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ORIGINAL ARTICLE

Antimicrobial prophylaxis in liver transplant patients – a multicenter survey endorsed by the European Liver and Intestine Transplant Association

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Summary

Perioperative infections remain an important problem for patients undergoing liver transplantation (LT). For prevention of these infections, perioperative prophylaxis has become the standard procedure. Yet, either guidelines or data on current practice are lacking. The aim of the study was to gain insight into prophylactic antimicrobial strategies used in Europe. A survey questionnaire was sent out to all LT centers that are member of the European Liver and Intestine Transplant Association. In the survey questionnaire, we asked for details on the prophylactic antimicrobial regimen used in LT recipients. The response rate was 48%. Antibiotic prophylaxis for elective LT was provided by a first-line betalactam antibiotic or co-trimoxazole in 25%. Seventy-three per cent of those centers surveyed gave an extended spectrum, and one center used a 6-month rotation strategy. Antifungal prophylaxis was administered in 35% of centers in all LT recipients, in 53% of centers in patients at risk, and in 12% of centers not at all. Cytomegalovirus prophylaxis was never administered in 10%. In 12% of the centers surveyed, all the patients received cytomegalovirus prophylaxis, and another 78% of the centers gave it only to risk groups. In Europe, there is a considerable variation in the different antibiotic, antifungal and cytomegalovirus prophylactic strategies used for LT. These findings underscore the need for randomized controlled trials to determine the optimal prophylactic antimicrobial regimen.

Introduction

In 2007, over 1700 patients received a liver transplantation in the Eurotransplant region (http://www.eurotransplant.nl/files/annual_report/AR2007_def.pdf).

This procedure is increasingly successful, with a 1-year survival rate of over 80% [1]. Prevention of infections is an important issue in the care of liver transplant recipients. Liver transplant recipients are especially vulnerable for developing infection in the perioperative period as a consequence of different factors leading to immune suppression, e.g. liver cirrhosis, malnutrition, prolonged duration of surgery, red blood cell transfusion, and immune suppression therapy. The incidence of infection after liver transplantation ranges from 53% to 79%, with most infections occurring in the first month after transplantation [2]. Infections can be categorized into donor-related, recipient-related, community-acquired and

nosocomial. The etiology is mostly bacterial, sometimes fungal, and viral [3].

The prevention of these infections is an important issue in the care of liver transplant recipients. However, data regarding current practices of perioperative prophylaxis for these infections in Europe are lacking. Therefore, we embarked on a survey and devised a survey questionnaire to get insight into the strategies that are used in European liver transplant centers to prevent perioperative infections.

Materials and methods

The study was performed using an electronic and postal survey questionnaire sent out to all European Liver transplant centers that are members of the European Liver and Intestine Transplant Association (ELITA). From ELITA, we received the list of e-mail and postal addresses of the staff members of the participating centers. We sent the survey questionnaire electronically on July 24th 2007. A previously planned first reminder was sent electronically on August 24th 2007, and a second on September 24th 2007. On October 14th 2007, the survey questionnaire was sent by regular mail to the nonresponding centers.

In the survey questionnaire, we asked for details on (i) the prophylactic antibiotic regimen used for liver transplant recipients undergoing liver transplantation in the following categories: elective liver transplantation, liver transplantation for acute-on-chronic disease, and liver transplantation for acute liver failure, (ii) the prophylactic antifungal, (iii) the anti-cytomegalovirus (CMV) regimen, (iv) the use of other prophylactic measures [isolation post liver transplantation, selective digestive tract decontamination (SDD), mupirocin nasal ointment and chlorhexidine body washes for methicillin-resistant *Staphylococcus aureus* (MRSA) skin decontamination], and (v) the use of microbiological surveillance by culture sampling.

