Annals of Reviews and Research

Juniper Publishers key to the Researchers

Review Article
Volume 3 Issue 3- August 2018

Ann Rev Resear

Late Infectious Complications after Liver Transplantation in Children

Anita Verma* and Anil Dhawan

Institute of Liver studies & King's College Hospital, UK

Submission: May 08, 2018; **Published:** August 29, 2018

***Corresponding author:** Anita Verma, Institute of Liver studies, King's College Hospital, London, SE5 9RS, UK, Email: anitaverma@nhs.net

Abbreviations: CMV: Cytomegalovirus; CRE: Carbapenem Resistant Enterobacteriaceae; RT: Respiratory Tract; LTR: Liver Transplant Recipients

Introduction

Infectious complications in children after liver transplantation are a major cause of morbidity and mortality. Most of the life-threatening infections are seen in the first few months after the operation and are related to their stay in the intensive care unit, invasive monitoring, anastomotic leaks and higher levels of immunosuppressive medications. Infections that happen after six months of liver transplant operation are considered as late infections. True incidence of the type of infections is difficult to establish as most of these patients are usually not managed in the liver transplant centre and the data may not be always provided to the transplant centre by local hospitals. Hence this subject has been only a matter of few research publications [1].

After 6 month we can divide liver transplant recipients into three groups, in term of their risk to acquire infections: Group 1: patients with good allograft function and low immunosuppression (comprising about 80% of the patient population). This group usually have very low risk of infections. Most common infections in this group of patients are community-acquired and include respiratory viruses: e.g., influenza, para-influenza, respiratory syncytial virus, human metapneumovirus, swine flu virus, coronaviruses. The common bacterial infections are Streptococcus pneumoniae (drug resistant), Haemophilus influenzae, MRSA, Mycobacterium tuberculosis. Gastrointestinal pathogens - Noravirus, Rotavirus, Compylobacter, Salmonella. Rarely atypical organisms such as Mycoplasma and Legionella. Paediatirc liver transplant recipients particularly young children who are unable to receive live vaccines before transplant are also prone to vaccine-preventable diseases- variciella, measles and mumps. Second category of patients (Group 2, about 10-15% of patient population), who have on going biliary complications secondary to anastomotic strictures or cholangiopathies secondary vascular problems are more likely to get infections due to endogenous flora coliforms, enterococci and emerging carbapenem resistant enterobacteraceae (CRE). Invasive procedures like cholangiography, percutaneous or endoscopic predispose further these patients to environmental pathogens like Pseudomonas hence it is important to consider the antibiotic cover for this type of organisms when using empiric antimicrobial therapies. Patients with recurrent cholangitis are exposed to repeated courses of antibiotics which make them prone to fungal infections. Hence antifungal cover depending on local epidemiology should be considered when response to standard antimicrobials is less than optimal. Third category of patients (Group 3, about 2-5% of patient population) who have difficult to treat allograft rejection requiring higher levels of immunosuppresion and or use of biological agents like mono or polyclonal antibodies. This group can present with severe opportunistic infections involving- P jiroveci, Cryptococcus neoformans, Nocardia and invasive fungi such as Aspergillus, Mucor and other molds. Reactivation of viruses- Herpes group: CMV, HSV encephalitis, EBV and Herpes zoster.

Treating physicians should also keep in mind travel associated pathogens, specific exposures to uncommon pathogens related to work, recreational activities and pets. We evaluated the incidence, risk factors and pathogens for late IC in 181 paediatric LTR between 2004 to 2008 at King's College Hospital, London. Follow-up end points were 2-year, death or re-transplantation. Overall incidence of late infections was 21.4% (39/181); predominant infections were due to viruses 19%, most common viral infection was due to cytomegalovirus (CMV) 10.4%, followed by respiratory tract viruses i.e. influenza, Swine flu, rhinovirus, adenovirus & gastrointestinal virus- noravirus. One patient each had cholangitis due to Candida albicans, bacteraemia (*E.faecium*), conjunctivitis (*S aueus*) and diarrhoea (*Compylobacter*).

Late Cytomegalovirus (CMV) Infection in Liver Transplant Recipients

Although late CMV infection is well studied in adult LTR but there is paucity of data in paediatric patients. The risk factors for late CMV infection described are prolonged antiviral prophylaxis, recurrent rejection while on antiviral prophylaxis and increased immunosuppression especially use of antilymphocyte products

[2]. Late CMV presentation can manifest as non-specific viral syndrome (fever, leukopenia, atypical lymphocytosis & thrombocytopenia) or involvement of visceral organ (common sites include the gastrointestinal tract, liver, and lungs) and the site of involvement varies according to the type of transplant. This is the first centre we analysed highest number of pedaitric LTR for late CMV complications. The overall 1st CMV infection after transplant was in 51%, 67%, 66% 10% in D-R+, D+R-, D+R+ & D-R- respectively. The overall incidence of late CMV infection in three high risk group (D-R+, D+R-, D+R+ excluding low risk patients D-R-) was 18/131 (13.7%). Most of these patients were young and had late post-transplant complications. Late rejection was seen in 25% of patients mainly in D+R- & D-R+ group. The most important finding was, D-R+ group showed very high rate of hepatitis (36%) on liver biopsies in comparison to 15 % in other two groups.

