ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2011 April 27; 3(4): 83-98

Baishideng Publishing Group
www.wjgnet.com

WJH World Journal of Hepatology

A peer-reviewed, online, open-access journal of hepatology

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2009-2013

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WJH

World Journal of Hepatology

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Monthly Volume 3 Number 4 April 27, 2011

World Journal of Hepatology
Volume 3 Number 4 April 27, 2011

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NAME OF JOURNAL
World Journal of Hepatology

LAUNCH DATE
October 31, 2009

SPONSOR
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
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PUBLISHING
Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
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http://www.wjgnet.com

PUBLICATION DATE
April 27, 2011

ISSN
ISSN 1948-5182 (online)

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ONLINE SUBMISSION
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World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i4.83

World J Hepatol 2011 April 27; 3(4): 83-92
ISSN 1948-5182 (online)

REVIEW

Infections in liver transplant recipients

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Received: October 20, 2010 Revised: December 6, 2010
Accepted: December 13, 2010
Published online: April 27, 2011

Abstract

Liver transplantation is a standard life-saving procedure for the treatment of many end-stage liver diseases. The success of this procedure may be limited by infectious complications. In this article, we review the contemporary state of infectious complications during the post-operative period, with particular emphasis on those that occur most commonly during the first 6 mo after liver transplantation. Bacteria, and less commonly *Candida* infections, remain the predominant pathogens during the immediate post-operative period, especially during the first month, and infections caused by drug-resistant strains are emerging. Infections caused by cytomegalovirus and *Aspergillus* sp. present clinically during the "opportunistic" period characterized by intense immunosuppression. As newer potent immunosuppressive therapies with the major aim of reducing allograft rejection are developed, one potential adverse effect is an increase in certain infections. Hence, it is essential for liver transplant centers to have an effective approach to prevention that is based on predicted infection risk, local antimicrobial resistance patterns, and surveillance. A better understanding of the common and most important infectious complications is anticipated to lead to improvements in quality of life and survival of liver transplant recipients.

Key words: Bacteremia; Candidemia; Cytomegalovirus; Aspergillosis; Transplant

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Romero FA, Razonable RR. Infections in liver transplant recipients. *World J Hepatol* 2011; 3(4): 83-92 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i4/83.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i4.83

INTRODUCTION

Liver transplantation is a life-saving procedure for many end-stage liver diseases. According to the United Network for Organ Sharing (UNOS), a total of 6331 liver transplantations were performed in the United States during 2008-2009, with a survival rate of 85% at one year[1-3]. Survival after liver transplantation has improved over the years, partly due to advances in surgical techniques, and a reduction in allograft rejection. However, there remain multiple preventable conditions that contribute to the poor prognosis of liver transplant recipients. Understanding these complications may optimize management strategies, and further improve the quality of life, and survival rate of patients.

Despite measures such as the use of protective barriers, antimicrobial prophylaxis, and vaccination, infections still represent a major cause of morbidity and mortality after liver transplantation[1,2,4-13]. It is estimated that up to 80% of liver recipients will develop at least one infection during the first year after transplantation, and, while most are successfully treated, some will result in death[14]. Indeed, opportunistic infections are a leading cause of death during the first three years after liver transplantation[4,9]. Often, the diagnosis of these infections is delayed

Table 1 Selected infections after liver transplantation

Time period after liver transplantation		
1st mo	**Between 1st and 6th mo**	**Beyond 6th mo**
General risks: surgical procedure, prolonged hospitalization, prior colonization, mechanical ventilation, indwelling vascular and urinary catheterization, donor-transmitted diseases, among others	General risks: over-immunosuppression, D+/R- mismatch status for viruses, allograft rejection, donor-transmitted diseases, repeated biliary tract manipulations, re-transplantation	General risks: variable High-risk patients include those with recurrent rejection and allograft dysfunction that would require intense immunosuppression
Bacterial infections including resistant pathogens – bloodstream infections, pneumonia, surgical site infections, intra-abdominal infections, abscesses, urosepsis, *Clostridium difficile* associated colitis	Bacterial infections continue to occur in some patients – bloodstream infections, pneumonia, abdominal infections, *C difficile* associated colitis	Minimal immunosuppression – usual community acquired infections and zoster
Herpes simplex virus infection – herpes labialis or genitalis with potential for disseminated disease *Candida* sp. infections – fungemia, abscesses, urosepsis	Opportunistic pathogens: cytomegalovirus, Epstein-Barr virus, human herpesvirus 6 and 7, *Aspergillus* species, Pneumocystis jirovecii, *Nocardia* species, *Mycobacterium* tuberculosis, endemic mycoses, Toxoplasma gondii, among others	Intense immunosuppression due to allograft rejection and dysfunction – infections occurring during the opportunistic period (see middle column) continue to occur; course of chronic viral hepatitis may be accelerated

because, as part of allograft-conserving strategies, immunosuppressive therapy diminishes inflammatory responses, and the clinical signs of infection may be blunted or absent, leading to delayed diagnosis and treatment[15].

There are three consecutive and often overlapping periods after liver transplantation that are associated with specific types of infections (Table 1). This article reviews the contemporary state of infections after liver transplantation, with special emphasis on bacterial infections (surgical site, intra-abdominal, and bloodstream infections) and selected viral [cytomegalovirus (CMV)] and fungal (*Candida* species and *Aspergillus* species) opportunistic pathogens.

BACTERIAL INFECTIONS

Bacterial pathogens are the most common causes of infection after liver transplantation. The highest incidence occurs during the first month after liver transplantation, and these infections predominantly involve the surgical site, the abdominal cavity, bloodstream, urinary system, and/or the respiratory tract[2,4,5,8,9,12,14,16-20]. Risk factors include biliary tract manipulation, prolonged hospitalization, and the necessity for surgical and other invasive procedures (Table 1)[14,16-18,21,22].

Virtually any bacteria can cause disease after liver transplantation, although the vast majority is caused by enterococcus, viridans streptococcus, *Staphylococcus aureus*, and members of the Enterobacteriaceae family[23-26]. There is an increasing trend towards antimicrobial resistance patterns among bacteria, although variations in prevalence rates among geographic regions and centers[23,26] have been found. In some centers, the prevalence rate of methicillin-resistant *S. aureus* (MRSA) colonization may exceed 80%[23,26], while vancomycin-resistant enterococcus (VRE) colonization may reach up to 55%[25]. There have been reported outbreaks of infections due to extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumonia* or *Escherichia coli*[27] and linezolid-resistant VRE[24]. Risk factors for resistant bacterial pathogens are prior antibiotic use, recurrent hospitalizations, the use of invasive interventions such as mechanical ventilation and indwelling devices, and severe underlying diseases[26].

Surveillance for resistant bacteria (MRSA and VRE) in liver recipients may guide prevention strategies. Since MRSA colonization has been associated with risk of later infection[28-32], infection control strategies should be an integral component of liver transplant programs in order to reduce its incidence and transmission. With surveillance, cohorting, contact isolation, and nasal decolonization, the incidence of MRSA after liver transplant has been reduced[30,31]. MRSA decolonization is often achieved with the use of 2% intranasal mupirocin and chlorhexidine baths. The benefits of decolonization with oral antibiotics are debatable, due to concerns about further enhancing drug resistance[23]. Active surveillance for VRE is also performed to prevent healthcare-associated transmission, however, there are no solid data to support antimicrobials to eradicate VRE carrier state[25].

Surgical site infections

One of the most common bacterial infections found to manifest itself early after liver transplantation, is surgical site infection, which has been estimated to occur in about 10% of patients[2]. This is most often manifested as erythema, induration, tenderness, and drainage at the surgical site. In some cases, leukocytosis and fever may occur. Surgical site infection occurs more commonly in liver recipients who require a large number of blood transfusions, thus implying a more complex nature and prolonged duration of the surgical procedure. Notably, centers that perform fewer transplant procedures per year (e.g. < 50) have a higher rate of surgical site infections[2].

Surgical site infections are most commonly caused by Gram-positive cocci such as *S. aureus* and enterococcus, although Gram-negative pathogens like *Escherichia coli*, *Acinetobacter baumannii,* and *Pseudomonas aeruginosa,* and fungal pathogens such as *Candida* spp may be involved[1,9,14,22]. It is not uncommon for multiple pathogens to cause surgical site infections after liver transplantation, hen-

ce it is important to obtain samples for culture so that optimal therapy can be administered.

While surgical site infections are common causes of morbidity during the early period after liver transplantation, they may not be associated with a significant increase in overall mortality[22]. Treatment of surgical site infections consists of a combination of surgical debridement and pathogen-directed antimicrobial therapy.

Intra-abdominal infections

Intra-abdominal infections account for 27%-47% of early bacterial infections after liver transplantation[1,11,17,33]. Intra-abdominal abscesses, peritonitis, and cholangitis commonly present during the first few weeks after liver transplant as fever, leukocytosis, and abdominal pain, although clinically asymptomatic cases which are mainly manifested with elevated liver enzymes are not uncommon. The offending pathogens of intra-abdominal infections are often polymicrobial and, at present, often include multi-drug-resistant isolates. Some of the important bacteria causing intra-abdominal infections are enterococci, including VRE, *S. aureus* including MRSA, *Candida* species, and Gram-negative bacilli such as *Pseudomonas* sp., *Klebsiella* sp., *Acinetobacter* sp., and *Enterobacter* sp.[17,20].

Intra-abdominal infections are significantly associated with higher all-cause mortality (they double the risk), graft loss (39% *vs* 7%), and re-transplantation[17]. Predisposing factors are Roux-en-Y choledochojejunostomy, hepatic artery thrombosis, or arterial stenosis[34]. Once clinically suspected, the test to document the presence of fluid collections is radiographic imaging, either through CT scan or ultrasound. Treatment of infected collections consists of percutaneous or open surgical drainage combined with prolonged antimicrobial therapy, guided by susceptibility testing.