Statistical analysis

Upon receipt of the survey questionnaires, the data were anonymously recorded and analysed in an electronic database. Data were reported as numbers and proportions of submitted answers. Not all questionnaires were filled in completely; therefore, the denominator may vary between different items. The total number of responses for each individual question was reported per item. Duration of antimicrobial therapy was reported as median (25th and 75th quartile). Difference between proportions was evaluated by the chi-squared test and a P-value <0.05 was regarded as statistically significant. We used the statistical software package MedCalc for Windows, version 10.1.2.0 (MedCalc Software, Mariakerke, Belgium).

Results

Of the 128 centers, 61 centers (48%) from 16 different countries returned the survey questionnaires (Fig. 1). Two centers did fill out the survey questionnaire incompletely, and two centers gave more than one answer to the question on antibiotic prophylaxis used. Thirty-eight centers (62%) sent their responses by e-mail, 11 (18%) by post, and 12 (20%) by fax. Figure 2 shows the number of liver transplantations performed annually by the participating centers (Fig. 2).

Antibiotic prophylaxis

Elective liver transplantation

Sixty centers (98% of the responding centers) answered this question. Antibiotic prophylaxis for recipients with elective liver transplantation was a first-line betalactam antibiotic (first generation cephalosporin, second generation cephalosporin, aminopenicillin plus betalactamase inhibitor, or carboxypenicillin plus betalactamase inhibitor)

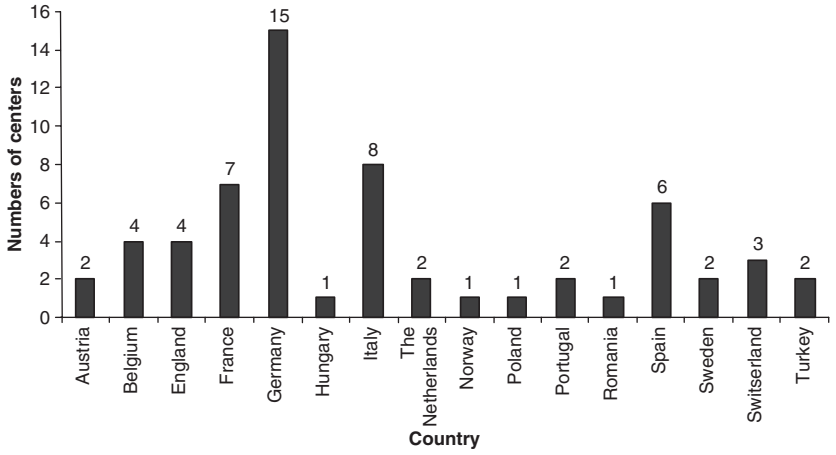

Figure 1 Distribution of the participating centers according to the country of origin.

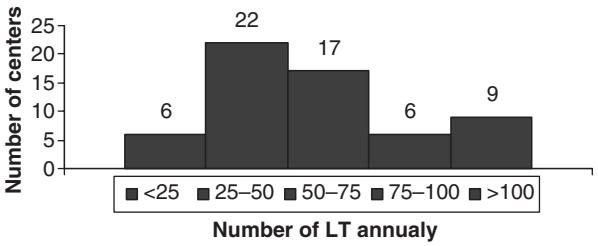

Figure 2 Number of liver transplantations performed annually (n = 60 centers).

or co-trimoxazole in 15 centers (25%). Forty-four centers (73%) gave an extended spectrum antibiotic regimen (third or fourth generation cephalosporin, glycopeptide, carbapenem or antipseudomonas antibiotic). In one center (2%), the antibiotic prophylactic regimen was switched every 6 months between two different types of broad-spectrum antibiotic prophylaxis (Table 1).

Six centers (10%) administered an antibiotic prophylactic regimen that included also methicillin-resistant Gram-positive pathogens, 39 centers (65%) targeted anaerobes (in three centers there was also an alternative antimicrobial regimen in which anaerobes were not included) and 22 centers (37%) targeted pseudomonas and other nonfermenters (in two centers, the alternative antimicrobial regimen did not cover pseudomonas and other nonfermenters).

One center (2%) gave additional metronidazole to the prophylaxis with a third generation cephalosporin and aminopenicillin in case of hepaticojejunostomy.