The anti CMV prophylaxis protocol included IV ganciclovir 5mg/kg twice daily for 2 weeks for D+R- starting at day 7 post-transplant, followed by CMV DNA monitoring till patient is discharged or when symptomatic for other groups. Late CMV disease was present in 5/131 (3.8%) patients. Less than 2% patients required the second line treatment with foscarnet. Late CMV infection was associated with increased morbidity but no mortality. Antiviral prophylaxis only delays the onset of viral replication, and therefore, it does not prevent the development of a primary infection, which is relatively common after prophylactic therapy has been completed [3]. In a study of 67 high-risk CMV liver transplant recipients (9 patients on oral ganciclovir, 58 patients on valganciclovir for 92 days), primary CMV disease was observed in 2%, 25%, 27%, 27%, and 29% of patients at 1, 3, 6, 12, and 24 months, respectively, after antiviral prophylactic therapy was stopped with similar incidences between the two treatment groups [2].

Patient who develop allograft rejection during prophylaxis are at an increased risk for developing delayed-onset CMV disease after cessation of prophylaxis, which has led to increased mortality [4-6]. Risk of delayed onset CMV disease could be prevented by minimization of immunosuppression or by prolonging CMV prophylaxis i.e., 6 months instead of 3 months. However, these measures are associated with risk of; graft rejection, drug toxicity, increased cost, emergence of drug resistance [7]. In adult patient's antiviral prophylaxis has been proven to be of benefit as without antiviral therapy-risk of CMV infection was reported to be 44-65%, in high risk CMV LT-recipients during first 12 month [8,9]. Meta-analysis on prophylaxis with ganciclovir or valganciclovir vs placebo showed significant reduction of - CMV infection, CMV disease & mortality in solid organ transplant recipients. Few other studies have reported improved survival and reduction of biopsy proven rejection [10,11].

However, there is no consensus on duration of antiviral prophylaxis. Prolonged duration of treatment could result in ganciclovir resistance. Resistance should be suspected if viral load persists while on antivirals, this could be confirmed by testing for genotypic mutations within the viral genes UL97 and/or UL54. Ganciclovir-resistant CMV disease was reported in up to 7% of high risk CMV recipients while none in CMV-seropositive recipients in a group of solid organ transplant recipients [12]. Ganciclovir resistant patients could be treated with foscarnet or cidofovir with or without immunoglobulin and reducing immunosuppression [13]. Other antiviral agents that could become available are oral maribavir, CMX-001, artesunate, and everolimus [14]. Increased understanding, as well as the use of newer diagnostic tests, antiviral therapy, and preventative strategies, have led to marked improvements in the prevention and management of many of the complications associated with post-transplant CMV infections in children.

Influenza Infection

The 2nd most common late viral infection was respiratory virus influenza. Reported incidence in SOT recipients is 2- 4%. In our data of 181 LTR 3% were admitted to hospital because of influenza infection. It is mainly upper respiratory tract (RT) disease, lower RT disease is estimated to occur in 1-5% of LTR. Parainfluenza & influenza were associated with high morbidity and mortality in very young LTR [15]. Oseltamivir is an effective agent with protective efficacy of 75% [16]. It is very important to consider early diagnosis and treatment for influenza infection in SOT recipients as it reduces the severity of influenza, shorten duration of viral shedding, reduce the frequency of lower RT complications e.g. bronchiolitis and pneumonia. Prevention is the most important strategy for influenza management-all LTR should have annual vaccine, 6 months after transplant surgery, if used before that immune response to vaccination could be suboptimal [17,18].

Carbapenem resistant Enterobacteriaceae (CRE)

Excessive use of antibiotics has led to emergence of multidrug resistant gram-negative bacteria. The emerging problems with the CRE is becoming an issue in LTR, because of not only it is harboured in gut for long but can spread rapidly to other patients if stringent infection control precautions are not followed. We encountered an outbreak of infection with Carbapenem resistant Enterobacteriaceae (CRE) in our unit lately. A very stringent infection control protocol including; quarantine of all new admission from other hospitals in to single rooms till results of screening swabs (rectal swabs) are negative for CRE [19-21] hand hygiene, environmental cleaning, and antibiotic stewardship helped to control the outbreak. Further continuation of active surveillance prevented the silent dissemination of these superbugs in this immunosuppressed population.

Conclusion

In conclusion the late infections after transplantation requiring hospital admission are not uncommon. Most severe infections occur in patients with biliary complications and during

How to cite this article: Anita Verma, Anil Dhawan. Late Infectious Complications after Liver Transplantation in Children. Ann Rev Resear. 2018; 3(3): 555613.

periods of increased immunosuppression. Careful monitoring and treatment could limit morbidity and avoid mortality.

