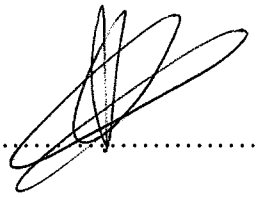
A Retrospective Review of Early Complications in Adult Liver Transplant Recipients at Wits Donald Gordon Medical Centre

Dr Sheetal Chiba

A research report submitted to the University of the Witwatersrand, Johannesburg in fulfilment for the requirements of the Degree of Master of Medicine 2018.

DECLARATION

I, Sheetal Chiba, declare that this research report is my own work, which is being submitted for the degree Master of Medicine (in the submissable format with my protocol and an extended literature review) in the department of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



.....

20th day of November 2018

ACNOWLEDGEMENTS

A heartfelt thanks goes to my two supervisors.

Dr GK Schleicher, many thanks for affording me the opportunity of doing this project. Your ongoing guidance, support and time set aside throughout this process, as well as your knowledge has certainly provided a solid foundation from which I could accomplish this project. Your dedication and work ethic has been a true inspiration.

Dr Lowman, for agreeing to be my second supervisor. Your expertise in the field and assistance has allowed me to achieve this goal.

Dr Fabian and Heather Maher for your guidance and assistance to complete this project.

Finally, to my loving husband Sumesh and my family, thank you for your endless support, love and patience throughout this journey.

This project is dedicated to my late mom, Premilla Chiba.

PRESENTATIONS ARISING FROM THIS PROJECT

1. Oral presentation

A Retrospective Review of Early Complications in Adult Liver Transplant Recipients at Wits Donald Gordon Medical Centre

Wits Donald Gordon Medical Centre Research Day 20th October 2017

ABSTRACT

Background

Deceased donor liver transplants (DDLT) are the only type of liver transplants performed in adults at WDGMC. Infections, graft dysfunction, biliary, gastro-intestinal tract (GIT), vascular, renal, respiratory and neurological complications are the most common complications in the early post-transplant period and account for most of the early morbidity and mortality.

Objectives

Firstly, to provide a descriptive analysis of all complications occurring in the first thirty days post operatively in adult liver transplant recipients. Secondly, to investigate any association between recipient demographic data (age and gender), ascites, diabetes and MELD score and subsequent complications.

Methods

A retrospective chart review of all adult DDLT recipients for the first thirty days post-transplant was performed at WDGMC for the period January 2015 to December 2016. Complications were classified as infectious or non-infectious. Categorical and continuous variables were analyzed. Fischer's exact test is used to assess the relationship between demographic data and the presence or absence of infectious complications, while independent sample t-test is used for non-infectious complications.

Results

78 DDLT were performed, with 6 mortalities (8%) in the first 30 days post transplantation. The median length of ICU stay was 6 days (range 2-30 days). The median age of transplant recipients was 54 years, with 54% males. In total 24 patients (31%) had infectious complications in the first 30 days. 16 patients (67% of the infectious cohort) had intra-abdominal sepsis. Six patients (25%) had lower respiratory tract infections, 6 (25%) had skin and soft tissue infections and 3 (13%) had urinary tract infections. Of all infectious complications, 7 patients (29% of the infectious cohort) developed bacteraemia. In total 55 patients (71%) had non-infectious complications. The most common was renal complications

which occurred in 37 patients (67%). 33 patients (60%) had GIT (hepatic, biliary and intestinal), 24 patients (44%) had respiratory, 13 (24%) had neurological, 10 patients (18%) had vascular, 11 patients (20%) had haematological, and 6 patients (11%) had cardiac complications respectively. Thirteen patients (24%) developed tacrolimus toxicity and 2 patients (4%) had other drug reactions. Acute rejection was suspected in 3 patients (5%). There was no significant association between any of the demographic variables (age, gender), ascites, diabetes mellitus, MELD score and the presence or absence of any complications (infectious and/or non-infectious).

Conclusion

This comprehensive report from South Africa documents complications that occurred within 30 days post liver transplantation in adult recipients.

Non-infectious complications occurred more commonly than infectious complications (71% vs. 31%). The most common infectious complication was intra-abdominal sepsis, and the most common non-infectious complication was renal dysfunction. There was no significant association between any of the demographic variables (age, gender), ascites, diabetes mellitus and MELD score and the presence or absence of any complications.

TABLE OF CONTENTS

ABBREVIATIONS

DDLT- deceased donor liver transplant

LDLT- living donor liver transplant

WDGMC- Wits Donald Gordon Medical Centre

MELD- model for end stage liver disease

ESLD- end stage liver disease

ACR- acute cellular rejection

CMV- cytomegalovirus

AKI- acute kidney injury

CNI- calcineurin inhibitor

MMF- mycophenolate mofetil

KDIGO- Kidney Disease Improving Global Outcomes

CKD- chronic kidney disease

OLT- orthotopic liver transplant

HRS- hepatorenal syndrome

ARDS- acute respiratory distress syndrome

HAT- hepatic artery thrombosis

NAFLD- non alcoholic fatty liver disease

DM- diabetes mellitus

IQR- interquartile range

ICU- intensive care unit

GSH- Groote Schuur Hospital

GIT- gastrointestinal

HAT- hepatic artery thrombosis

IVC- inferior vena cava

d- days

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 Introduction

1963 marks the first human liver transplant.[4,10] In adults, deceased donor liver transplants (DDLT) are the only type of transplant performed in sub-Saharan Africa, whilst living donor liver transplants (LDLT) are routinely performed worldwide.[4] There are only two adult liver transplant centers in sub-Saharan Africa, Groote Schuur Hospital (GSH) in the Western Cape and Wits Donald Gordon Medical Centre (WDGMC), both in South Africa.[4]

Indications for liver transplantation include acute fulminant liver failure and chronic end stage liver disease (ESLD) due to various causes, which include cirrhosis, biliary disease, vascular pathology and malignancy.[2] Liver transplantation is considered when decompensated cirrhosis or liver failure develops.[19-21] This is defined by the presence of a major complication of cirrhosis, which includes variceal bleeding, hepatic encephalopathy, refractory ascites, spontaneous bacterial peritonitis, portal vein thrombosis, hepatorenal and hepatopulmonary syndromes and hepatocellular carcinoma.[19-21] Chronic viral hepatitis, alcoholic and non-alcoholic steatohepatitis and haemochromatosis prove to be the leading causes of cirrhosis in developed countries.[18]

Allocation policies for liver transplantation are important due to the global shortage of donor organs, particularly in areas where transplant facilities are limited, such as sub-Saharan Africa.[2,4,] LDLT has to some degree alleviated the limited availability of donor liver organs, a practice prominent in Asia.[2,4] In 2002, the Organ Procurement Transplant Network in the United States of America implemented a liver allocation system which assists prioritization for liver transplantation.[2] Acute liver failure and immediate post graft failure are prioritized indications of liver transplantation, whilst patients with chronic liver disease are listed and await transplantation according to the severity of their illness based on the Model for End-Stage Liver Disease (MELD) score.[2] The MELD score is a reliable measure of mortality risk and disease severity employed in patients with ESLD for organ allocation.[2] The adult liver transplant protocol used at WDGMC includes standardized pre-, intra-, and post-operative

measures, and immunosuppression protocols followed on recipients of DDLT. (Refer Appendix 1.1)

Numerous non-infectious and infectious complications occur post liver transplantation.[1,4,13,15] Hepato-biliary complications include graft dysfunction, biliary leaks and strictures and recurrence of primary liver disease.[4,13,15] The latter encompasses a spectrum of all causes of ESLD, malignancy and metabolic causes of liver disease.[13,15]

Long term complications of immunosuppression can result in multi-system dysfunction, including endocrine involvement, renal disease, metabolic syndrome, accelerated atherosclerosis and metabolic bone disease.[9,12,16] The incidence of metabolic syndrome post liver transplantation is twice as frequent when compared to the general population.[9] Significant independent predictors of post transplantation metabolic syndrome described by Laish et al. include age, pre-transplant non alcoholic fatty liver disease, diabetes mellitus, body mass index and triglycerides.[9] Hypertriglyceridemia is an early complication, occurring in the first month post transplantation, whereas hypercholesterolaemia occurs in the first 6 months.[16] Myocardial infarction and cardiovascular death occurs more frequently in liver transplant recipients than age- and sex matched non-transplant individuals.[12]

Hepatic and extrahepatic non-infectious complications in the early post-operative period following liver transplantation have been extensively published in international literature.[9,12-16] Careful haemodynamic monitoring, fluid and electrolyte management and ventilatory support is crucial to minimize early post-operative complications.[15] Failure of this can result in multi-organ complications.[9,12,15,16] Inability to maintain metabolic homeostasis following liver transplant defines primary graft failure, a potentially fatal early complication.[15] Both hypovolaemia and increased cardiac preload, often complicated by pulmonary oedema, can result in poor graft perfusion, an important risk factor for graft failure.[15]

Acute cellular rejection (ACR) occurs most commonly within the first 2 weeks post liver transplantation, with a peak incidence at 7-10 days.[33] The rare phenomenon of hyper acute rejection occurs within the first 48 hours due to preformed antibodies.[15]

Biochemical findings (liver function tests) can be preserved in the face of ACR, a finding common to the early period.[33] The globally accepted definition of ACR is histologically proven rejection 0-90 days following liver transplantation.[33] Despite the discordant finding of normal biochemistry and histologically proven ACR, early protocol biopsies are no longer routinely advocated. Higher doses of immunosuppression therapy used to treat recurrent and chronic rejection is an important risk factor for the development of opportunistic infections.[42]

Biliary leaks and obstruction are usually observed in the early post-operative period, whilst strictures are a later complication.[15] Early biliary complications are classified as 0-4 weeks post transplantation, whereas late biliary complications occur thereafter, with both remaining a significant contributor of morbidity and mortality.[34] Older donor age, increased cold and warm ischaemia time, surgical technical difficulties, presence of cytomegalovirus (CMV) infection pre-transplantation, ABO mismatch and donation after cardiac-related death are a few risk factors which predispose recipients to biliary complications post liver transplantation.[34-40] Asymptomatic liver transplant recipients with elevated serum aminotransferase, bilirubin levels and ductal enzymes warrant further investigation to exclude biliary complications.[34-40]

Saner *et* al. describes encephalopathy as the commonest neurological complication post liver transplant in the first month, followed by seizures.[14] Neurological complications accounted for longer ICU stay compared to those with non-neurological complications. In this cohort, calcineurin inhibitor use did not significantly impact 30 day neurological outcomes.

Multifactorial aetiologies account for early renal complications, including hypovolaemia, sepsis, nephrotoxic drugs, underlying CKD, pre-existing hepato-renal syndrome and surgical complications.[15,22-24,27] Acute kidney injury (AKI), a major cause of morbidity and mortality following liver transplantation, has a variable incidence of 5-94% following orthotopic liver transplantation (OLT), with approximately 8-17% requiring renal replacement therapy.[46] The following independent risk factors for developing AKI post orthotopic liver transplantation are demonstrated by a Chinese study: blood loss, cold and warm ischaemia time, overexposure to calcineurin inhibitors (CNI) and combined immunosuppression

therapy (mycophenolate mofetil (MMF) and CNI use).[46] The RIFLE or AKIN criteria were used to define AKI in this study, in accordance with the (Kidney Disease Improving Global Outcomes) KDIGO guidelines.. This study did not demonstrate a significant relationship between MELD score, Child-Pugh score, pre-operative hypoalbuminaemia, cirrhosis, hepatic failure and duration of surgery and the development of AKI post transplantation. A 5 year retrospective study reveals an incidence of 52% of AKI within 72 hours post liver transplantation.[45] Other reported risk factors for developing AKI 72 hours post transplantation include female gender, weight greater than 100kgs, high Child-Pugh score, presence of underlying diabetes mellitus and a greater number of units of blood transfusion or fresh frozen plasma.[45]

Chronic kidney disease (CKD) is a well-documented complication following OLT and is associated with a higher mortality rate than liver transplant recipients without renal dysfunction.[28] As liver transplant recipients' survival increases, so does the incidence of renal dysfunction.[28] Pre-transplantation serum creatinine level have been identified to predict post-OLT renal dysfunction and survival.[27] A study in Pennsylvania suggests that the duration of renal dysfunction pre- OLT predicts recipients' renal outcomes, which may help identify patients in need of combined liver kidney transplantation.[27] The various causes of underlying CKD however did not prove significance.[27] This study cohort's spectrum of aetiology of underlying CKD included end stage hypertensive nephropathy, multifactorial glomerulonephritides , polycystic kidney disease, hepatorenal syndrome (HRS), lupus nephritis and drug induced nephropathy.[27]A study in the USA documents the incidence of CKD in liver transplant recipients as 14% at 3 years and 18% at 5 years post transplantation.[17] This study defined CKD as an estimated GFR <30 mL/min per 1.73 m^2.[17] Risk factors for developing CKD in this cohort included CNI exposure, older age, female gender, post-operative acute renal failure, pre-existing hypertension, diabetes and hepatitis C infection.[17] CNI exposure is a major risk factor for developing renal dysfunction post liver transplantation[17,45], while CNI dose reduction does not always improve renal function, but may delay progression of renal disease.[22-24] A significant improvement in renal function can be seen if CNI therapy is substituted with MMF or sirolimus in individuals whom have not yet developed irreversible renal injury from CNI toxicity.[25,26]

HRS, a serious complication of ESLD, requires prompt and aggressive medical treatment initiation, followed by liver transplantation.[29] Comparable renal outcomes are seen in hepatorenal and non-hepatorenal individuals post liver transplantation.[29] Mitzner et al suggests improvement in HRS type 1 with medical treatment using extracorporeal albumin dialysis with a molecular adsorbent recirculating system.[47] HRS type 1 and a greater MELD score are usually associated with poorer outcomes, both entities being documented predictors of outcome.[48] Combined liver-kidney transplantation for HRS remains controversial, a procedure generally performed on individuals with primary liver and kidney disease.[49]

Of both infectious and non-infectious respiratory complications post liver transplantation, pleural effusions, atelectasis, pulmonary oedema and pneumonia are more commonly noted in the early post-operative period, contributing to morbidity and mortality.[50] A multicenter prospective study however attributes only 2.4% of all mortalities to respiratory complications post liver transplantation.[50] In this study, approximately 80% of all respiratory deaths are non-infectious related, while pneumonia is the leading infectious cause in this study. Acute respiratory distress syndrome (ARDS), an early complication, can be a manifestation of severe reperfusion syndrome, prolonged surgical time, significant blood loss and severe sepsis.[15]