Fifty-nine centers (97% of the responding centers) answered the question on duration of antibiotic prophylaxis in elective liver transplantation. The median duration of antibiotic prophylaxis was 3 days (interquartile range: 2–3.75). However, the duration differed considerably among the centers. Almost half of the centers gave

Table 1. AB prophylaxis in elective liver transplantation.

Antibiotic 1	Antibiotic 2	Antibiotic 3	No. of centers	%
Prophylaxis with a first-line betalactam antibiotic or co-trimoxazole				
First gen cephalosporin			1	6.67
Second gen cephalosporin			4	26.7
Second gen cephalosporin	Metronidazole		2	13.3
Second gen cephalosporin	Aminopenicillin+ β-lactamase inhibitor		1	6.67
Aminopenicillin+ β-lactamase inhibitor			5	33.3
Carboxypenicillin+ β-lactamase inhibitor			1	6.67
Co-trimoxazole			1	6.67
			15	100
Extended spectrum AB prophylaxis				
Third gen cephalosporin			2	4.55
Third gen cephalosporin	Metronidazole		5	11.4
Third gen cephalosporin	Aminopenicillin		6	13.6
Third gen cephalosporin	Aminopenicillin+ β-B lactamase inhibitor		2	4.55
Third gen cephalosporin (glazidim)	Aminopenicillin+ β-lactamase inhibitor		1	2.27
Third gen cephalosporin	Glycopeptide		1	2.27
Third gen cephalosporin	Glycopeptide	Ofloxacin	1	2.27
Third gen cephalosporin	Aminopenicillin+ β-lactamase inhibitor	Fucidine acid	1	2.27
Piperacillin+/– β-lactamase inhibitor			10	22.7
Piperacillin+ β-lactamase inhibitor	Carbapenem		1	2.27
Piperacillin+ β-lactamase inhibitor	Ciprofloxacin		1	2.27
Aminopenicillin+ β-lactamase inhibitor	Ciprofloxacin		2	4.55
Monobactam	Glycopeptide		1	2.27
Aminoglycoside	Oxacillin		1	2.27
Aminoglycoside	Glycopeptide	Metronidazole	1	2.27
Carboxypenicillin	Oxacillin		1	2.27
Carboxypenicillin	Glycopeptide		1	2.27
Carbapenem			3	6.82
Cephalosporin	Penicillin		1	2.27
Third gen cephalosporin OR	Aminopenicillin+ β-lactamase inhibitor		1	2.27
Third gen cephalosporin OR	Piperacillin+ β-lactamase inhibitor		1	2.27
			44	100
Six-monthly switch of antibiotic prophylaxis				
Third gen cephalosporin+aminopenicillin	Piperacillin+ β-lactamase inhibitor		1	

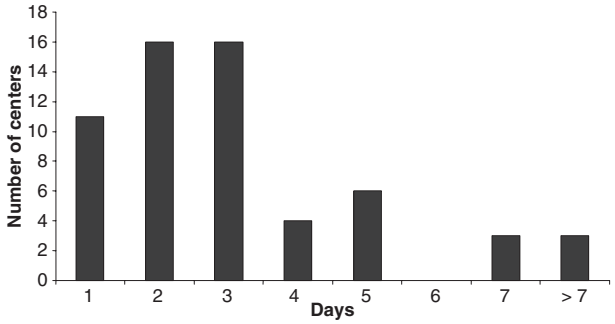

Figure 3 Days of antibiotic prophylaxis in different centers.

prophylaxis for maximal 2 days, while three others administered prophylaxis for 7 days or more (Fig. 3).

There was no difference in the use of first-line or broad-spectrum antibiotic prophylaxis between centers with a high volume of liver transplant procedures, and those with an intermediate or low volume (Table 2).