Bloodstream infections

Bloodstream infections may occur any time after liver transplantation, although the majority occur during the first post-operative month. Clinical manifestations most often include fever and rigors, accompanied by leukocytosis and organ-specific or localizing symptoms related to the potential source of the bloodstream infection, such as erythema and drainage at vascular catheter sites (catheter-related blood stream infections), cough and dyspnea (pneumonia), and dysuria and suprapubic and flank pain (urosepsis). Risk factors include intra-abdominal infection, the need for re-operation, prolonged use of indwelling vascular catheters, and acute allograft rejection[5,21]. The gastrointestinal tract is usually the most common source of bloodstream infections in liver transplant recipients, and thus they are most commonly due to enterococcus, viridans streptococcus, Gram-negative bacilli, or may even be polymicrobial[5,35]. Other less common sources of bloodstream infection after liver transplantation include the urinary tract (urosepsis), pulmonary system (pneumonia), or infections emanating from infected indwelling vascular catheters. Interestingly, when compared to other solid organ transplant recipients, there is a higher incidence of mortality due to Gram-negative bloodstream infection among liver transplant recipients[5,35].

Bacteria causing bloodstream infection after liver transplant are predominately Gram-positive cocci such as enterococcus, viridans streptococcus and *Staphylococcus* sp., however, there has been an increasing trend towards Gram-negative bacteria, particularly when the source is the gastrointestinal tract[5,35,36].Today, there is an increasing prevalence of multi-drug resistant bacteria such as MRSA, which may be the cause of as much as 50% of bloodstream infections in some centers[5]. Transplant candidates who are carriers of MRSA have a higher risk of bloodstream infection, and may thus benefit from decolonization prior to transplantation[30]. Likewise, VRE-colonized transplant recipients have a higher risk of infection, postoperative stay in the intensive care unit, and death[37,38]. VRE colonization may also serve as an indicator of a more severe illness, an increased incidence of biliary complications, and multiple previous abdominal surgeries[37,38].

E. coli is the most common Gram-negative bacilli causing bloodstream infection after liver transplantation, followed by *K. pneumoniae* and *P. aeruginosa*[35]. There is increasing resistance among these Gram-negative pathogens. The prevalence of ESBL-producing Gram-negative bacilli is now close to 13% in some centers[2,4,8,14], while 44% of *E. coli* isolates have developed resistance to quinolones[35], potentially due to common use of ciprofloxacin and norfloxacin as prophylaxis for spontaneous bacterial peritonitis, or levofloxacin as empiric therapy for community-acquired respiratory and urinary infections. Likewise, multidrug-resistant strains have been reported in as high as 62.5% of *A. baumannii*, 54.2% of *Stenotrophomonas maltophilia*, and 51.5% of *Pseudomonas* sp. isolates[19,21]. Outbreaks of carbapenem-resistant *Klebsiella spp.* bloodstream infections have occurred, with fatal outcomes[39].

Treatment of bloodstream infections should be directed towards the elimination of the predisposing factor, combined with pathogen-directed antimicrobial therapy that is guided by antimicrobial susceptibility testing. For persistent bloodstream infections, endocarditis should be evaluated by means of a transesophageal echocardiogram. Indwelling vascular and urinary catheters should be removed, intra-abdominal abscesses should be drained, and other potential nidus of infection should be surgically corrected, if feasible.

VIRAL INFECTIONS

Liver recipients are somewhat unique among transplant recipients because they are commonly chronically infected with hepatitis B or C viruses, often with an accelerated clinical course[40]. Respiratory and gastrointestinal viruses may occur throughout the post-liver transplant period, with seasonal variations for some viruses such as influenza and parainfluenza[41-43]. A list of selected viruses that affect liver transplant recipients is listed in Table 1. Among the opportunistic viral pathogens, the most commonly oc-

curring are members of the herpes virus group[44-47], of which CMV is most important in terms of its direct and indirect impact on liver transplant outcome.

Cytomegalovirus

CMV seroprevalence rates in humans ranges from 45% to 100%[48,49]. Its ability to establish latency inside cells leads to a high infection rate in transplant recipients[50,51]. While immunocompetent hosts are usually infected without symp toms, liver recipients often present with more severe clinical presentation, including tissue invasion. Liver recipients at highest risk of CMV infection and disease are those who have never had CMV infection until they receive a latently infected organ from a CMV-seropositive donor (CMV D+/R- mismatch). The risk of progression into CMV disease is magnified by the intense immuno suppression required to avoid or to treat allograft rejection.

The clinical impact of CMV disease after liver transplantation can be classified into: (1) an acute infection with clinical signs known as direct effects (fever, mononucleosis, and invasive organ disease); and (2) a broad range of immunomodulatory and vascular effects, referred to as indirect effects. The most common presentation of CMV disease consists of fever and bone marrow suppression (CMV syndrome). A more aggressive form includes tissue invasion, commonly affecting the gastrointestinal tract, and presenting as gastritis or colitis. This is most often manifests itself as abdominal pain and diarrhea. Endoscopic findings include mucosal erosions and ulcerations, but mild hyperemia or even normal mucosa may also be present[52]. A second clinical presentation that is fairly prevalent in liver recipients is CMV hepatitis, which usually presents with abnormal liver function tests in a cholestatic pattern[53]. CMV hepatitis can be confirmed by means of biopsy, where inclusion bodies with clusters of polymorphonuclear cells is the hallmark[12,53]. A tissue sample is often necessary to rule out the alternative diagnosis of allograft rejection. Other organs such as the central nervous system and the lungs may be infected, and present themselves through headache, delirium, changes in mental function, and cough and dyspnea, respectively. Current practice relies on biologic markers (CMV pp65 antigenemia or CMV DNA by polymerase chain reaction) as the earliest indicators of infection[12,53].

It is proposed that the indirect effects of CMV result from its immunomodulatory property[54-58]. Excessive production of interleukin 10, which is an important inhibitor of the immune response[54], could potentially be one of the mechanisms for the higher incidence of bacteremia, fungal and other viral infections [human herpesvirus 6 (HHV-6), HHV-7, Ebstein-Barr virus (EBV) associated post-transplant lymphoproliferative disorder (PTLD), and accelerated HCV course] in CMV-infected individuals. Infection of vascular networks supplying the transplanted organ may cause functional impairment, leading to the loss of the allograft[58].

Because of its negative impact on overall outcome, prevention of CMV disease is a key management strategy after liver transplantation. One major strategy is antiviral prophylaxis, wherein antiviral drugs such as valganciclovir or oral ganciclovir are given to patients for at least 3 mo after liver transplantation. However, antiviral prophylaxis is associated with delayed-onset CMV disease, which typically occurs soon after completion of prophylaxis. Delayed onset CMV disease is significantly associated with increased mortality and graft failure after liver transplantation[59-61]. Risk factors for delayed onset CMV disease are CMV D+/R- mismatch status, acute allograft rejection, and the corresponding increase in immunosuppression, especially with anti-lymphocyte antibodies[59,62]. The second strategy for CMV disease prevention is pre-emptive therapy, which relies on a close virologic follow-up through serial blood markers (such as viral load or pp65 antigenemia) as the trigger for antiviral therapy, usually with intravenous ganciclovir or valganciclovir[63]. A recent systematic review[64] showed a low incidence (2.6%) of CMV disease in patients who had received pre-emptive valganciclovir therapy, and no case of delayed onset CMV disease was observed. Pre-emptive strategy, which allows short-term low level CMV replication, may prime the immune system to develop CMV-specific immunity, thus preventing late-occurring CMV disease. On the other hand, patients receiving universal prophylaxis had a higher incidence of late onset CMV disease (9.9% at one year). Nonetheless, systematic reviews and meta-analysis have demonstrated the similar reduction in CMV disease for both prophylaxis and pre-emptive therapy strategies, but all-cause mortality appears to be reduced by prophylaxis but not by pre-emptive therapy[63]. There remains a concern for the rapidly replicating virus in CMV D+/R- transplant recipients, so that in this high-risk population, the recommendation is to use antiviral prophylaxis. For lower risk recipients (D+/R+ and D-/R+), universal prophylaxis or pre-emptive therapy regimens may be effectively used (Table 2)[65].

Treatment of CMV disease is with intravenous ganciclovir (5 mg/kg every 12 h) or oral valganciclovir (900 mg orally twice daily) (Table 2), combined with reduction in immunosuppression. Severe cases warrant the initial use of intravenous ganciclovir, while treatment of mild to moderate cases may be initiated upfront with oral valganciclovir. For severe cases, the addition of CMV-hyperimmune globulin as adjunct treatment may be considered. The efficacy of treatment should be guided by clinical and virologic assessments, often with serial weekly monitoring of viral load or antigenemia levels. The vast majority of CMV disease cases after liver transplantation, even those occurring at delayed onset, remain susceptible to ganciclovir. Non-responders should be tested for drug-resistant virus, with UL97 and UL54 gene sequencing. Therapy for drug-resistant CMV is tailored, based on the results of genotyping. Foscarnet and cidofovir are often used for treatment of ganciclovir-resistant UL97-mutant CMV strains, but they have a high risk of nephrotoxicity.

Table 2 Suggested prevention and treatment regimens for various infections after liver transplantation

