-glucan antigenemia for early diagnosis of invasive fungal infections in neutropenic patients with acute leukemia. Clin Infect Dis 2008;46:878–885.
[56] Singh N, Husain S. Invasive aspergillosis in solid organ transplant recipients. Am J Transplant 2009;9:S180–S191.
[57] Hadley S, Huckabee C, Pappas PG, Daly J, Rabkin J, Kauffman CA, et al. Outcomes of antifungal prophylaxis in high-risk liver transplant recipients. Transpl Infect Dis 2009;11:40–48.
[58] Grossi PA, Gasperina DD, Barchiesi F, Biancofiore G, Carafiello G, De Gasperi A, et al. Italian guidelines for diagnosis, prevention, and treatment of invasive fungal infections in solid organ transplant recipients. Transplant Proc 2011;43:2463–2471.
[59] Gavalda J, Len O, San Juan R, Aguado JM, Fortun J, Lumbreras C, et al. Risk factors for invasive aspergillosis in solid-organ transplant recipients: a case-control study. Clin Infect Dis 2005;41:52–59.
[60] Cruciani M, Mengoli C, Malena M, Bosco O, Serpelloni G, Grossi P. Antifungal prophylaxis in liver transplant patients: a systematic review and meta-analysis. Liver Transpl 2006;12:850–858.
[61] Fortun J, Martin-Davila P, Montejo M, Munoz P, Cisneros JM, Ramos A, et al. Prophylaxis with caspofungin for invasive fungal infections in high-risk liver transplant recipients. Transplantation 2009;87:424–435.
[62] Sun HY, Cacciarelli TV, Singh N. Micafungin *vs.* amphotericin B lipid complex for the prevention of invasive fungal infections in high-risk liver transplant recipients. Transplantation 2013;96:573–578.
[63] Aguado JM, Varo E, Usetti P, Pozo JC, Moreno A, Catalan M, et al. Safety of anidulafungin in solid organ transplant recipients. Liver Transpl 2012;18:680–685.
[64] Singh N, Paterson DL, Chang FY, Gayowski T, Squier C, Wagener MM, et al. Methicillin-resistant Staphylococcus aureus: the other emerging resistant gram-positive coccus among liver transplant recipients. Clin Infect Dis 2000;30:322–327.
[65] Paterson DL, Rihs JD, Squier C, Gayowski T, Sagnimeni A, Singh N. Lack of efficacy of mupirocin in the prevention of infections with Staphylococcus aureus in liver transplant recipients and candidates. Transplantation 2003;75:194–198.
[66] Munoz P. Multiply resistant gram-positive bacteria: vancomycin-resistant enterococcus in solid organ transplant recipients. Am J Transplant 2009;9:S50–S56.
[67] van Delden C, Blumberg EA. Multidrug resistant gram-negative bacteria in solid organ transplant recipients. Am J Transplant 2009;9:S27–S34.
[68] Ghanem G, Hachem R, Jiang Y, Chemaly RF, Raad I. Outcomes for and risk factors associated with vancomycin-resistant Enterococcus faecalis and vancomycin-resistant Enterococcus faecium bacteremia in cancer patients. Infect Control Hosp Epidemiol 2007;28:1054–1059.
[69] El-Khoury J, Fishman JA. Linezolid in the treatment of vancomycin-resistant Enterococcus faecium in solid organ transplant recipients: report of a multicenter compassionate-use trial. Transpl Infect Dis 2003;5:121–125.
[70] Rand KH, Houck H. Daptomycin synergy with rifampicin and ampicillin against vancomycin-resistant enterococci. J Antimicrob Chemother 2004;53:530–532.
[71] Barbour A, Schmidt S, Ma B, Schiefelbein L, Rand KH, Burkhardt O, et al. Clinical pharmacokinetics and pharmacodynamics of tigecycline. Clin Pharmacokinet 2009;48:575–584.
[72] Paterson DL, Singh N, Rihs JD, Squier C, Rihs BL, Muder RR. Control of an outbreak of infection due to extended-spectrum beta-lactamase–producing *Escherichia coli* in a liver transplantation unit. Clin Infect Dis 2001;33:126–128.
[73] Bergamasco MD, Barroso Barbosa M, de Oliveira Garcia D, Cipullo R, Moreira JC, Baia C, et al. Infection with Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae in solid organ transplantation. Transpl Infect Dis 2012;14:198–205.
[74] Anthony KB, Fishman NO, Linkin DR, Gasink LB, Edelstein PH, Lautenbach E. Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline. Clin Infect Dis 2008;46:567–570.

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[75] Zavascki AP, Goldani LZ, Li J, Nation RL. Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. J Antimicrob Chemother 2007;60:1206–1215.
[76] Plachouras D, Karvanen M, Friberg LE, Papadomichelakis E, Antoniadou A, Tsangaris I, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. Antimicrob Agents Chemother 2009;53:3430–3436.
[77] Kim A, Sutherland CA, Kuti JL, Nicolau DP. Optimal dosing of piperacillin-tazobactam for the treatment of Pseudomonas aeruginosa infections: prolonged or continuous infusion? Pharmacotherapy 2007;27:1490–1497.