References

1. Aberg F, Mäkisalo H, Höckerstedt K, Isoniemi H (2011) Infectious complications more than 1 year after liver transplantation: a 3-decade nationwide experience. Am J Transplant 11(2): 287-295.
2. Arthurs SK, Eid AJ, Pedersen RA, Dierkhising RA, Kremers WK, et al. (2007) Delayed-onset primary cytomegalovirus disease after liver transplantation. Liver Transpl 13(12): 1703-1709.
3. Razonable RR (2008) Cytomegalovirus infection after liver transplantation: current concepts and challenges. World J Gastroenterol 14(31): 4849-4860.
4. Limaye AP, Bakthavatsalam R, Kim HW, Kuhr CS, Halldorson JB, et al. (2004) Late-onset cytomegalovirus disease in liver transplant recipients despite antiviral prophylaxis. Transplantation 78(9): 1390-1396.
5. Razonable RR, Rivero A, Rodriguez A, Wilson J, Daniels J, et al. (2001) 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 184(11): 1461-1464
6. Kim JM, Kim SJ, Joh JW, Shin M, Moon JI, et al. (2010) The risk factors for cytomegalovirus syndrome and tissue-invasive cytomegalovirus disease in liver transplant recipients who have cytomegalovirus antigenemia. Transplant Proc 42(3): 890-894.
7. Lautenschlager I (2009) CMV infection, diagnosis and antiviral strategies after liver transplantation. Transpl Int 22(11): 1031-1040.
8. Paya CV, Wiesner RH, Hermans PE, Larson-Keller JJ, Ilstrup DM, et al. (1993) Risk factors for cytomegalovirus and severe bacterial infections following liver transplantation: a prospective multivariate time-dependent analysis. J Hepatol 18(2): 185-195.
9. Hodson EM, Jones CA, Webster AC, Strippoli GF, Barclay PG, et al. (2005) Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: a systematic review of randomised controlled trials. Lancet 365(9477): 2105-2115.
10. Falagas ME, Snydman DR, Ruthazer R, Griffith J, Werner BG, et al. (1997) Cytomegalovirus immune globulin (CMVIG) prophylaxis is associated with increased survival after orthotopic liver transplantation. The Boston Center for Liver Transplantation CMVIG Study Group. Clin Transplant 11(5 Pt 1): 432-437.
11. Slifkin M, Ruthazer R, Freeman R, Bloom J, Fitzmaurice S, et al. (2005) Impact of cytomegalovirus prophylaxis on rejection following orthotopic liver transplantation. Liver Transpl 11(12): 1597-1602.
12. Limaye AP, Corey L, Koelle DM, Davis CL, Boeckh M (2000) Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solidorgan transplants. Lancet 356(9230): 645-649.
13. Chou S (2008) Cytomegalovirus UL97 mutations in the era of ganciclovir and maribavir. Rev Med Virol 18(4): 233-246.
14. Eid AJ, Razonable RR (2010) New developments in the management of cytomegalovirus infection after solid organ transplantation. Drugs 70(8): 965-981.
15. Apalsch AM, Green M, Ledesma-Medina J, Nour B, Wald ER (1995) Parainfluenza and influenza virus infections in pediatric organ transplant recipients. Clin Infect Dis 20(2): 394-399.
16. Moscona A (2005) Neuraminidase inhibitors for influenza. N Engl J Med 353: 1363-1373.
17. Lawal A, Basler C, Branch A, Gutierrez J, Schwartz M, Schiano TD (2004) Influenza vaccination in orthotopic liver transplant recipients: absence of post administration ALT elevation. Am J Transplant 4(11): 1805-1809.
18. Madan RP, Tan M, Fernandez-Sesma A, Moran TM, Emre S, et al. (2008) A prospective, comparative study of the immune response to inactivated influenza vaccine in pediatric liver transplant recipients and their healthy siblings. Clin Infect Dis 46(5): 712-718.
19. Rosen HR, Corless CL, Rabkin J, Chou S (1998) Association of cytomegalovirus genotype with graft rejection after liver transplantation. Transplantation 66(12): 1627-1631.
20. Hellinger WC, Bonatti H, Machicao VI, Yao JD, Brumble LM, et al. (2006) Effect of antiviral chemoprophylaxis on adverse clinical outcomes associated with cytomegalovirus after liver transplantation. Mayo Clin Proc 81(8): 1029-1033.
21. Verma A, Philpotthoward J, Baker A, Heaton N, Wade J, Dhawan A (2013) Outbreak of bla VIM-4 Carbapenemase Producing Enterobacteriaceae in a Pediatric Liver Transplant Centre: A New Threat to Our Antibiotics Armamentarium. Liver Transpl 19(6 Supplement 1: S128.

How to cite this article: Anita Verma, Anil Dhawan. Late Infectious Complications after Liver Transplantation in Children. Ann Rev Resear. 2018; 3(3): 555613.