Infection	Prevention	Treatment
Bacterial infections	According to risk factors (i.e. cephalosporins or vancomycin)	Susceptibility-guided antimicrobial treatment
Herpes simplex virus	Acyclovir 400 mg PO BID for 4 wk (if they are not receiving drugs for CMV prevention)	Acyclovir 5 mg/kg every 8 h for mucocutaneous disease or 10 mg/kg every 8 h for encephalitis Valacyclovir 1 gram PO BID for less severe disease
Cytomegalovirus	Valganciclovir 900 mg daily for 3-6 mo Oral ganciclovir, 1 gram TID for 3-6 mo Preemptive therapy (guided by CMV PCR or antigenemia)	Valganciclovir PO 900 mg BID or ganciclovir Ⅳ 5 mg/kg BID. If severe or life-threatening disease, initiate therapy with Ⅳ ganciclovir. Treatment must continue until viral eradication is achieved, but not shorter than 2 wk CMV Ig may be considered for severe forms of disease like pneumonitis.
Varicella zoster virus	Pre-transplant vaccination	Valacyclovir 1-gram PO TID or Ⅳ acyclovir 10 mg/kg every 8 h Initiate with Ⅳ acyclovir for disseminated disease such as pneumonia or encephalitis VZV immunoglobulin adds no additional benefits and not recommended
Candida species	Fluconazole, echinocandin, or amphotericin B in high-risk recipients for 4 weeks	Amphotericin B 3 to 5 mg/kg Ⅳ daily Fluconazole 800 mg loading dose, then 400 mg PO daily Caspofungin at an initial dose of 70 mg followed by 50 mg daily Anidulafungin initial dose of 200 mg first day followed by 100 mg daily
Aspergillus species	Voriconazole, echinocandin, or amphotericin B in high-risk patients	Voriconazole 6 mg/kg Ⅳ BID on day 1 followed by 4 mg/kg BID daily; transition to oral regimen when clinically stable Echinocandins (caspofungin or anidulafungin) Amphotericin B preparations
Cryptococcus neoformans	Not recommended	Amphotericin B (conventional or liposomal) and flucytosine (5-FC) for at least 2 wk then fluconazole as long-term maintenance (e.g. 6 mo) Fluconazole 800 mg loading dose, then 400 mg PO daily for limited disease
Pneumocystis jirovecii	TMP- SMX 160/800 mg daily or three times per week Alternative: TMP-SMX 80/400 mg daily	TMP- SMX preferred; 15-20 mg/kg per day of TMP component in 3-4 divided doses (keep the sulfa level above 100); transition to oral regimen when clinically stable Alternatives: Pentamidine isethionate, trimethoprim-dapsone (in patients who are not deficient in glucose-6-phosphate dehydrogenase), atovaquone, and clindamycin-primaquine.
Toxoplasma gondii	TMP- SMX 160/800 mg daily	Pyrimethamine in combination with sulfadiazine or clindamycin.
Listeria monocytogenes	Not recommended but TMP- SMX for Pneumocystis prophylaxis may prevent some infections	Ampicillin 2 g Ⅳ every four hours plus Gentamicin 3 mg/kg per day Ⅳ in three divided doses Alternatives: TMP- SMX 10-20 mg/kg Ⅳ per day divided every 6 to 12 h Meropenem 2 g Ⅳ every eight hours
Nocardia asteroides	Not recommended but TMP- SMX for Pneumocystis prophylaxis may prevent some infections	TMP-SMX preferred; 8-10 mg/kg per day of TMP component in 2-4 divided doses; higher doses may be used in severe disease; transition to oral therapy when clinically stable

CMV: cytomegalovirus; VZV: Varicella zoster virus; HSV: herpes simplex virus; TMP–SMX: trimethoprim sulfamethoxazole.

FUNGAL INFECTIONS

Although various fungal species infect liver transplant recipients, by far the most common are the *Candida* species followed by the *Aspergillus* species. *Cryptococcus neoformans* occurs much less commonly in the form of meningitis, lung disease and cellulitis[66]. Endemic mycoses due to *Histoplasma capsulatum*, *Coccidiodes immitis*, and *Blastomyces dermatitidis* may occur in liver recipients from endemic regions, and among these, *C. immitis* often persist and require prolonged therapy[67]. Other less common fungi that may cause skin disease could potentially become invasive in liver transplant recipients, include *Alternaria* species, *Sporothrix schenckii*, *Trichophyton rubrum*, among others[68]. Finally, infection due to *Pneumocystis jirovecii* occurs primarily as diffuse bilateral pneumonitis, although the use of trimethoprim sulfamethoxazole prophylaxis has remarkably reduced its incidence after liver transplantation[69].

Candida species

Candida sp. accounts for over half of all invasive fungal infections in liver recipients[70]. Superficial and invasive candidiasis occurs early and often during the first 1-3 mo after liver transplantation[70]. *Candida albicans* is the single most common species, but collectively the non-*albicans* *Candida* species are now being reported more frequently from blood cultures. The distribution of the species varies among reports, including *C. glabrata*, *C. parapsilosis*, *C. tropicalis, C. kefyr, C. guilliermondii and C. krusei*[2,5,7,10,71-75]. This has implications in empiric antifungal treatment, since some of these isolates, particularly *C. glabrata* and *C. krusei*, are inherently resistant to fluconazole. The most common clinical presentation is mucosal candidiasis (e.g. oral thrush), but the much more worrisome illness, because of its impact on morbidity and mortality, is invasive candidiasis[70-76]. Invasive candidiasis is defined as the (1) direct microscopic evidence of the candida in a specimen obtained from a normally sterile site; (2) recovery of candida by

Table 3 Risk factors of fungal infections after liver transplantation

Candida species	*Aspergillus* species
Renal insufficiency	Renal insufficiency
Renal insufficiency (creatinine > 3.0 mg/dL)	Renal failure
Renal replacement therapy within the first 30 days after transplant	Need for dialysis
Surgical factors	Surgical factors
Prolonged transplant operation time (> 11 h)	Retransplantation
Second surgical intervention for any reason within 5 d of the initial transplant procedure	Microbial factors
Choledochojejunostomy anastomosis.	CMV infection
Transfusion of ⩾ 40 units of blood products during the surgery	Prior colonization
Microbial factors	Fulminant hepatic failure
Early fungal colonization (within 3 d after liver transplantation)	
Documented colonization (nasal, pharyngeal or rectal cultures)	
Fulminant hepatic failure	

CMV: cytomegalovirus.

culture of a sample obtained from a normally sterile site in a suspicious clinical setting; or (3) recovery of *Candida* species in one or more blood cultures (candidemia)[77]. Disseminated candidiasis is defined as an episode of candidemia with associated target-like abscesses in the liver or the spleen, or the presence of progressive retinal exudates on ophthalmologic examination[77].

The incidence of candidemia among transplant recipients ranges between 2%-8%[2,75], and the overall mortality associated with invasive fungal presentation has been reported to be as high as 77%[74]. Invasive candidiasis could be primary or secondary to infected catheters or surgical wounds[72]. Dissemination to involve distant sites such as the eyes and the bone may occur, and should warrant evaluation in the presence of clinical symptoms such as blurring of vision and bone pains, respectively. Surgical site infection, peritonitis, liver and abdominal abscesses, endophthalmitis, esophagitis, and urinary tract or anastomotic infections are the other clinical presentations of candidiasis[70,76].

Risk factors for invasive candidiasis are often related to the surgical procedure (such as prolonged or repeat operations and re-transplantation), high-transfusion requirement, previous *Candida* specie colonization during the perioperative period, and renal failure after liver transplantation (Table 3)[7,70,72,76,78]. Choleducho-jejunostomy anastomosis is especially associated with a higher risk of candidiasis when compared to choledoco-choledocho anastomosis[7].

The American Society of Transplantation recommends antifungal prophylaxis against *Candida* to high-risk liver recipients[70,76]. However, the duration of prophylaxis is not defined, with many centers providing it for 4 weeks. Echinocandins, azoles, and amphotericin B are the various options for antifungal prophylaxis[78]. Clinical studies have shown that fluconazole, itraconazole, or amphotericin B prophylaxis markedly reduced the incidence of invasive candidiasis in liver recipients[79-81]. Caspofungin also appears to be well tolerated[78] and has been shown to result in a low rate of invasive fungal infection[78,82]. However, a meta-analysis showed that, while antifungal prophylaxis in liver recipients significantly reduced the incidence of superficial and invasive fungal infection, it neither impacted on the overall mortality nor the need for empirical antifungal treatment[71]. Antifungal prophylaxis is not recommended for low-risk patients[83] due to concerns for toxicity, and may select for resistant strains[78,84].

Treatment of invasive candidiasis after liver transplantation is often a combination of antifungal therapy, elimination of nidus of infection, and reduction of immunosuppression. Empiric treatment of invasive candidiasis consists of the use of a broad-spectrum antifungal agent (such as caspofungin, micafungin and anidulafungin) in view of the increasing incidence of fluconazole-resistant strains due to non-*albicans Candida* species[2]. Once the species and its antifungal susceptibility pattern have been confirmed, a more focused treatment should be used. The vast majority of *C. albicans* remains susceptible to fluconazole and that should be the treatment of choice. The shift from *C. albicans* to non-*albicans* species in many clinical settings has most likely resulted from the widespread use of fluconazole prophylaxis[73]. Fluconazole resistance in invasive candidiasis should be suspected in patients who have received fluconazole during the 30 d prior to the illness. Abscesses and infected wounds need to be drained and debrided, while infected indwelling vascular and urinary catheters need to be removed. Potential sites of dissemination such as the eye (candidal retinitis and endophthalmitis) and the bones (osteomyelitis) should be examined.

Aspergillus species

After *Candida* sp., this highly aerobic mold is the second most common fungal infection in liver recipients, with invasive aspergillosis occurring in 1%-9.2%[85]. The risk factors are listed in Table 3[86,87]. Among the most notable risk factors are re-transplantation, which could bring about a 30-fold higher risk, and renal failure, especially with the requirement for renal replacement therapy, which could bring about a 15-25 fold increase in risk[85]. Other risk factors that have been described are fulminant hepatic failure, CMV disease, and prolonged ICU stay[85]. Mortality from invasive aspergillosis is high among liver recipients, so that treatment needs to be started early and aggres-

sively[13].

Aspergillus fumigatus is the most common offending species[85], whereas *A. niger, A. flavus* and *A. terreus* are less common[88]. In a recent study of the clinical features of invasive aspergillosis from 23 US transplant centers, the most common clinical presentation (90%) was lung infection[85]. Most infections occur during the first year, with a median time to diagnosis of 100 d. Other studies have described an earlier onset of invasive aspergillosis, such as within 30 d after liver transplantation, although others report a much more delayed onset of infection[85]. Notably, liver recipients with invasive fungal infection had the highest mortality reported, perhaps as result of the severity of the illness and the patient's underlying compromised status[13,88].

The possibility of invasive aspergillosis should be suspected in the presence of risk factors and suspicious clinical findings, and should be confirmed by one of the following: (1) lower respiratory tract infection symptoms, with associated risk factors and CT images showing well-circumscribed lesions with or without the halo sign, air-crescent sign or a cavity; (2) central nervous system infection with focal lesions on imaging or (3) recovery by culture of the mold[77]. Since sensitivity of fungal cultures is relatively low, it has been suggested that measuring aspergillus antigens such as galactomannan in clinical samples such as plasma, serum, bronchoalveolar lavage fluid, or CSF could be useful for diagnosis[85]. Special caution, however, is suggested in interpreting the galactomannan test in patients who are receiving β-lactam antibiotics (specifically piperacillin tazobactam and ampicillin) which cross-react with the assay, thereby providing false positive results[89,90]. These antimicrobials are semisynthetic derivatives from *Penicillium* species that contain galactofuran-bearing molecules, which react with the assay[91,92].