Infections following liver transplant have been widely published in both high and lower income countries.[1,4,5,10,11,13] Post transplant infections contribute to significant morbidity and mortality, yet often remain preventable.[1,5,7] Three periods following liver transplantation are associated with infections: within the first month, between 1 and 6 months and beyond 6 months.[1,5]

Infection profiles in the first month following liver transplantation mimic those of an immune-competent host following surgery.[1] In this time period bacterial infections are most prominent.[1,5] Operative risks, extended hospitalization and donor transmitted diseases are amongst the common causes of infections.[1,5] Roux-en-Y biliary anastomosis, prior multiple abdominal surgeries, the presence of post-operative CMV infection and graft dysfunction also confer an increased risk in developing bacterial infections post liver transplantation.[30-32] Nosocomial sources of infection, donor-derived infections, diabetes mellitus, hypoalbuminaemia and cytomegalovirus (CMV)

seropositivity are risk factors for bacterial infections following liver transplant.[1,5,11,15] Gram positive cocci and *Enterobacteriaceae* account for most bacterial pathogens,[1] whilst the abdomen and lungs appear to be the predominant sites of infection.[1,3,6]

Candida species, *Clostridium difficile* and herpes virus are frequently seen in the first month post liver transplantation.[1,5] Globally, *Candida* species is the commonest cause of systemic fungal infections seen in liver transplant recipients.[1,7] A review by Liu *et al.* has proposed the following risk factors associated with systemic fungal infections in liver transplant recipients: acute renal failure requiring haemodialysis or haemofiltration, number of fresh frozen plasma units transfused, cytopaenias, CMV infection and prolonged surgery.[7] Intensive immunosuppressive therapy remains the greatest predisposition to developing fungal infections[1,7] and also commonly results in *Clostridium difficile* colitis.[1,8] Importantly, higher doses of immunosuppression therapy used to treat recurrent and chronic rejection is an important risk factor for the development of these opportunistic infections.[42] Immunosuppression related infections usually occur in the first 3 months post transplantation, the period of greatest immunosuppression.[43,44] Antimicrobial use, frequent in the early post-operative period, is a risk factor for *Clostridium difficile*.[8] Fungal infection post liver transplant is life threatening and can be challenging to diagnose antemortem.[7]

Local data on liver transplantation and its early complications are scarce. A study from the liver transplant unit at GSH in Cape Town reviewed the first decade of liver transplants since its establishment in 1988.[10] Eighty nine transplants were performed on eighty three individuals, with cirrhosis being the leading indication of transplant in the adult group.[10] A favourable five-year survival rate of 64% was reported, with a 72% one-year graft survival rate.[10] A pertinent infectious complication was *de novo* hepatitis B infection in recipients without evidence of hepatitis B infection prior to transplant.[10] A significantly higher incidence of tuberculosis post transplantation was reported in this study, where tuberculosis is endemic, as compared to other studies worldwide.[10] Rejection, bleeding and sepsis were the early complications causing immediate post-transplant mortality and accounted for 29% of all deaths in this study.[10]

A study at WDGMC currently in-press, reports 206 DDLT performed over the decade 2004-2013.[4] This South African data demonstrates survival curves similar to those at international liver transplant centers where DDLT are performed.[4,10] The predominant indication for liver transplantation in this series is primary sclerosing cholangitis.[4] Biliary complications following DDLT appear most prominent in the study, followed by infectious complications.[4] Early complications, defined as the first 100 days following surgery in this study, include graft rejection, infection and biliary leaks, the latter occurring most commonly immediately post-surgery.[10] Hepatic artery thrombosis (HAT), predominantly occurring in the paediatric population, was noted as the most frequent vascular complication.[10] Most cases of HAT were reported as early post-operative complications.[10] The Donor Risk Index (DRI) was calculated in this study together with the MELD score, the former being more accurate in predicting poor survival following transplant.[4] In this study, a prolonged theatre time, DRI of 1.8-2.0 and the presence of ascites at the time of transplant was associated with increased mortality in recipients.[4]

There is limited literature on the outcomes of adult liver transplant programs in SA. Infections following liver transplantation remain an important cause of mortality in the early post transplantation period.[1,5,7] Sepsis is defined and categorised by the CDC/NHSN guidelines.[52] (Refer to Appendix 1.2) Emphasis on close surveillance for bacterial and fungal sepsis, early detection and adequate therapy remains pivotal in reducing mortality. It remains a clinical challenge to diagnose life-threatening infections in post-transplant recipients. Meticulous post-operative management with close haemodynamic, electrolyte and ventilatory monitoring is another area requiring awareness in order to improve morbidity and reduce mortality from non-infectious complications seen in the early post-operative period.[15]

STUDY AIM and OBJECTIVES

The aim of this retrospective study is to describe all complications in adult DDLT recipients within the first month following liver transplantation performed at the WDGMC, for the two-year period 01 January 2015 – 31 December 2016.

The objectives of this study are:

1) To identify and describe all complications in liver transplant recipients in the first month post transplantation.

2) To classify the complications as infectious or non-infectious causes within this time period.

3) To describe the microbiological profile of organisms causing infectious complications.

4) To describe and classify according to organ system all non-infectious complications.

5) To investigate the association between demographic data (age, gender), ascites and type 2 diabetes mellitus and the type of complication, for both infectious and non-infectious complications.

METHODS

This descriptive study will be conducted at Wits Donald Gordon Medical Centre (WDGMC). A retrospective database, clinical record and ICU chart review of all adult liver transplants during the period 2015-2016 will be conducted.

The following variables will be collected from the records:

Demographic: age, gender

Medical information: indication for liver transplant, MELD score, presence of diabetes, ascites and CMV status.

Transplant: date of transplant

Mortality: mortality in the first month post-transplant, date of death, cause of death

Duration of ICU stay

For infectious complications post-transplant in the first 30 days:

Presence of infection[52] (defined as per appendix 1.2)

Antibiotic administration (empiric[51] and culture directed antibiotic use)

Microbiological profile of infection

Source of sepsis[52] to be documented

Microbiological reports and serological markers of infection will be retrieved from the 4 laboratories involved in processing microbiologic specimens (Ampath Pathologists, Vermaak and Partners Pathologists, NHLS and Lancet Laboratories). Results tabulated as per Appendix 1.3.

Non-infectious complications within the first 30 days will be tabulated as per appendix 1.3. For all deaths within the first 30 days following liver transplantation the cause of

death will be documented, either from the available post mortem reports or from clinical records.

DATA ANALYSIS

Objectives 1) and 4): For the categorical variables, the frequency and percentages will be computed.

Objective 2): To compare the proportions of infectious and non-infectious complications, a chi-squared test of comparison will be used.

Objective 3): For continuous variables such as age, the Shapiro Wilk test of normality will be used to assess the distribution of data and where appropriate, the mean/standard deviation, median/interquartile range will be computed.

Objective 5): to fulfill this objective, univariate and/or multivariate logistic regression models will be fitted.

ETHICS

Ethical clearance will be applied for to the Human Ethics Research Committee of The University of the Witwatersrand.

TIMING

The start of the project will be determined by approval from the HERC and the Faculty's Research Committee.

	2016	2017							
	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug
Literature Review									
Preparing Protocol									
Protocol Assessment									
Ethics Application									
Collecting Data									
Data Analysis									
Writing Up-Thesis									
Writing Up-Paper									

FUNDING

This retrospective study does not require added funding. No new intervention or added testing is required. Any incidental costs such as travel and photocopying will be borne by the researcher.

ANTICIPATED CHALLENGES

Record review relies on information available on the current WDGMC liver transplant database. Information not available from this database limits accuracy of this study.

REFERENCES

1) Romero FA, Razonable RR. Infections in liver transplant recipients. World J Hepatol. 2011;3(4):83-92.

2) Zuckerman M, Loveland J. Selection and work-up for liver transplantation. SAMJ. 2012;102(11):876-8.

3) Kusne S, Dummer JS, Singh N, et al. Infections after liver transplantation. An analysis of 101 consecutive cases. Medicine (Baltimore). 1998;67(2):132-43.

4) Bentley A, Song E, Fabian J, et al. Outcomes of the First Ten Years of Adult Deceased Donor Liver Transplantation at Wits Donald Gordon Medical Centre. In press

5) Blair JE, Kusne S. Bacterial, Mycobacterial, and Protozoal Infections after Liver Transplantation—Part I. Liver Transpl. 2005;11(12):1452-59.

6) Singh N, Wagener MM, Obman A, et al. Bacteremias in liver transplant recipients: shift toward gram-negative bacteria as predominant pathogens. Liver Transpl. 2004;10(7):844-49.

7) Liu X, Ling Z Li L et al. Invasive fungal infections in liver transplantation. Int J Infect Dis. 2011;15(5):298-304.

8) Sullivan T, Weinberg A, Rana M, et al. The Epidemiology and Clinical Features of Clostridium Difficile Infection in Liver Transplant Recipients. Transplantation. 2016;100(9):1939-43.

9) Laish I, Braun M, Mor E, et al. Metabollic syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. Liver Transpl. 2011;17(1):15-22.

10) Botha J, Spearman C, Millar A, et al. Ten years of liver transplantation at Groote Schuur Hospital. SAMJ. 2000;90(9):880-3.

11) Hernandez MDP, Martin P, Simkins J. Infectious Complications After Liver Transplantation. Gastroenterol Hepatol. 2015;11(11);741-53.

12) Madhwal S, Atreja A, Albeldawi M, et al. Is Liver Transplantation a Risk Factor for Cardiovascular Disease? A Meta-Analysis of Observational Studies. Liver Transpl. 2012;18:1140-46.

13) Razonable RR, Findlay JY, O'Riordan A, et al. Critical Care Issues in Patients After Liver Transplantation. Liver Transpl. 2011;17:511-27.

14) Saner FH, Sotiropoulos GC, Gu Y, et al. Severe neurological events following liver transplantation. Arch Med Res. 2007;38(1):75-9.

15) Feltracco P, Barbieri S, Galligioni H, et al. Intensive care management of liver transplanted patients. World J Hepatol. 2011;3(3):61-71.

16) Gisbert C, Prieto M, Berenguer M. et al, et al. Hyperlipidemia in Liver Transplant Recipients: prevalence and risk factors. Liver Transpl Surg. 1997;3:416.

17) Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931.

18) Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. Am Fam Physician. 2006;54:756-62.

19) Liao WC, Hou MC, Chang CJ, et al. Potential precipitating factors of esophageal variceal bleeding: a case-control study. Am J Gastroenterol. 2011; 106:96.

20) Mumtaz K, Ahmed US, Abid S, et al. Precipitating factors and the outcome of hepatic encephalopathy in liver cirrhosis. J Coll Physicians Surg Pak 2010; 20:514.

21) Sundaram V, Shaikh OS. Hepatic encephalopathy: pathophysiology and emerging therapies. Med Clin North Am 2009;93:819.

22) Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. European FK506 Multicentre Liver Study Group. Lancet 1994;344:423.

23) U.S. Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med 1994;331:1110.

24) Canzanello VJ, Textor SC, Taler SJ, et al. Late hypertension after liver transplantation: a comparison of cyclosporine and tacrolimus (FK 506). Liver Transpl Surg 1998; 4:328.

25) Manzia TM, De Liguori Carino N, Orlando G, et al. Use of mycophenolate mofetil in liver transplantation: a literature review. Transplant Proc 2005;37:2616.

26) Neff GW, Montalbano M, Slapak-Green G, et al. Sirolimus therapy in orthotopic liver transplant recipients with calcineurin inhibitor related chronic renal insufficiency. Transplant Proc 2003; 35:3029.

27) Campbell, MS, Kotlyar DS, Brensinger CM, et al. Renal function after orthotopic liver transplantation is predicted by duration of pretransplantation creatinine elevation. Liver Transpl 2005;11: 1048–55.

28) O'Riordan A, Wong V, McCormick PA, et al. Chronic kidney disease post-liver transplantation. *Nephrology Dialysis Transplantation* 2006;21(9):2630-36.

29) Seu P, Wilkonson AH, Shaked A, et al. The hepatorenal syndrome in liver transplant recipients. The American Surgeon 1991;57(12):806-09.

30) Winston DJ, Emmanouilides C, Busuttil RW. Infections in liver transplant recipients. Clin Infect Dis 1995;21:1077.

31) Fishman JA. From the classic concepts to modern practice. Clin Microbiol Infect 2014;20 Suppl 7:4.

32) Paya CV, Wiesner RH, Hermans PE, et al. Risk factors for cytomegalovirus and severe bacterial infections following liver transplantation: a prospective multivariate time-dependent analysis. J Hepatol 1993;18:185.

33) Bartlett AS, Ramadas R, Furness S, et al. The natural history of acute histologic rejection without biochemical graft dysfunction in orthotopic liver transplantation: A systematic review. Liver Transpl. 2002; 8:1147–53.

34) Thuluvath PJ, Pfau PR, Kimmey MB, Ginsberg GG. Biliary complications after liver transplantation: the role of endoscopy. Endoscopy 2005; 37:857.

35) Pascher A, Neuhaus P. Biliary complications after deceased-donor orthotopic liver transplantation. J Hepatobiliary Pancreat Surg 2006; 13:487.

36) Sanchez-Urdazpal L, Gores GJ, Ward EM, et al. Ischemic-type biliary complications after orthotopic liver transplantation. Hepatology 1992;16:49.

37) Sanchez-Urdazpal L, Batts KP, Gores GJ, et al. Increased bile duct complications in liver transplantation across the ABO barrier. Ann Surg 1993; 218:152.

38) Maheshwari A, Maley W, Li Z, Thuluvath PJ. Biliary complications and outcomes of liver transplantation from donors after cardiac death. Liver Transpl 2007; 13:1645.

39) Fung JJ, Eghtesad B, Patel-Tom K. Using livers from donation after cardiac death donors--a proposal to protect the true Achilles heel. Liver Transpl 2007; 13:1633.

40) Welling TH, Heidt DG, Englesbe MJ, et al. Biliary complications following liver transplantation in the model for end-stage liver disease era: effect of donor, recipient, and technical factors. Liver Transpl 2008;14:73.

41) Jorgensen JE, Waljee AK, Volk ML, et al. Is MRCP equivalent to ERCP for diagnosing biliary obstruction in orthotopic liver transplant recipients? A meta-analysis. Gastrointest Endosc 2011;73:955.

42) Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med 1998;338:1741.

43) Torbenson M, Wang J, Nichols L, et al. Causes of death in autopsied liver transplantation patients. Mod Pathol 1998;11:37.

44) Chang FY, Singh N, Gayowski T, et al. Fever in liver transplant recipients: changing spectrum of etiologic agents. Clin Infect Dis 1998;26:59.