Liver transplantation for acute-on-chronic liver disease

Fifty-nine centers (97% of the responding centers) answered this question. For recipients with acute-on-chronic liver failure, 44 centers (75%) administered the same prophylactic antibiotic regimen as for elective liver transplantation, while 15 centers (25%) changed it. Of the centers that changed the antibiotic regimen, three increased the duration of treatment with the same antibiotic regimen, while 12 changed the type of antibiotic regimen. Of the centers that changed the type of antibiotic regimen, five centers changed from a first-line betalactam antibiotic to an extended spectrum antibiotic regimen.

As compared with the prophylaxis used in elective liver transplantation, two extra centers administered a prophylactic regimen that covers methicillin-resistant Gram-positive pathogens, three extra centers cover anaerobes (in one center there was also an alternative antimicrobial regimen in which anaerobes were not included), and seven extra centers cover pseudomonas and other nonfermenters. This makes a total of eight centers (14%) covering for methicillin-resistant Gram-positive pathogens, 42 centers (71%) for anaerobes, and 29 centers (49%) for pseudomonas and other nonfermenters, in case of liver transplantation for acute-on-chronic liver failure.

Table 2. Antibiotic regimen for elective liver transplantation dependent of the number of liver transplantations performed annually.

No. of LT	No. of centers	First-line AB	Extended spectrum AB
<50	28	5 (18%)	23 (82%)
50–75	17	4 (24%)	13 (76%)
>75	15	6 (40%)	9 (60%)
Total	60	15 (25%)	45 (75%)

$\chi^2 = 2.582$, df = 2, $P = 0.275$.

Liver transplantation for acute liver failure

Fifty-nine centers (97% of the responding centers) answered this question. For recipients with acute liver failure, 39 centers (66%) used the same antibiotic regimen as for elective liver transplantation, while 20 centers (34%) changed the regimen. Of the centers that changed the antibiotic regimen, six prolonged the duration of the same antibiotic regimen, while 14 changed the type of antibiotic regimen. Of the centers that changed the type of antibiotic regimen, six centers changed from a first-line betalactam antibiotic to an extended spectrum antibiotic regimen.

With regard to the spectrum of the administered agents, six extra centers administered a prophylactic regimen that target methicillin-resistant Gram-positive pathogens, four extra centers target anaerobes (in one center there was also an alternative antimicrobial regimen in which anaerobes were not included) and six extra centers target pseudomonas and other nonfermenters, as compared with the prophylaxis used in elective liver transplantation. In case of liver transplantation for acute liver failure, a total of 12 centers (20%) covered for methicillin-resistant Gram-positive pathogens, 43 centers (73%) for anaerobes and 28 centers (47%) for pseudomonas and other nonfermenters.

Antifungal prophylaxis

Sixty centers (98% of the responding centers) answered this question. Antifungal prophylaxis was administered routinely by 21 of the centers (35%) in all liver transplant recipients, and by 32 of the centers (53%) only in patients at risk for developing fungal infection. The remaining seven centers (12%) never administered antifungal prophylaxis (Table 3).

In the centers who gave antifungal prophylaxis to all liver transplant recipients, fluconazole was administered most frequently (15 centers, 71.4%), followed by amphotericin B (two centers, 9.5%), lipid-associated amphotericin B (one center, 4.8%), itraconazole (one center, 4.8%), and nystatin (one center, 4.8%). One center (4.8%) did not specify the prophylactic regimen. From these 21 centers, nine centers (43%) switched to another antifungal agent in case of a liver transplant recipient with a risk factor. These were all centers where fluconazole or nystatin was the first-line prophylaxis.

In centers that administered antifungal prophylaxis in risk groups, the risk groups most mentioned were

Table 3. Antifungal prophylaxis according to risk profile.