Antifungal prophylaxis against *Aspergillus* sp. could result in an important reduction in superficial and invasive infection, as well as mortality attributable to fungal infections[85]. However, antifungal prophylaxis does not reduce overall mortality or the need for empirical antifungal therapy[71]. The overall efficacy of universal antifungal prophylaxis is limited by the generally low incidence of invasive aspergillosis[85]. Hence, providing prophylaxis only to the high-risk patients would seem to be a more rational approach[71]. The American Society of Transplantation recommends the use of a lipid formulation of amphotericin B (3-5 mg/kg per day) or an echinocandin for liver recipients with factors that place them at high risk[85]; the duration of antifungal prophylaxis is during the initial hospital stay or for 4 wk after liver transplantation[85].

Prompt diagnosis and initiation of antifungal therapy, coupled with a reduction in the immunosuppressive regimen is essential for achieving optimal outcomes with invasive aspergillosis after liver transplantation[85]. The current guideline endorses voriconazole as the first-line choice for the treatment of invasive aspergillosis (Table 2)[88]. Antifungal therapy with amphotericin B preparations is now considered as second line therapy[87]. Echinocandins are effective for treatment, but they have been tested mainly as salvage therapy for invasive aspergillosis[85]. Of the echinocandins, caspofungin is currently approved by the US FDA for the treatment of invasive aspergillosis. Combination antifungal therapy has been reported in certain situations (such as severe disseminated disease), but the efficacy of this approach remains controversial[85]. The Infectious Disease Society of America reserves the option of combination antifungal regimens as salvage therapy for non-responsive cases of invasive aspergillosis[85,88]. Surgical excision or debridement remains an integral part of the management of invasive aspergillosis. The optimal duration of therapy depends on the response to therapy, and the patient's underlying immune function. Generally, treatment is continued for at least 12 wk, although it should be individualized, based on clinical response.

CONCLUSION

Infectious complications remain important preventable causes of morbidity and mortality among liver recipients. The vast majority of infections that occur during the immediate period after liver transplantation are often related either to surgical procedures, medical devices, or the need for prolonged hospitalization. During the highly intense period of immunosuppression, the most common opportunistic infections are cytomegalovirus and invasive fungal infections (candidiasis and less commonly aspergillosis). It is therefore essential to have in place an effective approach to prevention, based on predicted infection risk, local antimicrobial resistance patterns, and surveillance of specific risk factors. A better understanding of the common and important infectious complications is anticipated to improve quality of life and survival rate after liver transplantation.

REFERENCES

1 **Arnow PM**. Infections following orthotopic liver transplantation. *HPB Surg* 1991; **3**: 221-232; discussion 232-233

2 **Moreno A**, Cervera C, Gavaldá J, Rovira M, de la Cámara R, Jarque I, Montejo M, de la Torre-Cisneros J, Miguel Cisneros J, Fortún J, López-Medrano F, Gurguí M, Muñoz P, Ramos A, Carratalá J. Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. *Am J Transplant* 2007; **7**: 2579-2586

3 **Watt KD**, Burak KW, Deschênes M, Lilly L, Marleau D, Marotta P, Mason A, Peltekian KM, Renner E, Yoshida EM. Survival after liver transplantation for hepatitis C is unchanged over two decades in Canada. *Can J Gastroenterol* 2008; **22**: 153-154

4 **Watt KD**, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant* 2010; **10**: 1420-1427

5 **Bert F**, Larroque B, Paugam-Burtz C, Janny S, Durand F, Dondero F, Valla DC, Belghiti J, Moreau R, Nicolas-Chanoine MH. Microbial epidemiology and outcome of bloodstream infections in liver transplant recipients: an analysis of 259 episodes. *Liver Transpl* 2010; **16**: 393-401

6 **Charlton M**, Ruppert K, Belle SH, Bass N, Schafer D, Wiesner RH, Detre K, Wei Y, Everhart J. Long-term results and modeling to predict outcomes in recipients with HCV infec-

tion: results of the NIDDK liver transplantation database. *Liver Transpl* 2004; **10**: 1120-1130
7 **Collins LA**, Samore MH, Roberts MS, Luzzati R, Jenkins RL, Lewis WD, Karchmer AW. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. *J Infect Dis* 1994; **170**: 644-652
8 **del Pozo JL**. Update and actual trends on bacterial infections following liver transplantation. *World J Gastroenterol* 2008; **14**: 4977-4983
9 **Fishman JA**. Infection in solid-organ transplant recipients. *N Engl J Med* 2007; **357**: 2601-2614
10 **Horn DL**, Neofytos D, Anaissie EJ, Fishman JA, Steinbach WJ, Olyaei AJ, Marr KA, Pfaller MA, Chang CH, Webster KM. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin Infect Dis* 2009; **48**: 1695-1703
11 **Kim YJ**, Kim SI, Wie SH, Kim YR, Hur JA, Choi JY, Yoon SK, Moon IS, Kim DG, Lee MD, Kang MW. Infectious complications in living-donor liver transplant recipients: a 9-year single-center experience. *Transpl Infect Dis* 2008; **10**: 316-324
12 **Linden PK**. Approach to the immunocompromised host with infection in the intensive care unit. *Infect Dis Clin North Am* 2009; **23**: 535-556
13 **Neofytos D**, Fishman JA, Horn D, Anaissie E, Chang CH, Olyaei A, Pfaller M, Steinbach WJ, Webster KM, Marr KA. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis* 2010; **12**: 220-229
14 **Kawecki D**, Chmura A, Pacholczyk M, Lagiewska B, Adadynski L, Wasiak D, Czerwinski J, Malkowski P, Sawicka-Grzelak A, Kot K, Wroblewska M, Rowinski W, Durlik M, Paczek L, Luczak M. Bacterial infections in the early period after liver transplantation: etiological agents and their susceptibility. *Med Sci Monit* 2009; **15**: CR628-CR637
15 **Moon DB**, Lee SG. Liver transplantation. *Gut Liver* 2009; **3**: 145-165
16 **Tenza E**, Bernardo CG, Escudero D, Otero J, Quindós B, Miyar A, Vázquez L, Taboada F, Rodríguez M, González-Dièguez L, González-Pinto I, Barneo L. Liver transplantation complications in the intensive care unit and at 6 months. *Transplant Proc* 2009; **41**: 1050-1053
17 **Safdar N**, Said A, Lucey MR, Knechtle SJ, D'Alessandro A, Musat A, Pirsch J, McDermott J, Kalayoglu M, Maki DG. Infected bilomas in liver transplant recipients: clinical features, optimal management, and risk factors for mortality. *Clin Infect Dis* 2004; **39**: 517-525
18 **Kim SI**, Kim YJ, Jun YH, Wie SH, Kim YR, Choi JY, Yoon SK, Moon IS, Kim DG, Lee MD, Kang MW. Epidemiology and risk factors for bacteremia in 144 consecutive living-donor liver transplant recipients. *Yonsei Med J* 2009; **50**: 112-121
19 **Linares L**, García-Goez JF, Cervera C, Almela M, Sanclemente G, Cofán F, Ricart MJ, Navasa M, Moreno A. Early bacteremia after solid organ transplantation. *Transplant Proc* 2009; **41**: 2262-2264
20 **Reid GE**, Grim SA, Sankary H, Benedetti E, Oberholzer J, Clark NM. Early intra-abdominal infections associated with orthotopic liver transplantation. *Transplantation* 2009; **87**: 1706-1711
21 **Shi SH**, Kong HS, Xu J, Zhang WJ, Jia CK, Wang WL, Shen Y, Zhang M, Zheng SS. Multidrug resistant gram-negative bacilli as predominant bacteremic pathogens in liver transplant recipients. *Transpl Infect Dis* 2009; **11**: 405-412
22 **Asensio A**, Ramos A, Cuervas-Mons V, Cordero E, Sánchez-Turrión V, Blanes M, Cervera C, Gavalda J, Aguado JM, Torre-Cisneros J. Effect of antibiotic prophylaxis on the risk of surgical site infection in orthotopic liver transplant. *Liver Transpl* 2008; **14**: 799-805
23 **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** Suppl 4: S41-S49
24 **Herrero IA**, Issa NC, Patel R. Nosocomial spread of linezolid-resistant, vancomycin-resistant Enterococcus faecium. *N Engl J Med* 2002; **346**: 867-869
25 **Muñoz P**. Multiply resistant gram-positive bacteria: vancomycin-resistant enterococcus in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S50-S56
26 **van Delden C**, Blumberg EA. Multidrug resistant gram-negative bacteria in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S27-S34
27 **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
28 **Bert F**, Galdbart JO, Zarrouk V, Le Mée J, Durand F, Mentré F, Belghiti J, Lambert-Zechovsky N, Fantin B. Association between nasal carriage of Staphylococcus aureus and infection in liver transplant recipients. *Clin Infect Dis* 2000; **31**: 1295-1299
29 **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
30 **Russell DL**, Flood A, Zaroda TE, Acosta C, Riley MM, Busuttil RW, Pegues DA. Outcomes of colonization with MRSA and VRE among liver transplant candidates and recipients. *Am J Transplant* 2008; **8**: 1737-1743
31 **Singh N**, Paterson DL, Chang FY, Gayowski T, Squier C, Wagener MM, Marino IR. Methicillin-resistant Staphylococcus aureus: the other emerging resistant gram-positive coccus among liver transplant recipients. *Clin Infect Dis* 2000; **30**: 322-327
32 **Wertheim HF**, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, Nouwen JL. The role of nasal carriage in Staphylococcus aureus infections. *Lancet Infect Dis* 2005; **5**: 751-762
33 **Akin K**, Ozturk A, Guvenc Z, Isiklar I, Haberal M. Localized fluid collections after liver transplantation. *Transplant Proc* 2006; **38**: 627-630
34 **Said A**, Safdar N, Lucey MR, Knechtle SJ, D'Alessandro A, Musat A, Pirsch J, Kalayoglu M, Maki DG. Infected bilomas in liver transplant recipients, incidence, risk factors and implications for prevention. *Am J Transplant* 2004; **4**: 574-582
35 **Al-Hasan MN**, Razonable RR, Eckel-Passow JE, Baddour LM. Incidence rate and outcome of Gram-negative bloodstream infection in solid organ transplant recipients. *Am J Transplant* 2009; **9**: 835-843
36 **Singh N**, Wagener MM, Obman A, Cacciarelli TV, de Vera ME, Gayowski T. Bacteremias in liver transplant recipients: shift toward gram-negative bacteria as predominant pathogens. *Liver Transpl* 2004; **10**: 844-849
37 **McNeil SA**, Malani PN, Chenoweth CE, Fontana RJ, Magee JC, Punch JD, Mackin ML, Kauffman CA. Vancomycin-resistant enterococcal colonization and infection in liver transplant candidates and recipients: a prospective surveillance study. *Clin Infect Dis* 2006; **42**: 195-203
38 **Gearhart M**, Martin J, Rudich S, Thomas M, Wetzel D, Solomkin J, Hanaway MJ, Aranda-Michel J, Weber F, Trumball L, Bass M, Zavala E, Steve Woodle E, Buell JF. Consequences of vancomycin-resistant Enterococcus in liver transplant recipients: a matched control study. *Clin Transplant* 2005; **19**: 711-716
39 **Mathers AJ**, Cox HL, Bonatti H, Kitchel B, Brassinga AK, Wispelwey B, Sawyer RG, Pruett TL, Hazen KC, Patel JB, Sifri CD. Fatal cross infection by carbapenem-resistant Klebsiella in two liver transplant recipients. *Transpl Infect Dis* 2009; **11**: 257-265
40 **Levitsky J**, Doucette K. Viral hepatitis in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S116-S130