45) Hilmi IA, Damian D, Al-Khafaji A, et al. Acute kidney injury following orthotopic liver transplantation: incidence, risk factors, and effects on patient and graft outcomes. British Journal of Anaesthesia 2015;114(6):919-26.

46) Zongyi Y, Baifeng L, Funian Z, et al. Risk factors of acute kidney injury after orthotopic liver transplantation in China. Sci Rep 2017;7:41555.

47) Mitzner SR, Stange J, Klammt S, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis mars: Results of a prospective, randomized, controlled clinical trial. Liver Transplantation 2000;6(3):277-86.

48) Alessandria C, Ozdogan O, Guevara M, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: Relevance to liver transplantation. Hepatology 2005;41:1282–89.

49) Davis CL, Gonwa TA, Wilkinson AH. Identification of patients best suited for combined liver–kidney transplantation: Part II. Liver Transpl 2002;8:193–211.

50) Feltracco P, Carollo C, Barbieri S, et al. Early respiratory complications after liver transplantation. World J Gastroenterol 2013;19(48):9271-81.

51) Leekha S, Terrell C, Edson RS. General Principles of Antimicrobial Therapy. Mayo Clin Proc. 2011;86(2):156-67.

52) Centres for Disease Control and Prevention (2017). Sepsis 1 CDC. [online] Available at: http://cdc.gov/sepsis/index.html

CHAPTER 2: SUBMISSABLE ARTICLE

Title: A Retrospective review of early complications in adult liver transplant recipients' at the Wits Donald Gordon Medical Centre

Authors:

1. Sheetal Chiba
2. W. Lowman
3. G.K Schleicher

Affiliations: Divisions of Intensive Care and Hepatology, Wits Donald Gordon Medical Centre, Johannesburg, South Africa
Division of Hepatology, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa
Short title: Early complications in adult liver transplant recipients at Wits Donald Gordon Medical Centre
Conflict of Interest: Nil
Keywords: Early complications, liver transplant recipients, Wits Donald Gordon Medical Centre
Corresponding Author:
Sheetal Chiba
E-mail: sheetalchiba@yahoo.com
Mobile: 0722775359
Postal Address: 24a Trilby Street, Oaklands, Johannesburg. 2192

Word Count: 3701
Abstract Word Count: 445

Background

Deceased donor liver transplants (DDLT) are the only type of liver transplants performed in adults at WDGMC. Infections, graft dysfunction, biliary, gastro-intestinal tract (GIT), vascular, renal, respiratory and neurological complications are the most common complications in the early post-transplant period and account for most of the early morbidity and mortality.

Objectives

Firstly, to provide a descriptive analysis of all complications occurring in the first thirty days post operatively in adult liver transplant recipients. Secondly, to investigate any association between recipient demographic data (age and gender), ascites, diabetes and MELD score and subsequent complications.

Methods

A retrospective chart review of all adult DDLT recipients for the first thirty days post-transplant was performed at WDGMC for the period January 2015 to December 2016. Complications were classified as infectious or non-infectious. Categorical and continuous variables were analyzed. Fischer's exact test was used to assess the relationship between demographic data and the presence or absence of infectious complications, while independent sample t-test was used for non-infectious complications.

Results

78 DDLT were performed, with 6 mortalities (8%) in the first 30 days post transplantation. The median length of ICU stay was 6 days (range 2-30 days). The median age of transplant recipients was 54 years, with 54% males. In total 24 patients (31%) had infectious complications in the first 30 days. 16 patients (67% of the infectious cohort) had intra-abdominal sepsis. 6 patients (25%) had lower respiratory tract infections, 6 (25%) had skin and soft tissue infections and 3 (13%) had urinary tract infections. Of all infectious complications, 7 patients (29% of the infectious cohort) developed bacteraemia. In total 55 patients (71%) had non-infectious complications. The most common was renal complications which occurred in 37 patients (67%). 33 patients (60%) had GIT (hepatic, biliary and intestinal), 24 patients (44%) had respiratory, 13 (24%) had neurological, 10 patients

(18%) had vascular, 11 patients (20%) had haematological, and 6 patients (11%) had cardiac complications respectively. 13 patients (24%) developed tacrolimus toxicity and 2 patients (4%) had other drug reactions. Acute rejection was suspected in 3 patients (5%). There was no significant association between any of the demographic variables (age, gender), ascites, diabetes mellitus, MELD score and the presence or absence of any complications (infectious and/or non-infectious).

Conclusion

This comprehensive report from South Africa documents complications that occurred within 30 days post liver transplantation in adult recipients.

Non-infectious complications occurred more commonly than infectious complications (71% vs. 31%). The most common infectious complication was intra-abdominal sepsis, and the most common non-infectious complication was renal dysfunction. There was no significant association between any of the demographic variables (age, gender), ascites, diabetes mellitus and MELD score and the presence or absence of any complications.

Introduction

1963 marks the first human liver transplant.[4,10] In adults, deceased donor liver transplants (DDLT) are the only type of transplant performed in sub-Saharan Africa, whilst living donor liver transplants (LDLT) are routinely performed worldwide.[4] LDLT has alleviated the limited availability of donor liver organs, a practice prominent in Asia.[4,12]

There are only two adult liver transplant centers in sub-Saharan Africa, Groote Schuur Hospital in the Western Cape and Wits Donald Gordon Medical Centre (WDGMC), both in South Africa.[4] The adult liver transplant protocol used at WDGMC includes standardized operating procedures and immunosuppressive therapy for recipients of DDLT in the pre-, intra, and post-operative periods. (Refer to appendix 1.1)

Numerous non-infectious and infectious complications occur post liver transplantation.[1,4,13,15] Careful haemodynamic monitoring, fluid and electrolyte management and ventilatory support is crucial to minimize early post-operative complications.[15] Failure of this can result in multi-organ complications.[15] Inability to maintain metabolic homeostasis following liver transplant defines primary graft failure, a potentially fatal early complication.[15] Biliary leaks, biliary obstruction and hepatic artery thrombosis, are some of the most common hepato-biliary complications in the early post-operative period following liver transplantation.[15,27]

Complications of immunosuppression can result in sepsis, multi-organ dysfunction and graft failure.[12,14,16] Post transplant infections are a significant contributor of morbidity and mortality, yet remain potentially preventable.[1,5,29] Three periods following liver transplantation are associated with different infection profiles: within the first month, between 1 and 6 months and beyond 6 months.[1,5] Infections in the first month following liver transplantation mimic those of an immune-competent host, following surgery.[1] In this time period bacterial infections are most prominent.[1,5] Operative risks, extended hospitalization and donor transmitted diseases are amongst the common risk factors for development of infections.[1,5] Hospital acquired pathogens, donor-derived infections, diabetes mellitus, hypoalbuminaemia and cytomegalovirus (CMV) seropositivity are risk factors for bacterial infections following liver transplant.[1,5,11,15]

Preliminary data from a study in press at WDGMC, indicates that fungal infections are implicated in infection related mortalities, especially within the early post-operative period.[4] Globally, *Candida* species, is the commonest cause of systemic fungal infections seen in liver transplant recipients.[1,7] Following bacterial infections, *Clostridium difficile* and herpes virus are seen in the first month post-transplant.[1,5]

There is very little literature on the outcomes of adult liver transplant programs in SA. Emphasis on anticipation of sepsis, particularly bacterial and fungal, early detection and adequate therapy remains pivotal in prevention of mortality. Meticulous post-operative management with close haemodynamic, electrolyte and ventilatory monitoring is another area requiring awareness in order to improve morbidity and reduce mortality from non-infectious complications seen in the early post-operative period.[15]

Aim

To provide a descriptive analysis of all complications occurring in the first thirty days post operatively in adult liver transplant recipients at Wits Donald Gordon Medical Centre (WDGMC).

Materials and Methods

1. Study population

A retrospective chart review was conducted on all adult DDLT recipients for the first thirty days post-transplant. This was performed at WDGMC for the period January 2015 to December 2016. Permission to conduct the review was granted by the University of Witwatersrand Human Research Ethics Committee (Medical), approval certificate M170265 as included in appendix 1.4.

2. Data collection

The following information from all adult DDLT recipients was documented: age, gender, indication for transplant, presence of ascites, diabetes mellitus (DM) (types 1-3), hepatitis status (including A-C) and CMV status. CMV status from donors was obtained. Length of ICU stay was documented, up to the period of thirty days. Following liver transplantation, hospital charts and laboratory results were reviewed for the first 30 days, reporting all complications that occurred. This included death within the first 30 days. Non-infectious complications were reported by organ

involvement, as per the attached data collection sheet. (Refer Appendix 1.3) Due to the variety of complications noted, each organ system contained a category entitled "other", as only the most frequent complications were categorized solely. Infectious complications were identified upon chart review and correlated with serological/microbiology findings. Diagnoses and antibiotic use found on chart reviews were documented. Infectious pathogens, susceptibility to antimicrobial agents and site of infection were identified from the available microbiology reports, hospital charts, clinical information and serology reports. Site of infection was categorized according to the CDC/NHSN guidelines.[31] (Refer to Appendix 1.2)

Empiric[30] and/or directed anti-microbial therapy was documented. Patients with positive blood cultures were also recorded. Post mortem reports for the causes of death were requested from the forensic pathology department.

3. Assays

Analyses of blood serum samples and microbiology reports were performed by the following accredited laboratories according to good laboratory practice: South African National Health Laboratory Services (NHLS), Ampath Laboratories, Lancet Laboratories and Vermaak and Partners Pathologists. Where applicable, adult reference ranges were applied for the various blood tests.

4. Definitions

Adult cases referred to individuals 18 years and older.

The CMV status of donors was considered positive if the screening pre-donation serum CMV IgG serology was positive.

Hepatitis A status was considered positive if the hepatitis A Antibody serology was positive.

Chronic Hepatitis B status was considered positive if the hepatitis B surface antigen serology was positive and the hepatitis core IgM serology was negative.

Hepatitis C status was considered positive if the individual had a positive hepatitis C antibody serology and a positive hepatitis C viral load PCR.

Infection and infectious complications were classified according to the CDC/NHSN definition of sepsis and criteria for sepsis as attached in Appendix 1.2.[31]

As this project reviewed patients for the duration of only 30 days post transplantation, the length of ICU stay was truncated to 30 days, despite the possibility of exceeding this duration.

Length of ICU stay incorporated both ICU and High Care stay.

Directed antimicrobial therapy was defined as culture directed therapy, with confirmed susceptibility to the diagnosed pathogen.

Empiric antimicrobial therapy was defined as therapy based on clinical suspicion, in the absence of an identified pathogen and antimicrobial susceptibility.[30]

5. Statistical analysis

Data was analysed using SAS version 9.4 for windows. Categorical and continuous variables were used for this descriptive analysis. The former was represented by frequency and percentage tabulation and demonstrated on bar charts. Mean, standard deviation, median and interquartile range (IQR) represent continuous variables. Histograms were used to illustrate their distribution. The relationship between the presence/absence of infectious/non-infectious complications and age, DM in a recipient, ascites, and hepatitis status of both donor and recipients was depicted using Fischer's exact test. For the above, the phi coefficient measures the strength of association. Independent samples T test was used to assess the relationship between the presence/absence of infectious/non-infectious complications with age and MELD score. Cohen's d was used to measure the strength of association. Results were taken as statistically significant for p-values of less than 0.05.

Results

In the current study, in which 78 adult liver transplant recipients were retrospectively identified and reviewed over a two-year period, 63 recipients (81%) developed complications within the first month post orthotopic liver transplantation (OLT). Sixteen recipients of the 63 (25%) had 1 complication only, whilst the remainder experienced multiple complications. Twenty-four patients (31%) developed infectious complications and 55 patients (71%) developed non-infectious complications, respectively. Chronic liver cirrhosis with ESLD, diagnosed in 70 recipients (89%), was the most common indication for liver transplants in this cohort, with some individuals

having more than 1 underlying indication, as seen in figure 1. In this cohort, the 3 commonest causes of cirrhosis included: non-alcoholic fatty liver disease (NAFLD) (n=20, 29%), chronic viral hepatitis (n=19, 16%) and biliary pathology (n=14, 20%). Only 4 individuals (5%) required emergency liver transplantation due to acute fulminant liver failure.

Demographics, comorbidities and complications post transplantation

The median age of the 78 adult liver transplant recipients was 54 years (IQR 39-60). Fifty transplants (64%) were performed on male patients. The presence of ascites and DM pre-transplantation occurred in 36 recipients (46%) and 19 recipients (24%), respectively. Fifty-seven donors (73%) had a positive CMV serology status. The presence of diabetes mellitus, in 4 individuals (17%) of the infectious cohort and 15 (24%) of the non-infectious cohort, did not prove to be statistically associated with complications, as represented in figures 10,12 . The median MELD score of recipients pre-transplant was 20 (IQR 15-24). Of all 78 liver transplants performed, 6 (8%) resulted in mortality in the first thirty days post transplantation. The median length of ICU stay post transplantation was 6 days for the entire cohort. The median length of ICU stay for those who died within the first 30 days was 13 days (Range 7-30d). No association was found between continuous variables (age, pre-transplant MELD score) and infectious complications, as demonstrated by high p-values in figure 11. Likewise, no statistically significant association was evident when comparing these variables with non-infectious complications, also depicted in figure 11. Categorical variables (gender, diabetes mellitus, ascites, hepatitis) compared to the presence/absence of infectious and non-infectious complications also proved to be statistically insignificant as evident by high p-values in figure 12.

Patients with infectious complications (n=24)

In the first 30 days following liver transplantation, infectious complications (n=24, 31%) were less frequently seen than non-infectious complications (n=55, 71%), as represented in figure 2. As noted in figure 3, the majority of patients who developed infectious complications (n=16) developed intra-abdominal sepsis, accounting for 67% of the infectious complication cohort. Six (25%) of the transplant recipients who developed infectious complications were found to have lower respiratory tract infections. The same number of recipients also developed skin and soft tissue

infections (25%). Three recipients (13%) developed urinary tract infections. Seven patients of the infectious complication cohort (29%) developed a bacteraemia. In 10 recipients of the infectious complication cohort (42%), sepsis was clinically suspected but no specific pathogen was identified. Of the 14 recipients (58%) with pathogen proven infection, 100% were bacterial. In the 24 recipients with infectious complications, the most common antimicrobial therapies used were meropenem (n=15) and tigecycline (n=13). Fifteen recipients (63%) received directed antimicrobial therapy, 6 (25%) received empiric therapy, and 5 (21%) received both empiric and directed antimicrobial therapy as empiric therapy was considered appropriate and continued following available microbiology reports. *Klebsiella pneumoniae* was the commonest organism, isolated in 11 patients (46% of the infectious cohort). Ninety percent of infections due to *Klebsiella pneumoniae* had an intra-abdominal source, as reflected in figure 4. Access to post-mortem reports was not available and all cases of infectious complications (n=24) were diagnosed ante mortem.