Risk factor	No. of centers	Antifungal agent	No. of centers	%
No risk factors present		No prophylaxis	39	65
		Fluconazole	15	25
		Itraconazole	1	1.7
		Amphotericin B	2	3.3
		Lipid formulation of Amphotericin B	1	1.7
		Nystatin	1	1.7
		Not known	1	1.7
Any risk factor present	7	No prophylaxis	7	12
	53	Fluconazole	30	50
		Caspofungin	3	5
		Fluconazole OR Itraconazole	2	3.3
		Amphotericin B	5	8.3
		Lipid formulation of Amphotericin B	8	13.3
		Voriconazole	1	1.7
		Not known	2	3.3
		Amphotericin B OR Caspofungin	1	1.7
		Fluconazole OR Voriconazole OR Caspofungin	1	1.7
Re-operation (redo or revision)	22	Fluconazole	12	54.5
		Caspofungin	2	9.1
		Amphotericin B	2	9.1
		Lipid formulation of Amphotericin B	3	13.6
		Voriconazole	1	4.5
		Not known	1	4.5
		Fluconazole OR caspofungin	1	4.5
Primary graft dysfunction	17	Fluconazole	11	64.7
		Caspofungin	1	5.9
		Lipid formulation of Amphotericin B	2	11.7
		Fluconazole OR itraconazole	1	5.9
		Not known	1	5.9
		Itraconazole	1	5.9
Large volume transfusion	15	Fluconazole	10	66.6
		Caspofungin	1	6.7
		Lipid formulation of Amphotericin B	1	6.7
		Fluconazole or voriconazole	1	6.7
		Not known	2	13.3
Fulminant liver failure	10	Fluconazole	7	70
		Amphotercin B	1	10
		Amphotercin B OR caspofungin	1	10
		Not known	1	10
Anti rejection therapy	7	Fluconazole	7	100
Positive culture for fungi	4	Fluconazole	2	50
		Not known	1	25
		Caspofungin	1	25
AB >5 days	4	Fluconazole	4	100
Renal failure/dialysis	3	Lipid formulation of Amphotericin B	1	33.3
		Amphotercin B	1	33.3
		Caspofungin	1	33.3

primary graft dysfunction, large volume transfusion, anti-rejection therapy, re-operation, acute liver failure, renal failure, positive cultures for fungi and prolonged antibiotic treatment. In these risk groups, fluconazole was used mostly (Table 3), and the majority of these centers did not administer prophylaxis when no risk factors were present (22 centers, 73%).

CMV prophylaxis

Fifty-nine centers (97% of responding centers) answered this question. Routine CMV prophylaxis was never administered in six centers (10%), but most of these centers (four centers, 67%) started pre-emptive therapy when CMV polymerase chain reaction (PCR) or antigen

detection was positive. In seven centers (12%), all patients received CMV prophylaxis, and the remaining 46 centers (78%) only gave CMV prophylaxis to risk groups. Risk groups that were mentioned were donor CMV+ /recipient CMV- liver transplant recipients (46 centers, 100%), donor CMV+/recipient CMV+ liver transplant recipients (six centers, 13%), primary graft dysfunction (three centers, 7%), large volume transfusion (three centers, 7%), anti-rejection therapy (10 centers, 22%), re-operation (five centers, 11%), and acute liver failure (one center, 2%) (Table 4).

Other prophylactic measures

Sixty centers (98% of responding centers) answered this question. Twenty-four centers (40%) isolated the patients post liver transplantation, and 22 centers (37%) administered SDD. Twenty-eight centers (47%) applied mupirocin nasal ointment (six centers (10%) always, and 22 centers (37%) only in case of nasal carriage of *Staphylococcus aureus*). Thirty-one centers (52%) did chlorhexidine body washes [12 centers (20%) always and 19 centers (32%) only in case of MRSA skin contamination] (Table 5).

Table 4. CMV prophylaxis in risk groups.

Risk group	No. of centers	%
CMV+donor/CMV−recipient	46	100
CMV+donor/CMV+recipient	6	13.04
Primary graft dysfunction	3	6.52
Large volume transfusion	3	6.52
Anti rejection therapy	10	21.74
Re-operation	5	10.87
Fulminant liver failure	1	2.17

Table 5. Other prophylactic measures.