41 **Ison MG**, Green M. Adenovirus in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S161-S165
42 **Ison MG**, Michaels MG. RNA respiratory viral infections in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S166-S172
43 **Kumar D**, Morris MI, Kotton CN, Fischer SA, Michaels MG, Allen U, Blumberg EA, Green M, Humar A, Ison MG. Guidance on novel influenza A/H1N1 in solid organ transplant recipients. *Am J Transplant* 2010; **10**: 18-25
44 **Humar A**, Snydman D. Cytomegalovirus in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S78-S86
45 **Razonable RR**, Zerr DM. HHV-6, HHV-7 and HHV-8 in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S97-S100
46 **Pergam SA**, Limaye AP. Varicella zoster virus (VZV) in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S108-S115
47 **Zuckerman R**, Wald A. Herpes simplex virus infections in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S104-S107
48 **Bate SL**, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988-2004. *Clin Infect Dis* 2010; **50**: 1439-1447
49 **Cannon MJ**, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. *Rev Med Virol* 2010; **20**: 202-213
50 **Boin ID**, Boteon YL, Stucchi RS, Pereira MI, Portugal TC, Udo EY. Serological profile of pretransplantation liver patients. *Transplant Proc* 2010; **42**: 491-493
51 **Dahiya D**, Lee CF, Chan KM, Wu TJ, Chou HS, Cheng SS, Lee WC. A short-term preemptive treatment for cytomegalovirus infection in seropositive patients after liver transplantation. *J Hepatobiliary Pancreat Sci* 2011; **18**: 32-38
52 **Eid AJ**, Arthurs SK, Deziel PJ, Wilhelm MP, Razonable RR. Clinical predictors of relapse after treatment of primary gastrointestinal cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2010; **10**: 157-161
53 **Koffron A**, Stein JA. Liver transplantation: indications, pretransplant evaluation, surgery, and posttransplant complications. *Med Clin North Am* 2008; **92**: 861-888, ix
54 **van de Berg PJ**, Heutinck KM, Raabe R, Minnee RC, Young SL, van Donselaar-van der Pant KA, Bemelman FJ, van Lier RA, ten Berge IJ. Human cytomegalovirus induces systemic immune activation characterized by a type 1 cytokine signature. *J Infect Dis* 2010; **202**: 690-699
55 **Razonable RR**, Emery VC. Management of CMV infection and disease in transplant patients. 27-29 February 2004. *Herpes* 2004; **11**: 77-86
56 **Razonable RR**, Paya CV. Herpesvirus infections in transplant recipients: current challenges in the clinical management of cytomegalovirus and Epstein-Barr virus infections. *Herpes* 2003; **10**: 60-65
57 **Razonable RR**, Paya CV. Infections and allograft rejection - intertwined complications of organ transplantation. *Swiss Med Wkly* 2005; **135**: 571-573
58 **Baron C**, Forconi C, Lebranchu Y. Revisiting the effects of CMV on long-term transplant outcome. *Curr Opin Organ Transplant* 2010; **15**: 492-498
59 **Kim JM**, Kim SJ, Joh JW, Kwon CH, Shin M, Kim EY, Moon JI, Jung GO, Choi GS, Lee SK. Early and delayed onset cytomegalovirus infection of liver transplant recipients in endemic areas. *Transplant Proc* 2010; **42**: 884-889
60 **Husain S**, Pietrangeli CE, Zeevi A. Delayed onset CMV disease in solid organ transplant recipients. *Transpl Immunol* 2009; **21**: 1-9
61 **Arthurs SK**, Eid AJ, Pedersen RA, Kremers WK, Cosio FG, Patel R, Razonable RR. Delayed-onset primary cytomegalovirus disease and the risk of allograft failure and mortality after kidney transplantation. *Clin Infect Dis* 2008; **46**: 840-846
62 **Razonable RR**, Rivero A, Rodriguez A, Wilson J, Daniels J, Jenkins G, Larson T, Hellinger WC, Spivey JR, Paya CV. Allograft rejection predicts the occurrence of late-onset cytomegalovirus (CMV) disease among CMV-mismatched solid organ transplant patients receiving prophylaxis with oral ganciclovir. *J Infect Dis* 2001; **184**: 1461-1464
63 **Eid AJ**, Razonable RR. New developments in the management of cytomegalovirus infection after solid organ transplantation. *Drugs* 2010; **70**: 965-981
64 **Sun HY**, Wagener MM, Singh N. Prevention of posttransplant cytomegalovirus disease and related outcomes with valganciclovir: a systematic review. *Am J Transplant* 2008; **8**: 2111-2118
65 **Kotton CN**, Kumar D, Caliendo AM, Asberg A, Chou S, Snydman DR, Allen U, Humar A. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation* 2010; **89**: 779-795
66 **Singh N**, Forrest G. Cryptococcosis in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S192-S198
67 **Proia L**, Miller R. Endemic fungal infections in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S199-S207
68 **Kubak BM**, Huprikar SS. Emerging & rare fungal infections in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S208-S226
69 **Martin SI**, Fishman JA. Pneumocystis pneumonia in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S227-S233
70 **Pappas PG**, Silveira FP. Candida in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S173-S179
71 **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
72 **Hadley S**, Huckabee C, Pappas PG, Daly J, Rabkin J, Kauffman CA, Merion RM, Karchmer AW. Outcomes of antifungal prophylaxis in high-risk liver transplant recipients. *Transpl Infect Dis* 2009; **11**: 40-48
73 **Person AK**, Kontoyiannis DP, Alexander BD. Fungal infections in transplant and oncology patients. *Infect Dis Clin North Am* 2010; **24**: 439-459
74 **Singh N**. Fungal infections in the recipients of solid organ transplantation. *Infect Dis Clin North Am* 2003; **17**: 113-134, viii
75 **van Hal SJ**, Marriott DJ, Chen SC, Nguyen Q, Sorrell TC, Ellis DH, Slavin MA. Candidemia following solid organ transplantation in the era of antifungal prophylaxis: the Australian experience. *Transpl Infect Dis* 2009; **11**: 122-127
76 **Pappas PG**, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48**: 503-535
77 **De Pauw B**, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW, Patterson TF, Maschmeyer G, Bille J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Muñoz P, Odds FC, Perfect JR, Restrepo A, Ruhnke M, Segal BH, Sobel JD, Sorrell TC, Viscoli C, Wingard JR, Zaoutis T, Bennett JE. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46**: 1813-1821
78 **Fortún J**, Martín-Dávila P, Montejo M, Muñoz P, Cisneros JM, Ramos A, Aragón C, Blanes M, San Juan R, Gavaldá J, Llinares P. Prophylaxis with caspofungin for invasive fungal infections in high-risk liver transplant recipients. *Transplantation* 2009; **87**: 424-435

79 **Lumbreras C**, Cuervas-Mons V, Jara P, del Palacio A, Turrión VS, Barrios C, Moreno E, Noriega AR, Paya CV. Randomized trial of fluconazole versus nystatin for the prophylaxis of Candida infection following liver transplantation. *J Infect Dis* 1996; **174**: 583-588

80 **Sharpe MD**, Ghent C, Grant D, Horbay GL, McDougal J, David Colby W. Efficacy and safety of itraconazole prophylaxis for fungal infections after orthotopic liver transplantation: a prospective, randomized, double-blind study. *Transplantation* 2003; **76**: 977-983

81 **Winston DJ**, Pakrasi A, Busuttil RW. Prophylactic fluconazole in liver transplant recipients. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999; **131**: 729-737

82 **Winkler M**, Pratschke J, Schulz U, Zheng S, Zhang M, Li W, Lu M, Sgarabotto D, Sganga G, Kaskel P, Chandwani S, Ma L, Petrovic J, Shivaprakash M. Caspofungin for post solid organ transplant invasive fungal disease: results of a retrospective observational study. *Transpl Infect Dis* 2010; **12**: 230-237

83 **Pappas PG**, Andes D, Schuster M, Hadley S, Rabkin J, Merion RM, Kauffman CA, Huckabee C, Cloud GA, Dismukes WE, Karchmer AW. Invasive fungal infections in low-risk liver transplant recipients: a multi-center prospective observational study. *Am J Transplant* 2006; **6**: 386-391

84 **Singh N**. Antifungal prophylaxis in solid-organ transplant recipients: considerations for clinical trial design. *Clin Infect Dis* 2004; **39** Suppl 4: S200-S206

85 **Singh N**, Husain S. Invasive aspergillosis in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S180-S191

86 **Rosenhagen M**, Feldhues R, Schmidt J, Hoppe-Tichy T, Geiss HK. A risk profile for invasive aspergillosis in liver transplant recipients. *Infection* 2009; **37**: 313-319

87 **Baddley JW**, Andes DR, Marr KA, Kontoyiannis DP, Alexander BD, Kauffman CA, Oster RA, Anaissie EJ, Walsh TJ, Schuster MG, Wingard JR, Patterson TF, Ito JI, Williams OD, Chiller T, Pappas PG. Factors associated with mortality in transplant patients with invasive aspergillosis. *Clin Infect Dis* 2010; **50**: 1559-1567

88 **Singh N**, Pruett TL, Houston S, Muñoz P, Cacciarelli TV, Wagener MM, Husain S. Invasive aspergillosis in the recipients of liver retransplantation. *Liver Transpl* 2006; **12**: 1205-1209