Patients with non-infectious complications (n=55)

As demonstrated in figure 5, renal complications were the most frequently encountered non-infectious complication (n=37, 67% of the non-infectious cohort). This was followed by 33 recipients in whom GIT complications developed, which accounted for 60% of the non-infectious cohort. Thereafter, in descending frequency with percentages of the non-infectious complication cohort: respiratory complications (n=24, 44%), neurological complications and tacrolimus toxicity, both occurred in 13 patients each (24%), haematological (n=11, 20%), vascular (n=10, 18%), cardiac and graft failure both occurred in 6 recipients (11%), suspected acute rejection (n=3, 5%), and other drug reactions (n=2, 4%).

Of the renal non-infectious complications, as seen in figure 6, acute kidney injury (AKI) proved the most common finding (n=39, 71%). Sixteen recipients (42%) in the non-infectious cohort with renal complications experienced an infectious complication too. In 8 recipients (22%) the renal complications were considered to be directly due to sepsis. AKI not requiring dialysis appeared more prevalent than AKI requiring acute dialysis, (n=21, 38% and n=18, 33% respectively). Of all non-infectious GIT complications, hepatic complications developed most commonly (n=12, 22%),

followed by GIT bleed (n=10, 18%), biliary (n=8, 15%) and intestinal complications (n=7, 13%), as per figure 7. Of all the non-infectious respiratory complications (n=29), pleural effusions occurred most frequently (n=22), of which 64% were drained, as reflected in figure 8. Delirium was the most common neurological complication (n=11, 85% of all neurological complications). Of all vascular complications, illustrated in figure 9, hepatic artery thrombosis (n=6) was most prevalent, followed by portal vein complications (n=2), IVC complications (n=2) and other (n=1). Eleven patients (20% of the cohort with non-infectious complications) developed haematological complications, of which pancytopaenia (n=6, 55%) was the most frequent finding. Cardiac complications occurred in 6 recipients (11%), with cardiac failure being the most common finding (n=5, 83%). Graft failure (n=6) occurred in 11% of the non-infectious complication cohort. Drug reactions (n=2, 4%) occurred least commonly in this study. Acute rejection was clinically suspected in 3 patients (5%), but not biopsy proven within the 30day period of review.

Discussion

Local data on liver transplantation and its early complications remains scarce.[4,10] To date, there are very few local epidemiological studies assessing the outcomes post liver transplantation.[4,10] This is the first comprehensive 30 day report from Africa of all complications occurring in DDLT recipients following transplantation. The time period of 30 days post transplantation focuses on complications seen predominantly within the ICU/ High Care setting. In our cohort of 78 adult recipients, it is unsurprising that the major indication for liver transplantation is ESLD and cirrhosis. Cirrhosis, the result of numerous causes of ESLD, accounts for approximately 80% of all indications for liver transplantation throughout the USA,[17] consistent with this study. The increasing prevalence of obesity, diabetes and hyperlipidaemia in western countries contributes to the greater prevalence of NAFLD.[32] NAFLD is therefore estimated to occur 20-30% more frequently in western countries.[32]

In this cohort, non-alcoholic fatty liver disease (NAFLD) is the leading cause of cirrhosis (n=20, 29%), followed by chronic viral hepatitis (n=19, 16%) and biliary cirrhosis (n=14, 20%). This differs slightly from data published in both developing and developed countries, which indicate that hepatitis B and C, alcoholic steatohepatitis and hepatocellular carcinoma are the most common indications for liver

transplantation, in descending frequency.[4] Findings from local data at WDGMC and that published from Cape Town also differ, with primary sclerosing cholangitis and alcoholic steatohepatitis accounting for the most common causes of end stage cirrhosis requiring liver transplantation.[4,10] These studies include both adult and paediatric populations,[10] a possible reason for higher incidences of biliary disease, which is common to the paediatric population.[10] Possible contributors to the higher proportion of NAFLD in this study are the exclusive adult population and presence of type 2 DM (24%). Importantly, obesity is prevalent amongst South African adults, particularly females,[33] another possible reason of NAFLD, despite the male predominance in this cohort (64%). Unfortunately body mass index was not reliably documented at the time of transplantation in this cohort, but is frequently in range of 28-35 in the pre-transplant work up stage (personal communication Dr GK Schleicher).

This study reveals non-infectious complications (71%) to occur more commonly than infectious complications (31%) within the first 30 days post transplantation, differing from findings of the ten year retrospective review from WDGMC, currently in press.[4] The significantly shorter time frame (30d) of this study influences this finding, a period in which patients are susceptible to both acute infectious and non-infectious complications. Complications such as biliary strictures, CKD, CNI toxicity and opportunistic infections are a few anticipated complications expected over a longer time period of review, as per the WDGMC decade study.[4,10,15,24-26] Non-infectious biliary complications (20.9%) followed by infectious complications (19.9%) and vascular complications (17.5%) proved the most common outcomes from the decade review,[4] while renal (47%), GIT (42%), respiratory and infectious complications (31% each) are the most frequent findings of this study, as expressed as percentages of the total cohort (n=78). Vascular complications are expected to occur less frequently in this study, due to the short review period of this study.[4,27]

Importantly, biliary complications are reported as a component of GIT complications in this study. Biliary complications are approximately 50% lower in this study (10%) than the WDGMC decade-review.[4] Biliary leaks and obstruction are observed as early as 1 month post transplantation, while strictures tend to occur later, one of the likely reasons for this discordant finding.[15, 26] These findings are however still consistent with

the reported incidence of 10-25% of biliary complications following liver transplantation in developed countries.[19-25]

Hepatic artery thrombosis (HAT), the most frequent vascular complication (8%), parallels findings from the decade retrospective review performed at WDGMC.[4] The decade review reports an incidence of 5.3% of early HAT, which accounts for majority of vascular complications (17.5%).[4] Early HAT is defined as 0-100 days post-transplant in this decade-review.[4] A systematic review of 77 studies from developed and developing countries reports a lower incidence (2.9%) of early HAT (defined as the first 60 days) in adult liver transplant recipients.[27] The age references for paediatric and adult populations are not clearly defined in the systematic review.[27] This systematic review acknowledges a higher incidence of early HAT to occur in DDLT vs. LDLT, the latter being the major representation of trials reviewed.[27] The decade review performed in Cape Town, which includes both adult and paediatric groups, also revealed a low incidence of HAT (3.4%).[10] Despite DDLT being the only type of transplant performed in this study, the low incidence of early HAT is attributed to microsurgical techniques, routine post-transplant thrombo-embolism prophylaxis and the administration of aspirin in the paediatric population.[10]

This study reveals a 51% incidence of AKI post transplantation, consistent with studies from the USA, which report an incidence of 5-50% .[7,28] The incidence of renal complications was much lower (3.54%) in the retrospective decade-review at WDGMC, accounting for recipients with AKI requiring haemodialysis only,[4] considerably lower than this study's incidence of recipients requiring haemodialysis due to AKI (23%). Twenty two percent of recipients developed renal complications (AKI) secondary to sepsis. Bacterial infections are highly anticipated in the first month following liver transplantation, a time frame consistent to this study.[4,10] Sepsis leading to haemodynamic instability, hypoperfusion and acute tubular necrosis remain important contributors of renal complications,[3,7,12,14-16] highlighted in this study. Complications other than AKI requiring dialysis, aetiology of renal dysfunction and CNI toxicity requiring change in immunosuppressive therapy remain unreported by the decade review.[4] Twenty five percent of recipients with renal complications had underlying DM, an association that did not prove statistically significant to this study.

The small sample size appears to be one of the greatest limitations in proving statistical significance between the presence of DM and renal dysfunction.

Findings of respiratory complications are inconsistent between this study and the decade-review done at WDGMC.[4] This study's higher incidence of respiratory complications (37%) is predominantly attributed to pleural effusions, whilst the 6.8% incidence of respiratory complications noted in the WDGMC decade-review are a result of thromboembolism, as well as unspecified aetiologies requiring ventilation.[4] The lack of extensive categorical data in other studies limits data comparison to this comprehensive descriptive study.

Larger cohort studies demonstrate an incidence of 10-70% of acute rejection,[2] findings much higher than this study (4%) and the WDGMC decade review (11.7%).[4] Liver biopsies were not routinely performed during this study's period of review, with the presumptive diagnosis of acute rejection based on clinical and biochemical findings (liver function tests and international normalized ratio). Importantly, this study's limitations include its duration of review, recipients who have normal biochemistry despite possible underlying ACR and the time frame (0-90d) of the globally accepted definition of ACR. [4,8]

Bacterial infections as the predominant cause of infection in this study, within the first month post transplantation, concurs with literature worldwide.[1,4,5] Ten recipients (42%) of the infectious complication cohort had no specific identifiable pathogen, yet were clinically suspected to have infections. Sepsis with multi-organ failure was present in all cases of death in this cohort (8%). Fungal sepsis was considered to play a role in these patients with early mortality, based on positive beta-d-glucan serology and the poor response to broad spectrum antibiotics. However, this was not confirmed microbiologically and post mortem reports are unavailable to confirm the authors' suspicion of systemic fungal sepsis. The clinical limitation to accurately diagnose and microbiologically confirm life-threatening infections in recipients post solid organ transplantation remains an ongoing challenge.

Both South African studies reviewing outcomes over a 10-year period reveal a predominance of bacterial infections over viral and fungal infections.[4,10] This differs

with the well documented emergence of viral and fungal infections seen more commonly following 1 month after transplantation.[1,5] The findings of this study concur with international studies, reporting the commonest sites of infection as abdominal and lung in the first month post transplantation.[3,6] The frequent complication of bacteraemia following infection in these particular sites is also comparable to this cohort.[3,6] In this study, 67% of all infections are intra-abdominal, 25% skin and soft tissue and 25% lower respiratory tract infections. Interestingly, 83% of all skin and soft tissue infections were reported to originate from the surgical abdominal wound, consistent with international reports.[3,6] Furthermore, in keeping with international data,[3,6] 60% of all cases of bacteraemia have an intra-abdominal source of infection, whilst 20% have a lower respiratory source and the remaining 20% due to urinary tract infections.

Despite extensive documentation of the direct association between bacterial infections in the first month post transplantation and DM, hypoalbuminaemia, CMV seropositivity and donor derived infections, [1,5,11,15] this study could not confirm this association. However, ascites appears to negatively predict recipient and graft survival (P value 0.011 and hazard ratio 3.06) in the retrospective decade review done at WDGMC.[4] It is the author's assertion that the small sample size is a probable limitation of this retrospective review.

This cohort revealed a mortality of 8% of all recipients at 30 days post-transplant, unfortunately without access to post mortem reports. The trend toward improving survival, with decreasing death as time progresses is comparable to both local and international data.[4] The 30day period of review provides limitation for comparisons of recipient survival to other studies.

Conclusion

This comprehensive report from Africa documents all complications occurring within 30 days post liver transplantation in adult recipients.

Non-infectious complications occurred more commonly than infectious complications in the first 30 days post DDLT. There was no significant association between any demographic variables (age, gender), underlying ascites, diabetes mellitus and CMV status and complications.

Way forward

Despite the limitations of this study, these findings add valuable epidemiological information to the paucity of data that exists on complications in adult liver transplant recipients in sub-Saharan South Africa, particularly in the intensive care unit. Future plans include a larger prospective review over a longer time frame, with attention to causes of mortality, with the aim of deriving morbidity and/or mortality indices/scores to provide better outcomes for DDLT recipients.

Acknowledgements

Nil.

Disclosure statement

The authors have no conflict of interest to declare.