Other prophylactic measures	No. of centers	%
Isolation post LT		
Yes	24	40
Never	36	60
		100
SDD		
Yes	22	36.7
Never	37	61.7
No answer	1	1.67
		100
Mupirocin nasal ointment		
Yes, always	6	10
Yes, only nasal carriage of *Staphylococcus aureus*	22	36.7
Never	32	53.3
		100
Chlorhexidine body washes for MRSA skin decontamination		
Yes, always	12	20
Yes, only MRSA skin contamination	19	31.7
Never	29	48.3
		100

Table 6. Culture sampling.

Culture sampling	No. of centers	%
Blood	45	75
Throat	38	63.3
Perineum	21	35
Nose	37	61.7
Urine	53	88.3
Sputum and endotracheal aspirates	43	71.7
Stool	18	30
Abdominal drain fluid (when available)	46	76.7
Chest drain fluid (when available)	40	66.7
T tube bile	5	
All line when removed	1	
Vaginal secretion	1	
Drainage tips, wounds, eyes	1	
Preservation fluid	1	

Microbial surveillance culturing

Sixty centers (98% of responding centers) answered this question. Microbial surveillance culturing was performed in 57 centers (95%), with 5.6 as a mean number of body sites. Forty-five centers (75%) sampled blood, 38 (63%) throat, 21 (35%) perineum, 37 (62%) nose, 53 (88%) urine, 43 (72%) sputum or endotracheal aspirate, 18 (30%) stool, 46 (77%) abdominal fluid, and 40 (67%) chest drain fluid (Table 6).

Discussion

This study shows that there is a considerable variation in the antibiotic, antifungal and CMV prophylactic strategies used for patients undergoing liver transplantation in Europe.

As a consequence of the immune-depressed status, the liver transplant recipient is at particular risk for developing infectious complications in the perioperative period. Bacterial infections remain the most frequent infectious complication following liver transplantation [3,4]. Most bacterial infections in the first month after liver transplantation are catheter-related blood-stream infections, nosocomial infections of the surgical site, lungs, or urinary tract, or *Clostridium difficile* colitis[3,4]. The incidence of bacteremia is ranging from 25% to 35% [5]. Over the years, there is a shift in the predominant type of pathogens. In the 1980s, the vast majority of bacteremia was caused by Gram-negative bacteria. The source of

bacteremia was mostly intra-abdominal or biliary. In the mid-1990s, Gram-positive bacteria, *Staphylococcus aureus* and, especially in the United States, vancomycin-resistant *Enterococcus faecium*, were the major pathogens [5–8]. Around the millennium, the proportion of bacteremia caused by Gram-positive bacteria decreased from 75% to 48% and the same caused by Gram-negative bacteria increased from 25% to 52% in a liver transplant center in the United States. The predominant pathogens were MRSA, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [5].

Although MRSA is still an important pathogen, this study showed that, in elective liver transplantation, only a tenth of the centers gave an antibiotic prophylactic regimen that targets methicillin-resistant Gram-positive pathogens. When other prophylactic measures were applied (mupirocin nasal ointment or chlorhexidine body washes), the centers administered less prophylaxis that targets methicillin-resistant Gram-positive pathogens. Only 4% and 3% respectively, when applying mupirocin nasal ointment and chlorhexidine body washes.

For preventing infections with pathogens from the bowel, SDD still is a controversial approach. A recent meta-analysis showed that, although there was no reduction in overall incidence of infections, SDD significantly reduced bacterial infection caused by Gram-negative germs [2]. We found that a third of the centers administered SDD to liver transplant recipients. The centers that used SDD, administered less frequently an antibiotic prophylactic regimen that targets pseudomonas and other nonfermenters as compared with all centers.

Our data show that there is an important variation, both in the spectrum of antibiotic(s) used, as well as in the duration of prophylaxis. As there is variation in resistance pattern for antimicrobials, it will never be possible to extrapolate the results of randomized trials, even multi-center, to all European countries. Therefore, antimicrobial regimens used for prophylaxis should be based upon the local susceptibility patterns. However, the duration of antimicrobial prophylaxis should be explored in a multicentered randomized trial. In such a trial, each center can give the spectrum of antibiotic(s) of choice, but the duration of prophylaxis is randomized. In the meantime, an institution-specific regimen, based on institutional resistance patterns, colonization pattern of the patient, and previous antibiotic exposure (such as prophylaxis for spontaneous bacterial peritonitis in patients with hepatic failure) should be used.