[78] Garzoni C. Multiply resistant gram-positive bacteria methicillin-resistant, vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus (MRSA, VISA, VRSA) in solid organ transplant recipients. Am J Transplant 2009;9:S41–S49.
[79] Rosenthal VD, Maki DG, Mehta A, Alvarez-Moreno C, Leblebicioglu H, Higuera F, et al. International Nosocomial Infection Control Consortium report, data summary for 2002–2007, issued January 2008. Am J Infect Control 2008;36:627–637.
[80] Navarro MB, Huttner B, Harbarth S. Methicillin-resistant Staphylococcus aureus control in the 21st century: beyond the acute care hospital. Curr Opin Infect Dis 2008;21:372–379.
[81] Seybold U, Kourbatova EV, Johnson JG, Halvosa SJ, Wang YF, King MD, et al. Emergence of community-associated methicillin-resistant Staphylococcus aureus USA300 genotype as a major cause of health care-associated blood stream infections. Clin Infect Dis 2006;42:647–656.
[82] Santoro-Lopes G, de Gouvea EF, Monteiro RC, Branco RC, Rocco JR, Halpern M, et al. Colonization with methicillin-resistant Staphylococcus aureus after liver transplantation. Liver Transpl 2005;11:203–209.
[83] Singh N, Squier C, Wannstedt C, Keyes L, Wagener MM, Cacciarelli TV. Impact of an aggressive infection control strategy on endemic Staphylococcus aureus infection in liver transplant recipients. Infect Control Hosp Epidemiol 2006;27:122–126.
[84] Desai D, Desai N, Nightingale P, Elliott T, Neuberger J. Carriage of methicillin-resistant Staphylococcus aureus is associated with an increased risk of infection after liver transplantation. Liver Transpl 2003;9:754–759.
[85] Rubinstein E, Corey GR, Stryjewski ME, Kanafani ZA. Telavancin for the treatment of serious gram-positive infections, including hospital acquired pneumonia. Expert Opin Pharmacother 2011;12:2737–2750.
[86] Calfee DP, Salgado CD, Classen D, Arias KM, Podgorny K, Anderson DJ, et al. Strategies to prevent transmission of methicillin-resistant Staphylococcus aureus in acute care hospitals. Infect Control Hosp Epidemiol 2008;29:S62–S80.
[87] McNeil SA, Malani PN, Chenoweth CE, Fontana RJ, Magee JC, Punch JD, et al. Vancomycin-resistant enterococcal colonization and infection in liver transplant candidates and recipients: a prospective surveillance study. Clin Infect Dis 2006;42:195–203.
[88] Xia D, Yan LN, Xu L, Li B, Zeng Y, Wen TF, et al. Postoperative severe pneumonia in adult liver transplant recipients. Transplant Proc 2006;38:2974–2978.
[89] Aguado JM, Torre-Cisneros J, Fortun J, Benito N, Meije Y, Doblas A, et al. Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish society of infectious diseases and clinical microbiology. Clin Infect Dis 2009;48:1276–1284.
[90] Dorman SE, Chaisson RE. From magic bullets back to the magic mountain: the rise of extensively drug-resistant tuberculosis. Nat Med 2007;13:295–298.
[91] Torre-Cisneros J, Doblas A, Aguado JM, San Juan R, Blanes M, Montejo M, et al. Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) cohort. Clin Infect Dis 2009;48:1657–1665.
[92] Subramanian A, Dorman S. Mycobacterium tuberculosis in solid organ transplant recipients. Am J Transplant 2009;9:S57–S62.
[93] Munoz P, Rodriguez C, Bouza E. Mycobacterium tuberculosis infection in recipients of solid organ transplants. Clin Infect Dis 2005;40:581–587.
[94] Fernandez-Sabe N, Cervera C, Lopez-Medrano F, Llano M, Saez E, Len O, et al. Risk factors, clinical features, and outcomes of listeriosis in solid-organ transplant recipients: a matched case-control study. Clin Infect Dis 2009;49:1153–1159.
[95] Kosa KM, Cates SC, Adams-King J, O'Brien B. Improving foodborne illness prevention among transplant recipients. Health Promot Pract 2011;12:235–243.
[96] Roxby AC, Gottlieb GS, Limaye AP. Strongyloidiasis in transplant patients. Clin Infect Dis 2009;49:1411–1423.
[97] Moore PS. The emergence of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8). N Engl J Med 2000;343:1411–1413.
[98] Ariza-Heredia EJ, Razonable RR. Human herpes virus 8 in solid organ transplantation. Transplantation 2011;92:837–844.
[99] Pietrosi G, Vizzini G, Pipitone L, Di Martino G, Minervini MI, Lo Iacono G, et al. Primary and reactivated HHV8 infection and disease after liver transplantation: a prospective study. Am J Transplant 2011;11:2715–2723.
[100] Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005;352:1317–1323.
[101] Marcelin AG, Roque-Afonso AM, Hurtova M, Dupin N, Tulliez M, Sebagh M, et al. Fatal disseminated Kaposi's sarcoma following human herpesvirus 8 primary infections in liver-transplant recipients. Liver Transpl 2004;10:295–300.
[102] Clark NM. Nocardia in solid organ transplant recipients. Am J Transplant 2009;9:S70–S77.

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