Figure 1

Indication for liver transplant

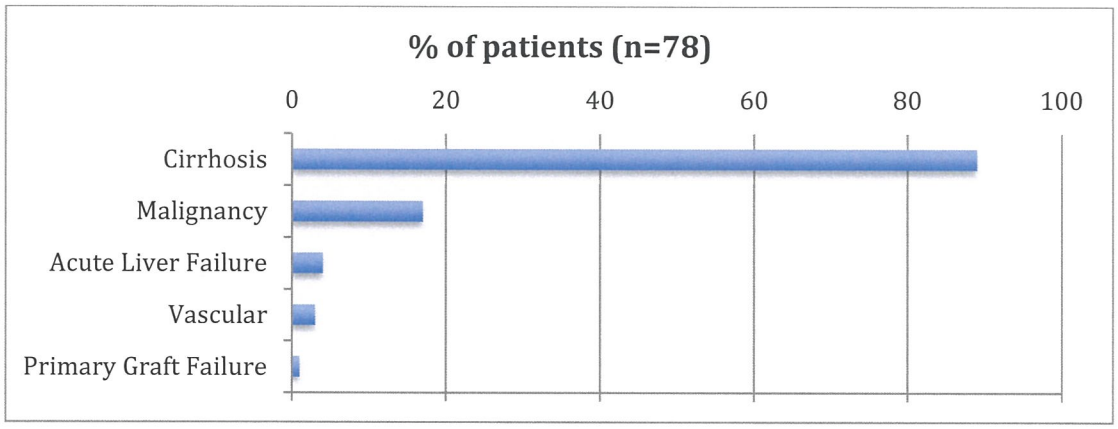


Figure 2

Non-infectious vs. Infectious Complications post-OLT

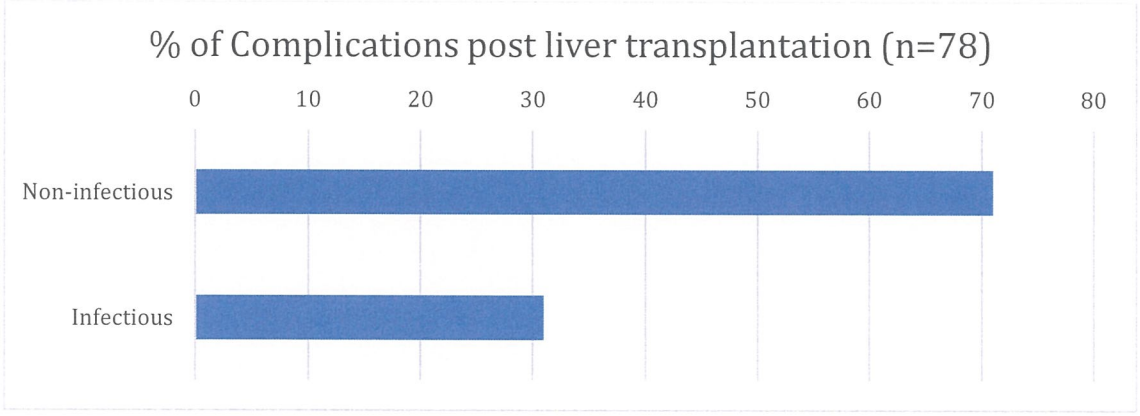


Figure 3

Primary site of infection

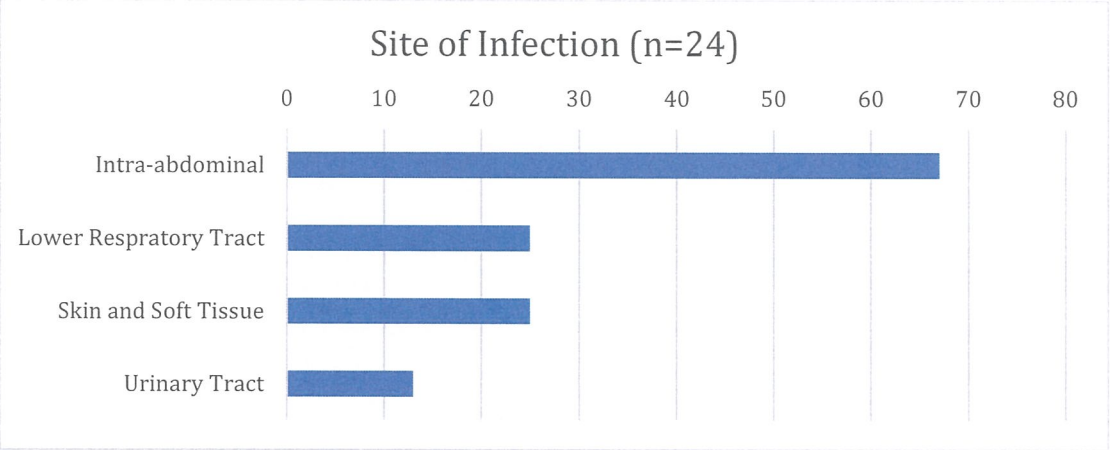


Figure 4

Culture proven pathogens causing infectious complications

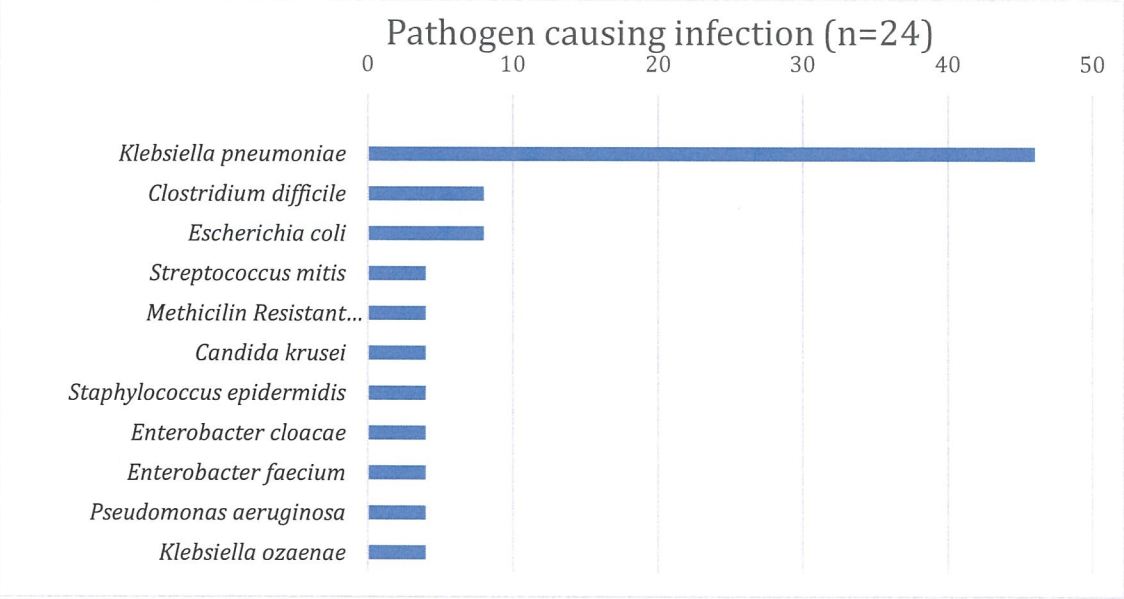


Figure 5

Non-infectious complications post-OLT

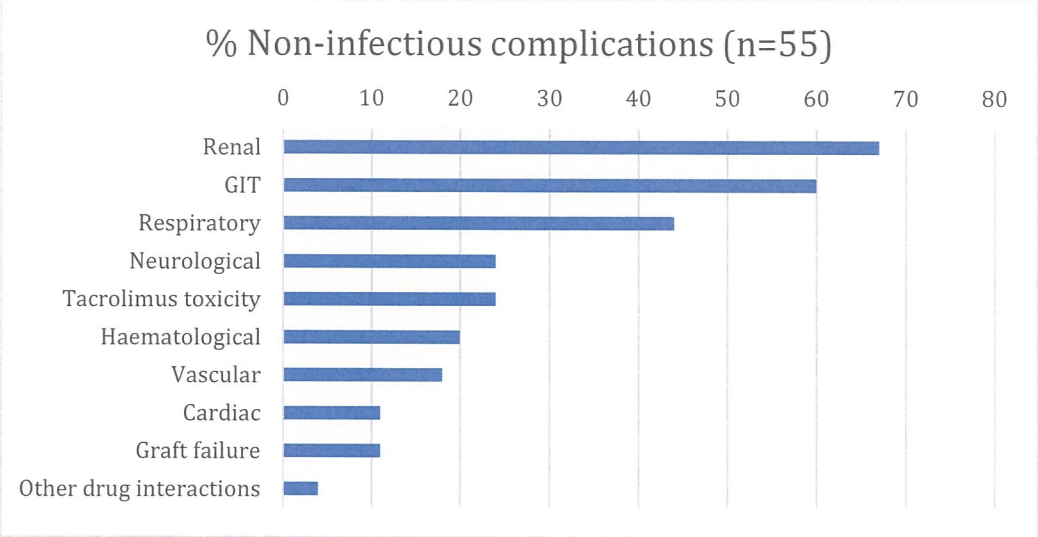


Figure 6

Renal complications post-OLT

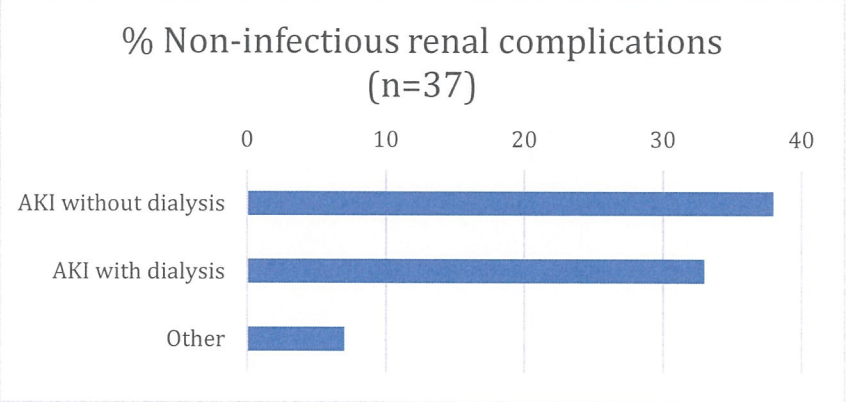


Figure 7

GIT complications post-OLT

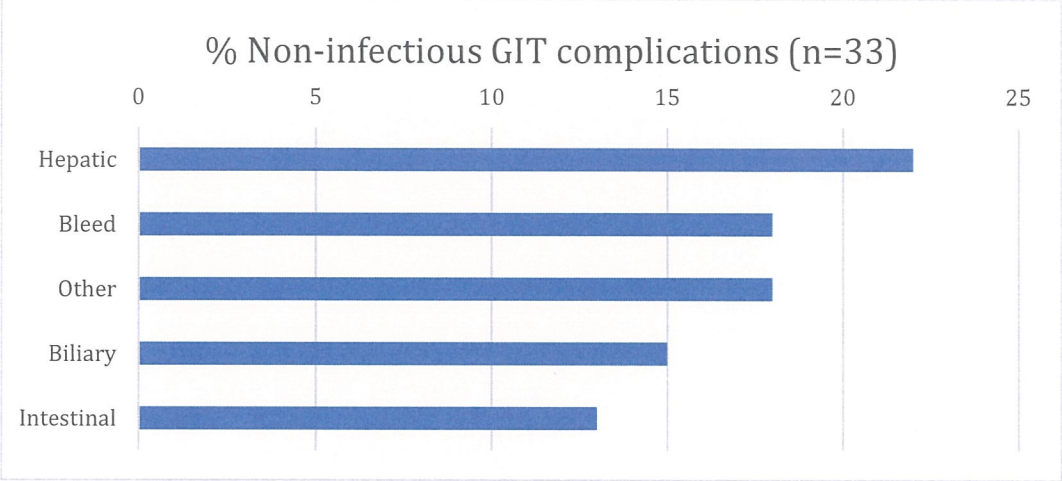


Figure 8

Respiratory complications post-OLT

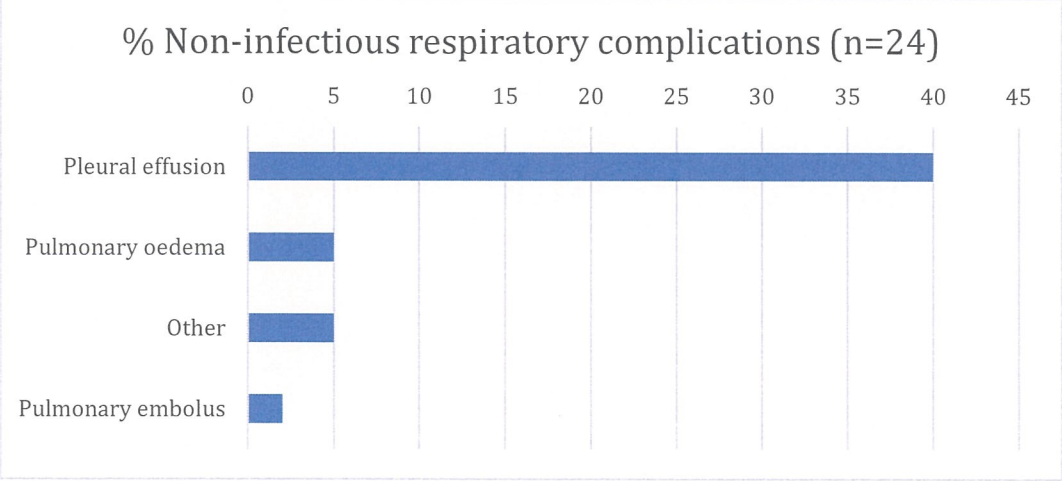
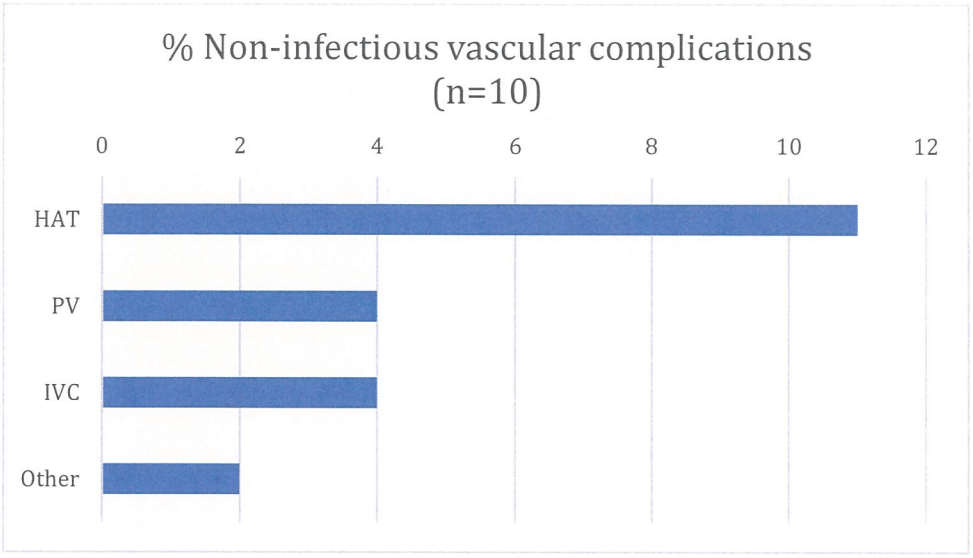


Figure 9

Vascular complications post-OLT



Reference: HAT- Hepatic Artery Thrombosis

PV- Portal Vein

IVC- Inferior vena Cava

Figure 10

Presence of comorbidity in respective cohort

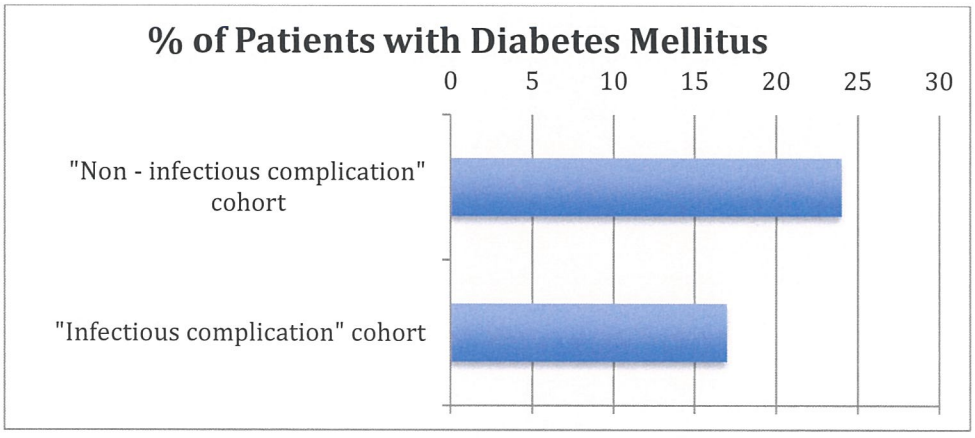


Figure 11

Relationship between continuous variables and the presence/absence of infectious and non-infectious complications