Fungal infections in the early post liver transplantation period are mostly caused by *Candida* species or *Aspergillus* species.

Invasive candidiasis is responsible for 62–91% of all invasive fungal infections in liver transplant recipients, with an associated mortality ranging from 11 % to 81% [9,10]. Risk factors for invasive candidiasis include pretransplantation fulminant hepatic failure, prolonged duration of surgery, large transfusion requirements, re-transplantation, renal failure, and antibiotic usage [4,10]. Fungal infection is mostly caused by *Candida albicans*, but there is an increased incidence of nonalbicans *Candida* species, particularly *Candida glabrata* [9,10]. Prophylaxis of candidiasis still remains controversial. A recent meta-analysis showed that antifungal prophylaxis significantly reduced fungal colonization, fungal infections, both superficial and invasive, and mortality resulting from fungal infection. However, prophylaxis may lead to an increased incidence of nonalbicans *Candida* infections, including *Candida glabrata*, and did not affect overall mortality [11].

A recent Cochrane review concluded that, for liver transplant recipients, antifungal prophylaxis with fluconazole significantly reduced the incidence of invasive fungal infections, with no definite mortality benefit. Fluconazole prophylaxis did not significantly increase invasive infections or colonization with fluconazole-resistant fungi. For itraconazole and liposomal amphotericin B, there is a dearth of data, but indirect comparison and one direct comparative trial suggested similar efficacy as for fluconazole. For recently marketed systemic antifungal agents, such as caspofungin and voriconazole, no data are available regarding their prophylactic efficacy [12].

The recent guidelines for treatment of candidiasis from the Infectious Disease Society of America recommend antifungal prophylaxis for high-risk liver transplant recipients during the early postoperative period (level of evidence A-1) [13]. At the moment, fluconazole still remains the antifungal agent of choice [4,10,14].

Invasive aspergillosis has been described in 1–8% of liver transplant recipients and is still associated with a high mortality rate ranging from 60% to 100% [4,9,10]. Almost a fifth of deaths in liver transplant recipients are attributable to invasive aspergillosis [10]. Risk factors include pretransplantation fulminant hepatic failure, poor allograft function, retransplantation, renal failure with requirement of renal replacement therapy, large transfusion requirements, and use of monoclonal antibodies [9]. No prospective, randomized studies showed that antifungal prophylaxis prevents invasive aspergillosis in liver transplant recipients and a recent meta-analysis and Cochrane review of antifungal prophylaxis shows no benefit [4,11,12]. Most centers base their decision to administer antifungal prophylaxis for infections caused by *Aspergillus* species on the recipients' risk factors and the prevalent rates of invasive aspergillosis at the center. When indicated, the recommendations are voriconazole or lipid formulation of amphotericin B for 4 weeks for treating at-risk patients [9,10].

Our data show that most centers give antifungal prophylaxis to at-risk patients. The antifungal agent used mostly is fluconazole. Despite the current recommendations, we see that a tenth of the centers never administer antifungal prophylaxis. A recent survey in North America shows similar results on the proportion of centers using antifungal prophylaxis and the use of fluconazole [15].

Latent viral infections with CMV, Epstein–Barr virus, other herpes viruses, hepatitis B virus, hepatitis C virus, or human immunodeficiency virus can cause a reactivation in the setting of immune suppression. Screening of donor and acceptor pre liver transplantation is important.

Of all the herpes viruses, CMV infection or disease is the most important in transplant recipients. Both reactivated donor- or acceptor virus can cause disease in liver transplantation recipients, but the greatest risk for CMV infection or disease occurs when a seronegative recipient receives a liver from a seropositive donor (D+/R−)[4].