89 **Fortún J**, Martín-Dávila P, Alvarez ME, Norman F, Sánchez-Sousa A, Gajate L, Bárcena R, Nuño SJ, Moreno S. False-positive results of Aspergillus galactomannan antigenemia in liver transplant recipients. *Transplantation* 2009; **87**: 256-260

90 **Viscoli C**, Machetti M, Cappellano P, Bucci B, Bruzzi P, Van Lint MT, Bacigalupo A. False-positive galactomannan platelia Aspergillus test results for patients receiving piperacillin-tazobactam. *Clin Infect Dis* 2004; **38**: 913-916

91 **Metan G**, Ağkuş C, Buldu H, Koç AN. The interaction between piperacillin/tazobactam and assays for Aspergillus galactomannan and 1,3-beta-D-glucan in patients without risk factors for invasive fungal infections. *Infection* 2010; **38**: 217-221

92 **Xavier MO**, Pasqualotto AC, Aquino VR, Sukiennik TC, Severo LC. Galactomannan detection from piperacillin-tazobactam brands available in the Brazilian market. *Braz J Infect Dis* 2009; **13**: 353-355

S- Editor Zhang HN **L- Editor** Herholdt A **E- Editor** Liu N

World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v3.i4.93

World J Hepatol 2011 April 27; 3(4): 93-98
ISSN 1948-5182 (online)

BRIEF ARTICLE

Asymptomatic primary biliary cirrhosis is not associated with increased frequency of cardiovascular disease

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Received: September 27,2010 Revised: January 12, 2011
Accepted: March 19, 2011
Published online: April 27, 2011

Abstract

AIM: To estimate the prevalence of cardiovascular events in Primary biliary cirrhosis (PBC) and to determine whether this risk is higher within specific subgroups of patients with PBC.

METHODS: We included 180 patients with PBC (cases) and 151 patients seen for HCV infection (controls). Medical records were reviewed and statistical analyses were performed as appropriate.

RESULTS: When compared to controls, PBC patients were older, leaner and had higher serum levels of total cholesterol, high density lipoprotein and low density cholesterol. There were more females in the PBC group (91.7% *vs* 43%, $P < 0.001$). More control subjects had smoked than the PBC patients (63.6% *vs* 35%, $P < 0.001$). The prevalence of hypertension, diabetes, coronary artery disease and stroke was similar between the two groups. Seven percent of controls and 10% of cases developed any type of cardiovascular disease ($P = 0.3$). Only 36.7% were asymptomatic at diagnosis. Three cardiovascular events were documented among asymptomatic patients (4.5%) and fifteen among symptomatic patients (13.2%; $P = 0.06$). Among PBC patients with fatigue, 10 (13.5%) had a cardiovascular event compared to 7 (6.7%) among patients without fatigue ($P = 0.1$).

CONCLUSION: Asymptomatic PBC patients do not have a greater frequency of cardiovascular disease; nor do patients suffering with fatigue.

Key words: Hyperlipidemia; Cardiovascular disease; Asymptomatic primary biliary cirrhosis; Fatigue

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Doycheva I, Chen C, Pan JJ, Levy C. Asymptomatic primary biliary cirrhosis is not associated with increased frequency of cardiovascular disease. *World J Hepatol* 2011; 3(4): 93-98 Available from: URL: http://www.wjgnet.com/1948-5182/full/v3/i4/93.htm DOI: http://dx.doi.org/10.4254/wjh.v3.i4.93

INTRODUCTION

PBC is a chronic cholestatic disease characterized by progressive immune-mediated destruction of interlobular bile ducts[1]. Serum cholesterol is frequently elevated in patients with primary biliary cirrhosis, albeit in a variable fashion[2]. Most of the cholesterol elevation is due to lipoprotein X, a lipoprotein fraction within the low density cholesterol (LDL) region[3]. Typically, we observe an increase in LDL cholesterol that parallels disease severity as a result of the progressive loss of LDL receptors in the liver, thus leading to failure of clearance by the hepatocytes[4]. The high density lipoprotein (HDL), on the other hand, tends to be higher in the earlier stages of disease and lower with more

advanced PBC[5].

In the general population, hyperlipidemia is well known to predict increased morbid-mortality from cardiovascular disease[6], the leading cause of death in the United States. Thus, especially as PBC affects middle-aged patients, the presence of hyperlipidemia in this population was initially thought to be associated with an increased risk of cardiovascular disease. However, a causation link between hyperlipidemia and cardiovascular disease in PBC could not be established, even when ultrasound imaging of the carotids was used for measurement of the intima-media thickness as a marker for subclinical cardiovascular disease[2,7]. This controversy has been revisited due to[1] evidence that patients with asymptomatic PBC may have an increased non liver-related mortality in comparison to patients with symptomatic PBC and[2] evidence that fatigue may be associated with increased cardiovascular deaths.

Thus, in the present study we aimed to investigate the frequency of cardiovascular disease [coronary artery disease (CAD), transient ischemic attack (TIA) and stroke (CVA)] in patients with PBC in comparison to controls and to determine if asymptomatic patients with PBC had an increased frequency of cardiovascular events compared to those symptomatic at initial diagnosis.

MATERIALS AND METHODS

Patients

Our cohort included consecutive patients with PBC seen for the first time at the University of Florida (Gainesville, Florida) between January 1, 1997 and December 31, 2005. Cases were identified by ICD code and subsequent chart review from a database of patients with cholestatic liver diseases seen at the Hepatology clinic at the University of Florida. A diagnosis of PBC required either histological confirmation and the presence of chronic cholestasis with or without positive antimitochondrial antibody (AMA) or a positive AMA titer above 1:40 associated with persistent elevation of serum alkaline phosphatase and without significant elevation of transaminases (less than 3 times upper limit of normal), even in the absence of a previous liver biopsy. Mild and advanced histological disease was defined as stage 0-2 and 3-4 respectively based on the Metavir scoring system. As a control group, we studied consecutive patients with chronic hepatitis C referred for HCV treatment at our institution during the same period of time.

The following information was collected for each patient: demographic data, laboratory and liver histology information, body mass index (BMI), smoking habits, history of hypertension, diabetes, coronary artery disease including acute myocardial infarction and angina, transient ischemic attack , ischemic and hemorrhagic stroke, date of liver transplant if performed, clinical presentation at initial diagnosis, medication history, date and cause of death if available. Patients were defined as initially asymptomatic if they did not have any symptoms attributable to PBC at the time of diagnosis, according to their recollection and information from the medical records. Symptoms attributable to PBC include fatigue without identifiable cause, pruritus, jaundice, gastrointestinal bleeding due to esophageal or gastric varices, hepatic encephalopathy, ascites or lower extremities edema.

The Mayo risk score was calculated, when possible, for each PBC patient with variables obtained at the time of initial presentation at the University of Florida. Mayo risk score = 0.871 × loge (bilirubin in mg/dL) + -2.53 × loge (albumin in g/dL) + 0.039 age in years + 2.83 loge (prothrombin time in seconds) + 0.859 edema[8]. Patients were followed as a historical cohort until the date of last visit, date of death or date of liver transplant.

Statistical analysis

Data are presented as means ± SD or median with range for continuous variables and as frequencies for categorical variables. Categorical variables were analyzed by the Chi-Square (c^2) or Fisher's exact test. Continuous variables were analyzed by the student-t test or Mann-Whitney nonparametric test. All reported *P* values were two-sided and a *P* value of less than 0.05 was considered to be statistical significant. All statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of cases and controls

A total of 180 patients with PBC ("cases") and 151 patients with chronic hepatitis C ("controls") were included in the study. Cases were followed for an average of 2.9 ± 2.8 years (range 0-11) and controls for an average of 3.2 ± 2.3 years (range 0-10). Table 1 shows baseline clinical characteristics of cases and controls. The majority of the cases were females and Caucasian was the predominant race in both groups. Compared with controls, cases were older (median age 56.3 years *vs* 49.8 years) and had higher levels of serum total cholesterol (median cholesterol 216 mg/dL *vs* 157.5 mg/dL), low density lipoprotein [(LDL), median LDL 127 mg/dL *vs* 80 mg/dL] and high density lipoprotein [(HDL), median HDL 54 mg/dL *vs* 48 mg/dL], whereas both groups had similar serum triglyceride levels. Despite being small in number, significantly more cases were on statin therapy than controls (Table 1).

As far as risk factors for cardiovascular disease, almost twice as many patients in the control group had smoking habits compared to patients with PBC. However, no difference was observed with respect to rates of hypertension, diabetes, overweight status or obesity. Approximately 7% of controls and 10% of cases developed a cardiovascular disease such as CAD, TIA or stroke. Despite having more significant hyperlipidemia, a well established risk for cardiovascular diseases, cases did not have significantly more cardiovascular events than controls (Table 1 and Figure 1).

Advanced fibrosis defined as a Metavir score = 3 was more common among controls than cases (78.9% *vs* 61.4%, *P* = 0.001, Table 1). Cases with advanced fibrosis had lower

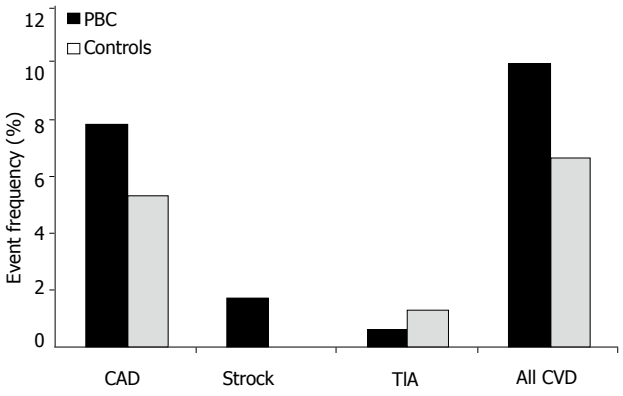

Figure 1 Cardiovascular risk in primary biliary cirrhosis versus controls. PBC: primary biliary cirrhosis; CAD: coronary artery disease; TIA: transient ischemic attack; CVD: cardiovascular disease.