Variable	Group	N	Mean	Std Dev	Median	Interquartile range		Minimum	Maximum	p-value for between-group test
Age	Overall	78	49,1	13,8	54	39	60	19	74	
	Infectious complication - no	54	50,5	12,6	56	40	60	22	74	0,33
	Infectious complication - yes	24	46,0	16,0	47	33	60	19	68	
	Non-infectious complication - no	15	52,4	13,1	56	42	63	27	68	0,29
	Non-infectious complication - yes	63	48,3	14,0	49	38	60	19	74	
Pre-transplant MELD scor	Overall	78	20,0	7,4	20	15	24	6	41	
	Infectious complication - no	54	19,4	7,4	19	14	24	6	41	0,22
	Infectious complication - yes	24	21,4	7,3	22	16	25	7	38	
	Non-infectious complication - no	15	18,1	6,1	17	15	22	7	31	0,28
	Non-infectious complication - yes	63	20,4	7,6	21	15	25	6	41	

Figure 12

Relationship between categorical variables and the presence/absence of infectious and non-infectious complications

		Overall		Infectious complication				p-value for between-group test	Non-infectious complication				p-value for between-group test
				No		Yes			No		Yes		
Variable	Category	n	%	n	%	n	%		n	%	n	%	
n		78		54		24			15		63		
Gender	Female	28	36	19	35	9	38	>0.99	5	33	23	37	>0.99
	Male	50	64	35	65	15	63		10	67	40	63	
Ascites	No	42	54	29	54	13	54	>0.99	9	60	33	52	0,77
	Yes	36	46	25	46	11	46		6	40	30	48	
Type 2 Diabetes	No	59	76	39	72	20	83	0,40	11	73	48	76	>0.99
	Yes	19	24	15	28	4	17		4	27	15	24	
Active Hepatitis A in recipient	Negative	76	97	52	96	24	100	>0.99	15	100	61	97	>0.99
	Positive	2	3	2	4	0	0		0	0	2	3	
Hepatitis B in recipient	Negative	69	88	47	87	22	92	0,71	14	93	55	87	>0.99
	Positive	9	12	7	13	2	8		1	7	8	13	
Hepatitis C in recipient	Negative	76	97	53	98	23	96	0,52	15	100	61	97	>0.99
	Positive	2	3	1	2	1	4		0	0	2	3	

References

1) Romero FA, Razonable RR. Infections in liver transplant recipients. World J Hepatol. 2011;3(4):83-92.

2) Bartlett AS, Ramadas R, Furness S, et al. The natural history of acute histologic rejection without biochemical graft dysfunction in orthotopic liver transplantation: A systematic review. Liver Transpl. 2002;8:1147–53.

3) Kusne S, Dummer JS, Singh N, et al. Infections after liver transplantation. An analysis of 101 consecutive cases. Medicine. 1998;67(2):132-43.

4) Bentley A, Song E, Fabian J, et al. Outcomes of the First Ten Years of Adult Deceased Donor Liver Transplantation at Wits Donald Gordon Medical Centre. In press.

5) Blair JE, Kusne S. Bacterial, Mycobacterial, and Protozoal Infections after Liver Transplantation-Part I. Liver Transpl. 2005;11(12):1452-59.

6) Singh N, Wagener MM, Obman A, et al. Bacteremias in liver transplant recipients: shift toward gram-negative bacteria as predominant pathogens. Liver Transpl. 2004;10(7):844-49.

7) Paramesh, AS, Roayaie S, Doan Y, et al. Post-liver transplant acute renal failure: factors predicting development of end-stage renal disease. Clinical Transplantation. 2004;18: 94–9.

8) Levitsky J, Goldberg D, Smith AR, et al. Acute Rejection Increases Risk of Graft Failure and Death in Recent Liver Transplant Recipients. Clin Gastroenterol Hepatol. 2017;15:584.

9) Zuckerman M, Loveland J. Selection and work-up for liver transplantation. SAMJ. 2012;102(11):876-8.

10) Botha J, Spearman C, Millar A, et al. Ten years of liver transplantation at Groote Schuur Hospital. SAMJ. 2000;90(9):880-3.

11) Hernandez MDP, Martin P, Simkins J. Infectious Complications After Liver Transplantation. Gastroenterol Hepatol. 2015;11(11):741-53.

12) Laish I, Braun M, Mor E, et al. Metabollic syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. Liver Transpl. 2011;17(1):15-22.

13) Razonable RR, Findlay JY, O'Riordan A, et al. Critical Care Issues in Patients After Liver Transplantation. Liver Transpl. 2011;17:511-27.

14) Madhwal S, Atreja A, Albeldawi M, et al. Is Liver Transplantation a Risk Factor for Cardiovascular Disease? A Meta-Analysis of Observational Studies. Liver Transpl. 2012;18:1140-46.

15) Feltracco P, Barbieri S, Galligioni H, et al. Intensive care management of liver transplanted patients. World J Hepatol. 2011;3(3):61-71.

16) Gisbert C, Prieto M, Berenguer M. et al. Hyperlipidemia in Liver Transplant Recipients: prevalence and risk factors. Liver Transpl Surg. 1997;3:416.

17) Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015;148:547.

18) Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. Am Fam Physician. 2006;54:756-62.

19) Stratta RJ, Wood RP, Langnas AN, et al. Diagnosis and treatment of biliary tract complications after orthotopic liver transplantation. Surgery. 1989;106(4):675-84.

20)Greif F, Bronsther OL, Van Thiel DH, et al. The incidence, timing, and management of biliary tract complications after orthotopic liver transplantation. Ann Surg. 1994; 219:40.

21) Rerknimitr R, Sherman S, Fogel EL, et al. Biliary tract complications after orthotopic liver transplantation with choledochocholedochostomy anastomosis: endoscopic findings and results of therapy. Gastrointest Endosc. 2002; 55:224.

22) Pfau PR, Kochman ML, Lewis JD, et al. Endoscopic management of postoperative biliary complications in orthotopic liver transplantation. Gastrointest Endosc. 2000; 52:55.

23) Thuluvath PJ, Atassi T, Lee J. An endoscopic approach to biliary complications following orthotopic liver transplantation. Liver Int. 2003; 23:156.

24) Thethy S, Thomson BNj, Pleass H, et al. Management of biliary tract complications after orthotopic liver transplantation. Clin Transplant. 2004; 18:647.

25) Seehofer D, Eurich D, Veltzke-Schlieker W, et al. Biliary complications after liver transplantation: old problems and new challenges. Am J Transplant. 2013;13:253.

26) Thuluvath PJ, Pfau PR, Kimmey MB et al. Biliary complications after liver transplantation: the role of endoscopy. Endoscopy 37. 2005;37:857.

27) Bekker J, Ploem S, De Jong, KP. Early Hepatic Artery Thrombosis after Liver Transplantation: A Systematic Review of the Incidence, Outcome and Risk Factors. American Journal of Transplantation. 2009;9:746–57.

28) Corman, SL, Coley KC, Schonder KS. Effect of Long-term Tacrolimus Immunosuppression on Renal Function in Liver Transplant Recipients. Pharmacotherapy. The Journal of Human Pharmacology and Drug Therapy. 2006;26:1433–37.

29) Liu X, Ling Z Li L et al. Invasive fungal infections in liver transplantation. Int J Infect Dis. 2011;15(5):298-304.

30) Leekha S, Terrell C, Edson RS. General Principles of Antimicrobial Therapy. Mayo Clin Proc. 2011;86(2):156-67.

31) Centres for Disease Control and Prevention (2017). Sepsis 1 CDC. [online] Available at: http://cdc.gov/sepsis/index.html.

32) Le MH, Devaki P, Ha NB, et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States. PLoS One. 2017;12(3):e0173499.

33) T Puoane, K Steyn, D Bradshaw, et al. Obesity in South Africa: The South African Demographic and Health Survey. 2002;10:1038–48.

CHAPTER 3 APPENDICES

1.1 Liver Transplant Protocol

Appendix A

Wits University Donald Gordon Medical Centre

Adult Liver Transplant Protocol

Pre-op:

- **No patient to be accepted without prior discussion with ICU consultant and nursing shift leader (to ensure bed availability and intensivist cover)**
- **Inform Blood bank (5666) of transplant and of patient's Blood Group (find out from transplant co-ordinator)**
- **Admission bloods: FBC, U&E, CMP, random Glucose, LFT, PI/PTT, CRP, PCT, Fibrinogen, Compat**
- **Order 10units Packed cells (leukodepleted), 10units FFP, and 3 Mega-units Platelets as Red Label Blood stat (Trenstar 5999)**
- **CXR, ECG**
- **NPO**
- **Consent**
- **Get patients` Transplant File from transplant co-ordinator**

Intra-op:

- **Induction of immunosuppression with Zenepax 75mg IV STAT + Solumedrol 1g IV STAT on induction**

Post-op:

- **Often ventilated due to acidosis and high lactates. Start with BILEVEL ventilation (PEEP=10, TV=6-8ml/kg). Change to Spontaneous Assisted Breathing as soon as patient is awake and responsive. Extubate when metabolically and haemodynamically stable.**
- **Run 1L 5% D/W with 150ml 8,5% Sodabic (if acidotic), or Balsol (if not acidotic and normal potassium) at 100ml/hr**
- **Stress Ulcer prophylaxis with Nexiam 40 mg IV BD**
- **Morphine titration for pain (NO Perfalgan or NSAIDS)**
- **Dipeptivan 100mg IV BD over 4 hrs each**
- **Albusol 20% IV @ 10-20 ml/hr**
- **Fluid bolus (use Voluven) and/or Dobs if MAP <70 mmHg**
- **Hourly HGT and insulin infusion**
- **4 hourly ABG**
- **Start maintenance immunosuppression:**
    - **Solu-Medrol 40mg IV QID – wean steroids over 5-6 days down to Prednisone/Methylprednisolone 40mg daily**

    - **Prograf 1mg NGT/PO BD - Adjust Prograf dose daily to achieve Tacrolimus trough levels of 6-8.**
    - **Cellcept 1g IV BD – change to oral Cellecept 1g PO BD**
    - **Repeat Zenepax 75mg IV on D5**
- **Prophylaxis:**
    - **Valcyte 450mg PO BD (*not* NGT)**
    - **Bactrim 1 tab PO dly**
    - **Fluconazole 200mg IV/PO dly**

1.2 CDC/NHSN DEFINITION AND CRITERIA FOR SEPSIS

CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting

Teresa C. Horan, MPH, Mary Andrus, RN, BA, CIC, and Margaret A. Dudeck, MPH

Atlanta, Georgia

CDC/NHSN SURVEILLANCE DEFINITION OF HEALTH CARE–ASSOCIATED INFECTION

For the purposes of NHSN surveillance in the acute care setting, the CDC defines an HAI as a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s). There must be no evidence that the infection was pre- sent or incubating at the time of admission to the acute care setting.

HAIs may be caused by infectious agents from endogenous or exogenous sources.

d Endogenous sources are body sites, such as the skin, nose, mouth, gastrointestinal (GI) tract, or vagina that are normally inhabited by microorganisms.

d Exogenous sources are those external to the patient, such as patient care personnel, visitors, patient care equipment, medical devices, or the health care environment.

Other important considerations include the following:

d Clinical evidence may be derived from direct observation of the infection site (eg, a wound) or review of information in the patient chart or other clinical records.SEPd For certain types of infection, a physician or surgeon diagnosis of infection derived from direct observation during a surgical operation, endoscopic examination, or other diagnostic studies or from clinical judgment is an acceptable criterion for an HAI, unless there is compelling evidence to the contrary. For example, one of the criteria for SSI is ''surgeon or attending physician diagnosis.'' Unless stated explicitly, physician diagnosis alone is not an acceptable criterion for any specific type of HAI.

d The following infections are not considered health care associated:

s Infections associated with complications or extensions of infections already present on admission, unless a change in pathogen or symptoms strongly suggests the acquisition of a new infection;

d The following conditions are not infections:SEPs Colonization, which means the presence of microorganisms on skin, on mucous membranes, in open wounds, or in excretions or secretions but are not causing adverse clinical signs or symptoms; andSEP inflammation that results from tissue response to injury or stimulation by noninfectious agents, such as chemicals.

Table 1. CDC/NHSN major and specific types of health care–associated infections

UTI Urinary tract infection

SUTI Symptomatic urinary tract infection

ASB Asymptomatic bacteriuria OUTI Other infections

of the urinary tract

SSI Surgical site infection

SIP Superficial incisional primary SSI

SIS Superficial incisional secondary SSI

DIP Deep incisional primary SSI

DIS Deep incisional secondary SSI

Organ/space Organ/space SSI. Indicate specific type:

Eye, ear, nose, throat, or mouth infection

CONJ Conjunctivitis EYE Eye, other than conjunctivitis EAR Ear, mastoid

ORAL Oral cavity (mouth, tongue, or gums)

SINU Sinusitis UR Upper respiratory

tract, pharyngitis, laryngitis, epiglottitis

Gastrointestinal system infection

GE Gastroenteritis

GIT Gastrointestinal (GI) tract

HEP Hepatitis IAB Intraabdominal, not specified elsewhere

NEC Necrotizing enterocolitis

Lower respiratory tract infection, other than pneumonia

BRON Bronchitis, tracheobronchitis, tracheitis, without evidence of pneumonia

LUNG Other infections of the lower respiratory tract

Reproductive tract infection

EMET Endometritis EPIS Episiotomy VCUF Vaginal cuff OREP Other infections

of the male or female reproductive tract

Skin and soft tissue infection

SKIN Skin

ST Soft tissue

DECU Decubitus ulcer

BURN Burn

BRST Breast abscess or mastitis

UMB Omphalitis

PUST Pustulosis CIRC Newborn circumcision

Systemic Infection

DI Disseminated infection

LCBI Laboratory-confirmed bloodstream infection

CSEP Clinical sepsis

PNEU Pneumonia

. PNU1 Clinically defined pneumonia

. PNU2 Pneumonia with specific laboratory findings

. PNU3 Pneumonia in immunocompromised patient

BJ Bone and joint infection

BONE Osteomyelitis JNT Joint or bursa DISC Disc space

CNS Central nervous system

IC Intracranial infection

MEN Meningitis or ventriculitis

SA Spinal abscess without meningitis

CVS Cardiovascular system infection

VASC Arterial or venous infection ENDO Endocarditis CARD Myocarditis or pericarditis MED Mediastinitis

CRITERIA FOR SPECIFIC TYPES OF INFECTION

Once an infection is deemed to be health care associated according to the definition shown above, the specific type of infection should be determined based on the criteria

detailed below. These have been grouped into 13 major type categories to facilitate data analysis. For example, there are 3 specific types of urinary tract infections (symptomatic urinary tract infection, asymptomatic bacteriuria, and other infections of the urinary tract) that are grouped under the major type of Urinary Tract Infection. The specific and major types of infection used in NHSN and their abbreviated codes are listed in Table 1, and the criteria for each of the specific types of infection follow it.