In literature, there is sometimes confusion between the terminology 'CMV infection' and 'CMV disease'. CMV infection is used when viral proteins (pp65 antigenemia) or viral nucleic acid (DNA PCR) are detected in any body fluid or tissue specimen. The CMV infection can be asymptomatic or symptomatic. Asymptomatic CMV infection occurs when the patient has no clinical signs or symptoms. Patients with a symptomatic CMV infection have clinical signs or symptoms (fever, neutropenia and/or thrombocytopenia) but no evidence of end-organ disease. Tissue-invasive CMV disease occurs when patients have evidence of end-organ disease (based on organ-specific symptoms and histologic evidence of invasive CMV). The term CMV disease refers to both 'symptomatic CMV infection' and 'tissue-invasive CMV disease' [4].

For the prevention of CMV disease, there are two possible strategies: prophylaxis or pre-emptive therapy. Prophylaxis involves administration of therapy to all patients during the period that they are at risk. In case of pre-emptive therapy, the antiviral therapy is targeted toward a subset of patients with early viral replication, in an attempt to prevent the progression of asymptomatic infection to CMV disease [4,16]. A meta-analysis of randomized and nonrandomized trials involving solid organ transplant recipients has shown that the overall risk reduction for CMV disease was comparable for universal prophylaxis and pre-emptive therapy with ganciclovir. There was also no difference between the strategies for all-cause mortality or rejection [16,17]. A placebo-controlled trial showed that, after liver transplantation, ganciclovir is a safe and effective method for the prevention of CMV disease [18]. Given the strong evidence from this high-quality study, we expected the high penetration of CMV prophylaxis as shown in this survey. Most centers use CMV prophylaxis in patients at risk, and a minority uses pre-emptive therapy. A recent survey in the US and Canadian liver transplant centers shows that prophylaxis is preferred over pre-emptive therapy by the majority of transplant centers, and that prophylaxis was the most common prevention strategy for all donor/recipients subtypes, except D−/R− who often received no prophylaxis [19].

There are several limitations in a survey like this. First, although the intention was to report on antimicrobial prophylaxis in all European liver transplant centers, the response rate of 48% limits our conclusions to the practice in these centers. On the other hand, these results represent the practice in 16 different European countries, and the response rate was up to the goal that could be reasonably expected. Given the lack of consensus and evidence-based data, and the importance of control of infection and antimicrobial resistance patterns, we feel that a European initiative for registration and regulation is warranted. Second, there is most likely a possibility of reporting bias. Physicians may be prone to report the desired answer instead of reporting their current practice. In order to prevent this, we recorded the surveys anonymously. This was also mentioned to the participating physicians in the accompanying letter. Finally, this survey does not report on the prophylactic regimen for *Pneumocystis carinii*. Although there is in literature no evidence for using this in liver transplant recipients, we cannot rule out that some centers actually include this in the perioperative prophylactic antimicrobial regimen.

Conclusion

In Europe, there is a marked variation in the antibiotic, antifungal and CMV prophylactic strategies used for liver transplantation recipients.

This variation is most pronounced in case of antibiotic prophylaxis. The variation exists in both the spectrum of antibiotic(s) used, and the duration of prophylaxis. Randomized studies are needed to determine the optimal duration of prophylactic antibiotic regimen. For the type of antibiotic agent used, treatment should be based upon local susceptibility patterns and microbial ecology.

For antifungal prophylaxis, there is less variation in indication and type of agent used. Most centers give antifungal prophylaxis to at-risk patients, and the agent used mostly is fluconazole. Despite the evidence and the current recommendations of the Infectious Disease Society of America, a tenth of the centers never administer antifungal prophylaxis. Finally, there was a high penetration of CMV prophylaxis to at-risk patients.

Authorship

EH: initial idea. EV, EH, JDW, DV, SB, DV, XR, HVV, JD, EH: designed study. : EV, EH: collected data. EV, EH, JDW, DV, SB: analysed data. EV: wrote the first draft of the paper. All authors commented on the paper and approved the final version.

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