Table 1 Baseline characteristics of patients with primary biliary cirrhosis and controls

Variables	Controls *n* = 151	PBC *n* = 180	*P* value
Age (years)	49.8 (20-72)	56.3 (22-74)	< 0.001
Female gender	65 (43)	165 (91.7)	< 0.001
Caucasian	123 (81.5)	158 (87.8)	0.1
AMA	0 (0)	137 (77.8)	
BMI (kg/m^2)	28 (17-50)	26.8 (17.6-51)	0.09
Hypertension	49 (32.5)	48 (26.8)	0.3
Diabetes	21 (13.9)	26 (14.5)	0.9
Smoking	96 (63.6)	62 (35)	< 0.001
Stage of disease[a]			0.001
0-2	28 (21.1)	64 (38.6)	
3-4	105 (78.9)	102 (61.4)	
Total cholesterol (mg/dL)	157.5 (73-320)	216 (81-2055)	< 0.001
LDL (mg/dL)	80 (20-189)	127 (12–539)	< 0.001
HDL (mg/dL)	48 (20-101)	54 (17-163)	0.001
Triglyceride (mg/dL)	117 (19-2334)	104 (32-736)	0.2
Statin use	2 (1.3)	15 (8.3)	0.004
CAD	8 (5.3)	14 (7.8)	0.4
TIA	2 (1.3)	1 (0.6)	0.6
Stroke	0 (0)	3 (1.7)	0.3
Any CVD	10 (6.6)	18 (10)	0.3

PBC: primary biliary cirrhosis; AMA: antimitochondrial antibody; BMI: body mass index; LDL: low density lipoprotein; HDL: high density lipoprotein; CAD: coronary artery disease; TIA: transient ischemic attack; CVD: cardiovascular disease. Continuous variables are expressed as median (range). Categorical variables are expressed as number (frequency). [a]Based on the Metavir scoring system

serum triglyceride levels compared to cases with mild to moderate fibrosis (Table 2). Otherwise, there was no significant difference of serum total cholesterol, HDL or LDL levels between cases with mild to moderate and cases with advanced fibrosis (Table 2).

Cardiovascular events in cases with asymptomatic and symptomatic disease

Cases were further divided into two subgroups based on the presence or absence of symptoms. Approximately two thirds of cases were symptomatic. Among the 114 symptomatic patients, 73 (64%) had fatigue and 57 (50%) had pruritus. There was a trend toward higher serum cholesterol level in asymptomatic patients ($P = 0.06$) (Table 3). Nevertheless, there was no significant difference in other characteristics, including stage of disease, between the two subgroups (Table 3). Despite a trend toward more of "any cardiovascular disease" in the symptomatic subgroup ($P = 0.06$), there was no significant difference in the frequency of individual cardiovascular events between the two subgroups (Table 3).

When cases were divided into those with and without self reported fatigue, a trend towards higher serum total cholesterol levels was observed in cases without fatigue. This trend was not accompanied by significant differences with respect to cardiovascular risk factors or number of events between the two groups (Table 4).

Table 2 Serum lipid levels in different stages of primary biliary cirrhosis based on the Metavir scoring system

	Stage 0-2	Stage 3-4	*P* value
Total cholesterol (mg/dL)	229.5 (129-2055)	210 (81-612)	0.3
HDL (mg/dL)	56 (20-102)	53 (20-163)	0.4
LDL (mg/dL)	130.5 (52-239)	127 (12-539)	0.9
Triglyceride (mg/dL)	128 (47-736)	98.5 (32-462)	0.008

PBC: primary biliary cirrhosis; HDL: high density lipoprotein; LDL: low density lipoprotein. Data are expressed as median (range).

Table 3 Characteristics of patients with asymptomatic and symptomatic primary biliary cirrhosis

Variables	Asymtomatic *n* = 66	Symptomatic *n* = 114	*P* value
Age (years)	56.7 (31-74)	56.0 (22-73)	0.4
Female gender	58 (87.9)	107 (93.9)	0.2
Caucasian	60 (90.9)	98 (86)	0.3
AMA	50 (78.1)	87 (77.7)	1
BMI	26.2 (19-43)	27 (17.6-51)	0.4
Hypertension	19 (29.2)	29 (25.4)	0.6
Diabetes	12 (18.5)	14 (12.3)	0.3
Smoking	18 (28.6)	44 (38.6)	0.2
Stage of fibrosis[a]			0.6
0-2	21 (35.6)	43 (40.2)	
3-4	38 (64.4)	64 (59.8)	
Total cholesterol (mg/dL)	223.5 (84-2055)	209.5 (81-612)	0.06
LDL (mg/dL)	134 (34-505)	123 (12-539)	0.2
HDL (mg/dL)	57 (17-163)	53 (20-118)	0.5
Triglyceride (mg/dL)	105 (32-527)	104 (32-736)	0.6
Statin use	8 (12.1)	7 (6.1)	0.2
CAD	3 (4.5)	11 (9.6)	0.22
TIA	0	1 (0.9)	1
Stroke	0 (0)	3 (2.6)	0.3
Any CVD	3 (4.5)	15 (13.2)	0.06

PBC: primary biliary cirrhosis; AMA: antimitochondrial antibody; BMI: body mass index; LDL: low density lipoprotein; HDL: high density lipoprotein; CAD: coronary artery disease; TIA: transient ischemic attack; CVD: cardiovascular disease. Continuous variables are expressed as median (range). Categorical variables are expressed as number (frequency). [a]Based on the Metavir scoring system

DISCUSSION

Our study suggests that hyperlipidemia in patients with

Table 4 Characteristics of cases with and without fatigue

	With fatigue *n* = 74	Without fatigue *n* = 104	*P* value
Age (years)	54.3 (22-73)	57.1 (31-74)	0.4
Female gender	71 (95.9)	92 (88.5)	0.08
Caucasian	63 (85.1)	93 (89.4)	0.4
AMA	57 (77)	79 (78.2)	0.9
BMI (kg/m^2)	27 (17.6-39.2)	26.2 (17.6-51)	0.4
Hypertension	18 (24.3)	29 (28.2)	0.6
Diabetes	10 (13.5)	15 (14.6)	0.8
Smoking	26 (35.1)	36 (35.6)	0.9
Stage of fibrosis[a]			0.7
0-2	26 (37.1)	38 (40.4)	
3-4	44 (62.9)	56 (59.6)	
Total cholesterol (mg/dL)	203 (83-612)	217 (81-2055)	0.06
LDL (mg/dL)	123.5 (29-539)	131 (12-505)	0.2
HDL (mg/dL)	55 (20-118)	54 (17-163)	0.5
Triglyceride (mg/dL)	110 (32-462)	104 (32-736)	0.6
Statin use	6 (8.1)	9 (8.7)	0.9
CAD	7 (9.5)	7 (6.7)	0.5
TIA	1 (1.4)	0 (0)	0.4
Stroke	2 (2.7)	0 (0)	0.2
Any CVD	10 (13.5)	7 (6.7)	0.1

AMA: antimitochondrial antibody; BMI: body mass index; LDL: low density lipoprotein; HDL: high density lipoprotein; CAD: coronary artery disease; TIA: transient ischemic attack; CVD: cardiovascular disease. Continuous variables are expressed as median (range). Categorical variables are expressed as number (frequency). [a]Based on the Metavir scoring system

PBC is not associated with higher risk for atherosclerotic events when compared to a control group consisting of patients with non-cholestatic liver disease. PBC patients had higher total cholesterol, LDL and HDL with similar incidence of cardiovascular and cerebrovascular events. Furthermore, we found no difference in the rate of cardiovascular events between symptomatic and asymptomatic patients and no difference in cardiac events in patient with fatigue.

Reports on the effect of hyperlipidemia associated with PBC on the risk of cardiovascular mortality in this population are conflicting. In a study by Crippin *et al*, 312 patients with PBC were followed prospectively for a median of 7.4 years and the risk of death related to atherosclerotic disease was not increased in patients with hyperlipidemia[9]. Alloca *et al* assessed intima-media thickness (IMT) with carotid artery ultrasound as a surrogate marker for subclinical atherosclerosis[7]. In this study, the control population consisted of a combination of healthy individuals and patients with hepatitis C. The investigators demonstrated increased IMT values in controls with hyperlipidemia but not in patients with PBC and corresponding serum levels of total cholesterol. Our findings are in agreement with these studies.

We also evaluated confounding risk factors for cardiovascular disease in both PBC patients and controls: although there were more smokers in the controls and a female predominance in the PBC group, hypertension, diabetes and obesity occurred with similar frequency. Interestingly, the lower smoking rate in PBC is in contrast with case control studies which have found excess smoking in patients with PBC [10-12]. This finding is likely to be related to the fact that our controls consisted of patients with HCV instead of the general population.

All PBC patients in our study were on ursodeoxycholic acid (UDCA), the current mainstay of therapy. UDCA is known to have cholesterol-lowering effect due to improvement of cholestasis and modifications of cholesterol metabolism. Both effects are most likely due to changes in endogenous bile acid composition[13]. However, data is lacking regarding the effect of UDCA on the development and progression of cardiovascular disease (CVD). In addition, 8.3 % of patients in the PBC group had received or were receiving statins at the time of diagnosis compared to only 1.3 % of the control group. A recent study by Stojakovic and colleagues demonstrated a possible beneficial effect of low dose atorvastatin in patients with additional risk factors for CVD and early stage of disease[14]. They followed 19 patients treated with 10 mg of atorvastatin for one year and observed reduced cholesterol levels and endothelial inflammation, as well as improved vascular function as reflected by flow-mediated dilation of the brachial artery. Importantly, atorvastatin was safe in that population. Nevertheless, a reduction in risk of cardiovascular events and mortality in patients with PBC and hyperlipidemia treated with statins has not been demonstrated yet; therefore the small number of events in the present study cannot be attributed to the use of statins by a minority of subjects.

One third of PBC patients in our study were asymptomatic at the time of diagnosis and there was no increased mortality from CAD in this population. We found that asymptomatic patients have slightly higher cholesterol levels in comparison with symptomatic ones. Prince *et al* reached a similar conclusion with respect to cholesterol levels[15]. However, that study also found a significant increase in ischemic heart disease among asymptomatic patients (14.9%) in comparison to symptomatic patients (5.9%) with PBC. Although it is possible that these differences are due to the smaller population size in the present study, the finding of increased cardiovascular deaths in asymptomatic PBC patients has not been validated by other studies[16].