UTI-URINARY TRACT INFECTION SUTI-Symptomatic urinary tract infection

A symptomatic urinary tract infection must meet at least 1 of the following criteria:

1. Patient has at least 1 of the following signs or symptoms with no other recognized cause: fever (.388C), urgency, frequency, dysuria, or suprapubic tenderness and patient has a positive urine culture, that is, 10^5 microorganisms per cc of urine with no more than 2 species of microorganisms.

2. Patient has at least 2 of the following signs or symptoms with no other recognized cause: fever (388C), urgency, frequency, dysuria, or suprapubic tenderness

and at least 1 of the following

1 positive dipstick for leukocyte esterase and/ or nitrate

2 pyuria (urine specimen with $10 white blood cell [WBC]/mm^3 or $3 WBC/high-power field of unspun urine)

3 organisms seen on Gram's stain of unspun urine

4 at least 2 urine cultures with repeated isolation of the same uropathogen (gram-negative bacteria or Staphylococcus saprophyticus) with 10^2 colonies/mL in non- voided specimens

5 #10^5 colonies/mL of a single uropathogen (gram-negative bacteria or S saprophyticus) in a patient being treated with an effective antimicrobial agent for a urinary tract infection

f. physician diagnosis of a urinary tract infection

g. physician institutes appropriate therapy for a urinary tract infection.

BSI-BLOODSTREAM INFECTION

LCBI-Laboratory-confirmed bloodstream infection

LCBI criteria 1 and 2 may be used for patients of any age, including patients #1 year of age.

LCBI must meet at least 1 of the following criteria:

1. Patient has a recognized pathogen cultured from 1 or more blood

cultures and organism cultured from blood is not related to an infection at another site. (See Notes 1 and 2.)

2. Patient has at least 1 of the following signs or symptoms: fever (.388C), chills, or

hypotension and signs and symptoms and positive laboratory results are not related to an infection at another site and common skin contaminant (ie, diphtheroids [Corynebacterium spp], Bacillus [not B anthracis] spp, Propionibacterium spp, coagulase-negative staphylococci [including S epidermidis], viridans group streptococci, Aerococcus spp, Micrococcus spp) is cultured from 2 or more blood cultures drawn on separate occasions. If common skin contaminant organisms from the cultures are speciated but no anti- biograms are done or they are done for only 1 of the isolates, it is assumed that the organisms are the same. If the common skin contaminants from the cultures have antibiograms that are different for 2 or more antimicrobial agents, it is assumed that the organisms are not the same. For the purpose of NHSN antibiogram reporting, the category interpretation of inter- mediate (I) should not be used to distinguish whether 2 organisms are the same.

CSEP-CLINICAL SEPSIS

CSEP may be used only to report primary BSI in neonates and infants. It is not used to report BSI in adults and children.

PNEU-PNEUMONIA

There are 3 specific types of pneumonia: clinically defined pneumonia (PNU1), pneumonia with specific laboratory findings (PNU2), and pneumonia in immunocompromised patients (PNU3). Listed below are general comments applicable to all specific types of pneumonia, along with abbreviations used in the algorithms and reporting instructions. Table 8 shows threshold values for cultured specimens used in the surveillance diagnosis of pneumonia.

BJ–BONE AND JOINT INFECTION BONE-Osteomyelitis

Osteomyelitis must meet at least 1 of the following criteria:

1. Patient has organisms cultured from bone.

2. Patient has evidence of osteomyelitis on direct examination of the bone during a surgical operation or histopathologic examination.

3. Patient has at least 2 of the following signs or symptoms with no other recognized cause: fever (.388C), localized swelling, tenderness, heat, or drainage at suspected site of bone infection and at least 1 of the following: a. organisms cultured from blood b. positive blood antigen test (eg, H influenzae, S pneumoniae)

JNT-Joint or bursa

Joint or bursa infections must meet at least 1 of the following criteria:

1. Patient has organisms cultured from joint fluid or synovial biopsy.

2. Patient has evidence of joint or bursa infection seen during a surgical operation or histopathologic examination.

3. Patient has at least 2 of the following signs or symptoms with no other recognized cause: joint pain, swelling, tenderness, heat, evidence of effusion or limitation of motion and at least 1 of the following:

a. organisms and white blood cells seen on Gram's stain of joint fluid

b. positive antigen test on blood, urine, or joint fluid

c. cellular profile and chemistries of joint fluid compatible with infection and not explained by an underlying rheumatologic disorder

d. radiographic evidence of infection (eg, abnormal findings on x-ray, CT scan, MRI, radiolabel scan [gallium, technetium, etc]).

DISC-Disc space infection

Vertebral disc space infection must meet at least 1 of the following criteria:

1. Patient has organisms cultured from vertebral disc space tissue obtained during a surgical operation or needle aspiration.

2. Patient has evidence of vertebral disc space infection seen during a surgical operation or histopathologic examination.

3. Patient has fever (.388C) with no other recognized cause or pain at the involved vertebral disc space and radiographic evidence of infection, (eg, abnormal findings on x-ray, CT scan, MRI, radiolabel scan [gallium, technetium, etc]).

CNS-CENTRAL NERVOUS SYSTEM INFECTION

IC-Intracranial infection (brain abscess, subdural or epidural infection, encephalitis)

Intracranial infection must meet at least 1 of the following criteria:

1. Patient has organisms cultured from brain tissue or dura.

2. Patient has an abscess or evidence of intracranial infection seen during a surgical operation or histopathologic examination.

3. Patient has at least 2 of the following signs or symptoms with no other recognized cause: head- ache, dizziness, fever (.388C), localizing neurologic signs, changing level of consciousness, or confusion and at least 1 of the following:

a. organisms seen on microscopic examination of brain or abscess tissue obtained by needle aspiration or by biopsy during a surgical operation

or autopsy

b. positive antigen test on blood or urine

c. radiographic evidence of infection, (eg, abnormal findings on ultrasound, CT scan, MRI, radionuclide brain scan, or arteriogram)

d. diagnostic single antibody titer (IgM) or 4- fold increase in paired sera (IgG) for pathogen

4. and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

a. organisms seen on microscopic examination of brain or abscess tissue obtained by needle aspiration or by biopsy during a surgical operation or autopsy

b. positive antigen test on blood or urine c. radiographic evidence of infection, (eg, abnormal findings on ultrasound, CT scan, MRI, radionuclide brain scan, or arteriogram) d. diagnostic single antibody titer (IgM) or 4- fold increase in paired sera (IgG) for pathogen and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

MEN-Meningitis or ventriculitis

Meningitis or ventriculitis must meet at least 1 of the following criteria:

1. Patient has organisms cultured from cerebrospinal fluid (CSF).

2. Patient has at least 1 of the following signs or symptoms with no other recognized cause: fever (.388C), headache, stiff neck, meningeal signs, cranial nerve signs, or irritability and at least 1 of the following:

a. increased white cells, elevated protein, and/ or decreased glucose in CSF

b. organisms seen on Gram's stain of CSF c. organisms cultured from blood d. positive antigen test of CSF, blood, or urine e. diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

SA-Spinal abscess without meningitis

An abscess of the spinal epidural or subdural space, without involvement of the cerebrospinal fluid or adjacent bone structures, must meet at least 1 of the following criteria:

1. Patient has organisms cultured from abscess in the spinal epidural or subdural space.

2. Patient has an abscess in the spinal epidural or subdural space seen during a surgical operation or at autopsy or evidence of an abscess seen during a histopathologic examination.

3. Patient has at least 1 of the following signs or symptoms with no other recognized cause: fever (.388C), back pain, focal tenderness, radiculitis, paraparesis, or paraplegia and at least 1 of the following:

a. organisms cultured from blood

b. radiographic evidence of a spinal abscess (eg, abnormal findings on myelography, ultrasound, CT scan, MRI, or other scans [gallium, technetium, etc]).

VASC-Arterial or venous infection

Arterial or venous infection must meet at least 1 of the following criteria:

1. Patient has organisms cultured from arteries or veins removed during a surgical operation and blood culture not done or no organisms cultured from blood.

2. Patient has evidence of arterial or venous infection seen during a surgical operation or histopathologic examination.

3. Patient has at least 1 of the following signs or symptoms with no other recognized cause: fever (.388C), pain, erythema, or heat at involved vascular site and more than 15 colonies cultured from intravascular cannula tip using semiquantitative culture method and blood culture not done or no organisms cultured from blood.

4. Patient has purulent drainage at involved vascular site and blood culture not done or no organisms cultured from blood.

ENDO-Endocarditis

Endocarditis of a natural or prosthetic heart valve must meet at least 1 of the following criteria:

1. Patient has organisms cultured from valve or vegetation.

2. Patient has 2 or more of the following signs or symptoms with no other recognized cause: fever (.388C), new or changing murmur, embolic phenomena, skin manifestations (ie, petechiae, splinter hemorrhages, painful subcutaneous nodules), congestive heart failure, or cardiac conduction abnormality and at least 1 of the following:

a. organisms cultured from 2 or more blood cultures

b. organisms seen on Gram's stain of valve when culture is negative or not done

c. valvular vegetation seen during a surgical operation or autopsy

d. positive antigen test on blood or urine (eg, H influenzae, S pneumoniae, N meningitidis, or Group B Streptococcus) and

e. evidence of new echocardiogram and vegetation seen on

CARD-Myocarditis or pericarditis

Myocarditis or pericarditis must meet at least 1 of the following criteria:

1. Patient has organisms cultured from pericardial tissue or fluid obtained by needle aspiration or during a surgical operation.

2. Patient has at least 2 of the following signs or symptoms with no other recognized cause: fever (.388C), chest pain, paradoxical pulse, or in- creased heart size at least 1 of the following:a. abnormal EKG consistent with myocarditis or pericarditisb. positive antigen test on blood (eg, H influenzae, S pneumoniae)

3. c. histologic examination of heart tissue shows evidence of myocarditis or pericarditisd. 4-fold rise in type-specific antibody with or without isolation of virus from pharynx or fecese. pericardial effusion identified by echocardiogram, CT scan, MRI, or angiography.

At least 1 of the following:a. abnormal EKG consistent with myocarditis or pericarditisb. positive antigen test on blood (eg, H influenzae, S pneumoniae) evidence of myocarditis or pericarditis on histologic examination of heart tissued. 4-fold rise in type-specific antibody with or without isolation of virus from pharynx or fecese. pericardial effusion identified by echocardiogram.

MED-Mediastinitis

Mediastinitis must meet at least 1 of the following criteria:

Patient has organisms cultured from mediastinal tissue or fluid obtained during a surgical opera- tion or needle aspiration. Patient has evidence of mediastinitis seen during a surgical operation or histopathologic examination. Patient has at least 1 of the following signs or symptoms with no other recognized cause: fever (.388C), chest pain, or sternal instability and atleast 1 of the following:

a. purulent discharge from mediastinal area

b. organisms cultured from blood or discharge from mediastinal area

c. mediastinal widening on x-ray.4.

EENT-EYE, EAR, NOSE, THROAT, OR MOUTH INFECTION

CONJ-Conjunctivitis

Conjunctivitis must meet at least 1 of the following criteria:

1. Patient has pathogens cultured from purulent exudate obtained from the conjunctiva or contiguous tissues, such as eyelid, cornea, meibomian glands, or lacrimal glands.

2. Patient has pain or redness of conjunctiva or around eye and at least 1 of the following:

a. WBCs and organisms seen on Gram's stain of exudate

b. purulent exudate c. positive antigen test (eg, ELISA or IF for Chlamydia trachomatis, herpes simplex virus, adenovirus) on exudate or conjunctival scraping

d. multinucleated giant cells seen on microscopic examination of conjunctival exudate or scrapings

e. positive viral culture

f. diagnostic single antibody titer(IgM)or4-fold increase in paired sera (IgG) for pathogen.

EYE-Eye, other than conjunctivitis

An infection of the eye, other than conjunctivitis, must meet at least 1 of the following criteria:

1. Patient has organisms cultured from anterior or posterior chamber or vitreous fluid.

2. Patient has at least 2 of the following signs or symptoms with no other recognized cause: eye pain, visual disturbance, or hypopyon and at least 1 of the following:

a. physician diagnosis of an eye infection

b. positive antigen test on blood (eg, H influenzae, S pneumoniae)

c. organisms cultured from blood.

EAR-Ear mastoid

Ear and mastoid infections must meet at least 1 of the following criteria:

Otitis externa must meet at least 1 of the following criteria:

1. Patient has pathogens cultured from purulent drainage from ear canal.

2. Patient has at least 1 of the following signs or symptoms with no other recognized cause: fever (.388C), pain, redness, or drainage from ear canal and organisms seen on Gram's stain of purulent drainage.

Otitis media must meet at least 1 of the following criteria:

1. Patient has organisms cultured from fluid from middle ear obtained by tympanocentesis or at surgical operation.

2. Patient has at least 2 of the following signs or symptoms with no other recognized cause: fever (.388C), pain in the eardrum, inflammation, re- traction or decreased mobility of eardrum, or fluid behind eardrum.

UR-Upper respiratory tract, pharyngitis, laryngitis, epiglottitis

Upper respiratory tract infections must meet at least 1 of the following criteria:

1. Patient has at least 2 of the following signs or symptoms with no other recognized cause: fever (.388C), erythema of pharynx, sore throat, cough, hoarseness, or purulent exudate in throat and at least 1 of the following:a. organisms cultured from the specific siteb. organisms cultured from bloodc. positive antigen test on blood or respiratory secretionsd. diagnostic single antibody titer (IgM) or 4- fold increase in paired sera (IgG) for pathogen

2. Patient has an abscess seen on direct examina- tion, during a surgical operation, or during a histopathologic examination.

GE-Gastroenteritis

Gastroenteritis must meet at least 1 of the following criteria:

1. Patient has an acute onset of diarrhea (liquid stools for more than 12 hours) with or without vomiting or fever (.388C) and no likely noninfectious cause (eg, diagnostic tests, therapeutic regi- men other than antimicrobial agents, acute exacerbation of a chronic condition, or psycho- logic stress).

2. Patient has at least 2 of the following signs or symptoms with no other recognized cause: nau- sea, vomiting, abdominal pain, fever (.388C), or headache

and at least 1 of the following:

a. an enteric pathogen is cultured from stool or rectal swab

b. an enteric pathogen is detected by routine or electron microscopy

c. an enteric pathogen is detected by antigen or antibody assay on blood or feces

d. evidence of an enteric pathogen is detected by cytopathic changes in tissue culture (toxin assay)

e. diagnostic single antibody titer (IgM) or 4- fold increase in paired sera (IgG) for pathogen.