Among the symptomatic patients, 64% had fatigue as one of the presenting symptoms. The patients with fatigue had a similar lipid profile and rate of atherosclerotic events in comparison to those without fatigue. These results are in agreement with the findings from Bjornsson *et al* who followed 208 patients with PBC and found that fatigue was a predictor of liver-related mortality and need for transplantation but not of non-liver-related mortality[17]. Only the older patients had an increase in cardiovascular complications. In contrast, Jones *et al* found that patients with severe fatigue have a higher rate of cardiac deaths than liver-related mortality in a four year follow up[18]. In subsequent studies, the authors hypothesized that this increased mortality due to cardiovascular events was related to autonomic dysfunction in patients with

PBC[19]. Further studies investigating the role of fatigue as a predictor for CVD are needed.

Our study is limited by its retrospective nature and small number of events. Also, our control group consisted of hepatitis C patients and a very recent study showed that HCV infection is associated with lower lipid levels[20], but this information was not available at the time of initiation of the study. In addition, there are more males in the control group compared to the cases. One could initially consider that with more males there is an increased risk of cardiovascular events and that is the reason why no difference was seen in comparison to cases. However, it is important to notice that cases were older and most were post-menopausal, thus with a risk of cardiovascular events similar to that encountered in males.

Despite these limitations, we found that hyperlipidemia associated with PBC does not seem to be associated with an increased risk for atherosclerotic events. Thus, the need for treatment should be assessed on an individual basis and take into account the presence of additional known risk factors. Furthermore, our study did not show an increased risk for CVD among asymptomatic patients or those with fatigue. Further investigation involving a larger patient population followed for a longer period of time is warranted to confirm these findings, perhaps including multiple centers.

COMMENTS

Background

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease associated with hyperlipidemia. In comparison to the general population, hyperlipidemia in PBC is not clearly associated with increased risk for cardiovascular disease. Approximately 50% of patients are asymptomatic at diagnosis; fatigue is the most common symptom in early stage.

Research frontiers

Previous studies have shown that patients with asymptomatic PBC and those presenting with fatigue only may have increased cardiovascular mortality.

Innovations and breakthroughs

This study did not find a difference in the frequency of cardiovascular events between symptomatic and asymptomatic patients with PBC. In addition, patients with fatigue were not at an increased risk of cardiovascular events compared to PBC patients without fatigue.

Applications

The need for treatment of hyperlipidemia in PBC patients should be assessed on individual basis and according to the presence of additional known risk factors.

Terminology

Cardiovascular events included coronary artery disease presenting with myocardial infarction or angina, transient ischemic attack and stroke.

Peer review

This is an important research question and is very relevant. The disease primary biliary cirrhosis is rare in many parts of the world and the research is novel. The paper reads well and adds to the current body of literature.

REFERENCES

1 **Talwalkar JA,** Lindor KD. Primary biliary cirrhosis. *Lancet* 2003; **362**: 53-61

2 **Longo M,** Crosignani A, Battezzati PM, Squarcia Giussani C, Invernizzi P, Zuin M, Podda M. Hyperlipidaemic state and cardiovascular risk in primary biliary cirrhosis. *Gut* 2002; **51**: 265-269

3 **Chang PY,** Lu SC, Su TC, Chou SF, Huang WH, Morrisett JD, Chen CH, Liau CS, Lee YT. Lipoprotein-X reduces LDL atherogenicity in primary biliary cirrhosis by preventing LDL oxidation. *J Lipid Res* 2004; **45**: 2116-2122

4 **Gylling H,** Farkkila M, Vuoristo M, Miettinen TA. Metabolism of cholesterol and low- and high-density lipoproteins in primary biliary cirrhosis: cholesterol absorption and synthesis related to lipoprotein levels and their kinetics. *Hepatology* 1995; **21**: 89-95

5 **Jahn CE,** Schaefer EJ, Taam LA, Hoofnagle JH, Lindgren FT, Albers JJ, Jones EA, Brewer HB Jr. Lipoprotein abnormalities in primary biliary cirrhosis. Association with hepatic lipase inhibition as well as altered cholesterol esterification. *Gastroenterology* 1985; **89**: 1266-1278

6 **Pekkanen J,** Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, Tyroler HA. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med* 1990; **322**: 1700-1707

7 **Allocca M,** Crosignani A, Gritti A, Ghilardi G, Gobatti D, Caruso D, Zuin M, Podda M, Battezzati PM. Hypercholesterolaemia is not associated with early atherosclerotic lesions in primary biliary cirrhosis. *Gut* 2006; **55**: 1795-1800

8 **Angulo P,** Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Kamath PS, Dickson ER. Utilization of the Mayo risk score in patients with primary biliary cirrhosis receiving ursodeoxycholic acid. *Liver* 1999; **19**: 115-121

9 **Crippin JS,** Lindor KD, Jorgensen R, Kottke BA, Harrison JM, Murtaugh PA, Dickson ER. Hypercholesterolemia and atherosclerosis in primary biliary cirrhosis: what is the risk? *Hepatology* 1992; **15**: 858-862

10 **Gershwin ME,** Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, Lindor KD, Kaplan MM, Vierling JM. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. *Hepatology* 2005; **42**: 1194-1202

11 **Howel D,** Fischbacher CM, Bhopal RS, Gray J, Metcalf JV, James OF. An exploratory population-based case-control study of primary biliary cirrhosis. *Hepatology* 2000; **31**: 1055-1060

12 **Prince MI,** Ducker SJ, James OF. Case-control studies of risk factors for primary biliary cirrhosis in two United Kingdom populations. *Gut* 2010; **59**: 508-512

13 **Balan V,** Dickson ER, Jorgensen RA, Lindor KD. Effect of ursodeoxycholic acid on serum lipids of patients with primary biliary cirrhosis. *Mayo Clin Proc* 1994; **69**: 923-929

14 **Stojakovic T,** Claudel T, Putz-Bankuti C, Fauler G, Scharnagl H, Wagner M, Sourij H, Stauber RE, Winkler K, Marz W, Wascher TC, Trauner M. Low-dose atorvastatin improves dyslipidemia and vascular function in patients with primary biliary cirrhosis after one year of treatment. *Atherosclerosis* 2010; **209**: 178-183

15 **Prince MI,** Chetwynd A, Craig WL, Metcalf JV, James OF. Asymptomatic primary biliary cirrhosis: clinical features, prognosis, and symptom progression in a large population based cohort. *Gut* 2004; **53**: 865-870

16 **Van Dam GM,** Gips CH. Primary biliary cirrhosis in The Netherlands. An analysis of associated diseases, cardiovascular risk, and malignancies on the basis of mortality figures. *Scand J Gastroenterol* 1997; **32**: 77-83

17 **Bjornsson E,** Kalaitzakis E, Neuhauser M, Enders F, Maetzel H, Chapman RW, Talwalkar J, Lindor K, Jorgensen R. Fatigue measurements in patients with primary biliary cirrhosis and the risk of mortality during follow-up. *Liver Int* 2010; **30**: 251-258

18 **Jones DE,** Bhala N, Burt J, Goldblatt J, Prince M, Newton JL. Four year follow up of fatigue in a geographically defined primary biliary cirrhosis patient cohort. *Gut* 2006; **55**: 536-541

19 **Newton JL,** Hudson M, Tachtatzis P, Sutcliffe K, Pairman J, Burt JA, Jones DE. Population prevalence and symptom

associations of autonomic dysfunction in primary biliary cirrhosis. *Hepatology* 2007; **45**: 1496-1505
20 **Corey KE,** Kane E, Munroe C, Barlow LL, Zheng H, Chung RT. Hepatitis C virus infection and its clearance alter circulating lipids: implications for long-term follow-up. *Hepatology* 2009; **50**: 1030-1037

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Online Submissions: http://www.wjgnet.com/1948-5182office
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World J Hepatol 2011 April 27; 3(4): I
ISSN 1948-5182 (online)

Acknowledgments to reviewers of *World Journal of Hepatology*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Hepatology*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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www.wjgnet.com

World J Hepatol 2011 April 27; 3(4): I
ISSN 1948-5182 (online)

Events Calendar 2011

January 14-15, 2011
AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011
Miami, FL 33101, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011
San Francisco, CA 94143, United States

January 27-28, 2011
Falk Workshop, Liver and Immunology, Medical University, Franz-Josef-Strauss-Allee 11
Regensburg 93053, Germany

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 17-20, 2011
APASL 2011-The 21st Conference of the Asian Pacific Association for the Study of the Liver
Bangkok, Thailand

February 22, 2011-March 04, 2011
Canadian Digestive Diseases Week 2011
Vancouver, BC, Canada

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation
Dublin, Ireland

March 3-5, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL 32614, United States

March 7-11, 2011
Infectious Diseases: Adult Issues in the Outpatient and Inpatient Settings
Sarasota, FL 34234, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011
Birmingham, England, United Kingdom

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology 2011
Jacksonville, FL 34234, United States

March 18, 2011
UC Davis Health Informatics: Change Management and Health Informatics, The Keys to Health Reform
Sacramento, CA 94143, United States

March 25-27, 2011
MedicReS IC 2011
Good Medical Research, Istanbul, Turkey

March 26-27, 2011
26th Annual New Treatments in Chronic Liver Disease
San Diego, CA 94143, United States

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

May 7-10, 2011
Digestive Disease Week
Chicago, IL 60446, United States

May 19-22, 2011
1st World Congress on Controversies in the Management of Viral Hepatitis (C-Hep), Palau de Congressos de Catalunya, Av. Diagonal, 661-671
Barcelona 08028, Spain

May 21-24, 2011
22nd European Society of Gastrointestinal and Abdominal Radiology Annual Meeting and Postgraduate Course
Venise, Italy

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn,
Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV
SPIGC, II ESYS
Napoli, Italy

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
Barcelona, Spain

October 19-29, 2011
Cardiology & Gastroenterology Tahiti 10 night CME Cruise
Papeete, French Polynesia

October 22-26, 2011
19th United European Gastroenterology Week
Stockholm, Sweden

October 28-November 2, 2011
ACG Annual Scientific Meeting & Postgraduate Course
Washington, DC 20001, United States

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World J Hepatol 2011 April 27; 3(4): I-V
ISSN 1948-5182 (online)

INSTRUCTIONS TO AUTHORS

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Name of journal

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

Indexed and Abstracted in

PubMed Central, PubMed, Digital Object Identifer, and Directory of Open Access Journals.

Published by

Baishideng Publishing Group Co., Limited

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Supportive foundations: The complete name and number of supportive foundations should be provided, e.g., Supported by National Natural Science Foundation of China, No. 30224801

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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

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Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

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Conference paper

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Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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