GIT-Gastrointestinal tract (esophagus, stomach, small and large bowel, and rectum) excluding gastroenteritis and appendicitis

Gastrointestinal tract infections, excluding gastroenteritis and appendicitis, must meet at least 1 of the fol- lowing criteria:

1. Patient has an abscess or other evidence of infection seen during a surgical operation or histopathologic examination.

2. Patient has at least 2 of the following signs or symptoms with no other recognized cause and compatible with infection of the organ or tissue involved: fever (.388C), nausea, vomiting, abdominal pain, or tenderness andat least 1 of

pathogen.

GIT-Gastrointestinal tract (esophagus, stomach, small and large bowel, and rectum) excluding gastroenteritis and appendicitis

Gastrointestinal tract infections, excluding gastroenteritis and appendicitis, must meet at least 1 of the fol- lowing criteria:

1. Patient has an abscess or other evidence of infection seen during a surgical operation or histopathologic examination.

2. Patient has at least 2 of the following signs or symptoms with no other recognized cause and compatible with infection of the organ or tissue involved: fever (.388C), nausea, vomiting, abdominal pain, or tenderness and at least 1 of the following:

a. organisms cultured from drainage or tissue obtained during a surgical operation or endoscopy or from a surgically placed drain

b. organisms seen on Gram's or KOH stain or multinucleated giant cells seen on microscopic examination of drainage or tissue obtained during a surgical operation or endoscopy or from a surgically placed drain

c. organisms cultured from blood

d. evidence of pathologic findings on radio- graphic examination

e. evidence of pathologic findings on endo scopic examination (eg, Candida esophagitis or proctitis).

HEP-Hepatitis

Hepatitis must meet the following criterion:

Patient has at least 2 of the following signs or symptoms with no other recognized cause: fever (.388C), anorexia, nausea, vomiting, abdominal pain, jaundice, or history of transfusion within the previous 3 months

And at least 1 of the following:

a. positive antigen or antibody test for hepatitis A, hepatitis B, hepatitis C, or delta hepatitis

b. abnormal liver function tests (eg, elevated ALT/ AST, bilirubin)

c. cytomegalovirus (CMV) detected in urine or oropharyngeal secretions.

Intraabdominal infections must meet at least 1 of the following criteria:

1. Patient has organisms cultured from purulent material from intraabdominal space obtained during a surgical operation or needle aspiration.

2. Patient has abscess or other evidence of intraabdominal infection seen during a surgical operation or histopathologic examination.

3. Patient has at least 2 of the following signs or symptoms with no other recognized cause: fever (.388C), nausea, vomiting, abdominal pain, or jaundice

and at least 1 of the following:

a. organisms cultured from drainage from surgically placed drain (eg, closed suction drainage system, open drain, T-tube drain)

b. organisms seen on Gram's stain of drainage or tissue obtained during surgical operation or needle aspiration

c. organisms cultured from blood and radio- graphic evidence of infection (eg, abnormal findings on ultrasound, CT scan, MRI, or ra- diolabel scans [gallium, technetium, etc] or on abdominal x-ray).

LRI-LOWER RESPIRATORY TRACT INFECTION, OTHER THAN PNEUMONIA

BRON-Bronchitis, tracheobronchitis, bronchiolitis, tracheitis, without evidence of pneumonia

Tracheobronchial infections must meet at least 1 of the following criteria:

1. Patient has no clinical or radiographic evidence of pneumonia and patient has at least 2 of the following signs or symptoms with no other recognized cause: fever (.388C), cough, new or increased sputum production, rhonchi, wheezing and at least 1 of the following: a. positive culture obtained by deep tracheal aspirate or bronchoscopy b. positive antigen test on respiratory secretions.

a. organisms cultured from material obtained by deep tracheal aspirate or bronchoscopy

b. positive antigen test on respiratory secretions

c. diagnostic single antibody titer (IgM) or 4- fold increase in paired sera (IgG) for pathogen.

PNEU-PNEUMONIA

There are 3 specific types of pneumonia: clinically defined pneumonia (PNU1), pneumonia with specific laboratory findings (PNU2), and pneumonia in immu- nocompromised patients (PNU3). Listed below are gen- eral comments applicable to all specific types of pneumonia, along with abbreviations used in the algo- rithms (Tables 4-7) and reporting instructions. Table 8 shows threshold values for cultured specimens used in the surveillance diagnosis of pneumonia. Figures 1 and 2 are flow

diagrams for the pneumonia algo- rithms that may be used as data collection tools.

LUNG-Other infections of the lower respiratory tract

Other infections of the lower respiratory tract must meet at least 1 of the following criteria:

1. Patient has organisms seen on smear or cultured from lung tissue or fluid, including pleural fluid.

2. Patient has a lung abscess or empyema seen during a surgical operation or histopathologic examination.

3. Patient has an abscess cavity seen on radiographic examination of lung.

Reporting instructions

d Report concurrent lower respiratory tract infection and pneumonia with the same organism(s) as PNEU.

d Report lung abscess or empyema without pneumonia as LUNG.

REPR-REPRODUCTIVE TRACT INFECTION EMET-Endometritis

Endometritis must meet at least 1 of the following criteria:

1. Patient has organisms cultured from fluid or tis- sue from endometrium obtained during surgical operation, by needle aspiration, or by brush biopsy.

2. Patient has at least 2 of the following signs or symptoms with no other recognized cause: fever, abdominal pain, uterine tenderness, or purulent drainage from uterus.

OREP-Other infections of the male or female reproductive tract (epididymis, testes, prostate, vagina, ovaries, uterus, or other deep pelvic tissues, excluding endometritis or vaginal cuff infections)

Other infections of the male or female reproductive tract must meet at least 1 of the following criteria:

1. Patient has organisms cultured from tissue or fluid from affected site.

2. Patient has an abscess or other evidence of infection of affected site seen during

a surgical operation or histopathologic examination.

3. Patient has 2 of the following signs or symptoms with no other recognized cause: fever (.388C), nausea, vomiting, pain, tenderness, or dysuria and at least 1 of the following: a. organisms cultured from blood b. physician diagnosis.

d Report endometritis as EMET. d Report vaginal cuff infections as VCUF.

SST-SKIN AND SOFT TISSUE INFECTION SKIN-Skin

Skin infections must meet at least 1 of the following criteria:

1. 2. Patient has purulent drainage, pustules, vesicles, or boils. Patient has at least 2 of the following signs or symptoms with no other recognized cause: pain or tenderness, localized swelling, redness, or heat and at least 1 of the following:

a. organisms cultured from aspirate or drainage from affected site; if organisms are normal skin flora (ie, diphtheroids [Corynebacterium spp], Bacillus [not B anthracis] spp, Propionibacterium spp, coagulase-negative staphylococci [including S epidermidis], viridans group streptococci, Aerococcus spp, Micrococcus spp), they must be a pure culture

b. organisms cultured from blood

c. positive antigen test performed on infected tissue or blood (eg, herpes simplex, varicella zoster, H influenzae, N meningitidis)

d. multinucleated giant cells seen on microscopic examination of affected tissue

e. diagnostic single antibody titer (IgM) or 4- fold increase in paired sera (IgG) for

pathogen.

ST-Soft tissue (necrotizing fascitis, infectious gangrene, necrotizing cellulitis, infectious myositis, lymphadenitis, or lymphangitis)

Soft tissue infections must meet at least 1 of the following criteria:

1. Patient has organisms cultured from tissue or drainage from affected site.

2. Patient has purulent drainage at affected site.

3. Patient has an abscess or other evidence of infection seen during a surgical operation or histo pathologic examination.

4. Patient has at least 2 of the following signs or symptoms at the affected site with no other recognized cause: localized pain or tenderness, red- ness, swelling, or heat and at least 1 of the following: a. organisms cultured from blood b. positive antigen test performed on blood or urine (eg, H influenzae, S pneumoniae, N meningitidis, Group B Streptococcus, Candida spp) c. diagnostic single antibody titer (IgM) or 4- fold increase in paired sera (IgG) for pathogen.

DECU-Decubitus ulcer, including both superficial and deep infections

Decubitus ulcer infections must meet the following criterion:

Patient has at least 2 of the following signs or symptoms with no other recognized

cause: redness, tender- ness, or swelling of decubitus wound edges and

at least 1 of the following:

a. organisms cultured from properly collected fluid or tissue (see Comments)

b. organisms cultured from blood.

Comments

d Purulent drainage alone is not sufficient evidence of an infection.

d Organisms cultured from the surface of a decubitus ulcer are not sufficient evidence that the ulcer is infected. A properly collected specimen from a decubitus ulcer involves needle aspiration of fluid or biopsy of tissue from the ulcer margin.

BURN-Burn

Burn infections must meet at least 1 of the following criteria:

1. Patient has a change in burn wound appearance or character, such as rapid eschar separation, or dark brown, black, or violaceous discoloration of the eschar, or edema at wound margin and histologic examination of burn biopsy shows invasion of organisms into adjacent viable tissue. 2. Patient has a change in burn wound appear- ance or character, such as rapid eschar sep- aration, or dark brown, black, or violaceous discoloration of the eschar, or edema at wound margin and at least 1 of the following:

a. organisms cultured from blood in the absence of other identifiable infection

b. isolation of herpes simplex virus, histologic identification of inclusions by light or electron microscopy, or visualization of viral particles by electron microscopy in biopsies or lesion scrapings.

3. Patient with a burn has at least 2 of the following signs or symptoms with no other recognized cause: fever (.388C) or hypothermia (,368C), hypotension, oliguria (,20 cc/hr), hyperglycemia at previously tolerated level of dietary carbohydrate, or mental confusion and at least 1 of the following:

a. histologic examination of burn biopsy shows invasion of organisms into adjacent viable tissue

b. organisms cultured from blood

c. isolation of herpes simplex virus, histologic identification of inclusions by light or electron microscopy, or visualization of viral particles by electron microscopy in biopsies or lesion scrapings.

SYS-SYSTEMIC INFECTION DI-Disseminated infection

Disseminated infection is infection involving multiple organs or systems, without an apparent single site of infection, usually of viral origin, and with signs or symptoms

with no other recognized cause and compatible with infectious involvement of multiple organs or systems.

BRST-Breast abscess or mastitis

A breast abscess or mastitis must meet at least 1 of the following criteria:

1. Patient has a positive culture of affected breast tissue or fluid obtained by incision and drainage or needle aspiration.

2. Patient has a breast abscess or other evidence of infection seen during a surgical operation or histopathologic examination.

3. Patient has fever (.388C) and local inflammation of the breast and physician diagnosis of breast abscess.

General comments

1. Physician diagnosis of pneumonia alone is not an acceptable criterion for healthcare–associated pneumonia.

   Although specific criteria are included for infants and children, pediatric patients may meet any of the other pneumonia specific site criteria.

   Ventilator-associated pneumonia (ie, pneumonia in persons who had a device to assist or control respiration continuously through a tracheostomy or by endotracheal intubation within the 48-hour period before the onset of infection, inclusive of the weaning period) should be so designated when reporting data.

4. When assessing a patient for presence of pneumonia, it is important to distinguish between changes in clinical status due to other conditions such as myocardial infarction, pulmonary embolism, respiratory distress syndrome, atelectasis, malignancy, chronic obstructive pulmonary disease, hyaline membrane disease, bronchopulmonary dysplasia, etc. Also, care must be taken when assessing intubated patients to distinguish between tracheal colonization, upper respiratory tract infections (eg, tracheobronchitis), and early onset pneumonia. Finally, it should be recognized that it may be difficult to determine health care– associated pneumonia in the elderly, infants, and immunocompromised patients because such conditions may mask typical signs or symptoms associated with pneumonia. Alternate specific criteria for the elderly, infants and immunocom- promised patients have been included in this definition of health care–associated pneumonia.

5. Health care–associated pneumonia can be characterized by its onset: early or late. Early onset pneumonia occurs during the first 4 days of hospitalization and is often caused by Moraxella catarrhalis, H influenzae, and S pneumoniae. Causative agents of late onset pneumonia are frequently gram negative bacilli or S aureus, including methicillin-resistant S aureus. Viruses (eg, influenza A and B or respiratory syncytial virus) can cause early and late onset nosocomial pneumonia, whereas yeasts, fungi, legionellae, and Pneumocystis carinii are usually pathogens of late onset pneumonia.

6. Pneumonia due to gross aspiration (for example, in the setting of intubation in the emergency room or operating room) is considered health care associated if it meets any specific criteria and was not clearly present or incubating at the time of admission to the hospital.

7. Multiple episodes of health care–associated pneumonia may occur in critically ill patients with lengthy hospital stays. When determining whether to report multiple episodes of health care–associated pneumonia in a single patient, look for evidence of resolution of the initial infection. The addition of or change in pathogen alone is not indicative of a new episode of pneumonia. The combination of new signs and symptoms and radiographic evidence or other diagnostic testing is required.

8. Positive Gram stain for bacteria and positive KOH (potassium hydroxide) mount for elastin fibers and/or fungal hyphae from appropriately collected sputum specimens are important clues that point toward the etiology of the infection. However, sputum samples are frequently contaminated with airway colonizers and therefore must be interpreted cautiously. In particular, Candida is commonly seen on stain, but infrequently causes healthcare-associated pneumonia.

1.3 Data Collection Sheet

DATA COLLECTION SHEET						✓	×
Age							
Gender							
Date of tranplant							
Indication for liver transplant							
Presence of	Ascites						
	T2 Diabetes Mellitus						
Viral status:	CMV status of R*						
	CMV status of D^						
	Hepatitis Status of R*						
	Hepatitis Status of D^						
Current Status:	Alive						
	Demised, date of death						
	Cause of death						
Duration of ICU stay							
COMPLICATIONS POST LT:							
	Infectious						
	Non-infectious						
Infectious	diagnosed ante or postmortem						
	pathogen						
	drug sensitivity						
	drug resistance						
	Antimicrobial therapy:						
	directed						
	empiric						
	site of infection						
	Bacteraemia?						
Non-infectious	COMPLICATION	CATEGORY					
	Graft dysfunction	Primary non-function					
		Secondary					
		Secondary to?					
	Rejection	Acute					
		Hypercute					
	Biliary	Leak					
		Obstruction					
		Stricture					
		Other					
	Vascular	Hepatic artey thrombosis					
		Portal Vein					
		IVC^^					
		Other					
	Cardiac	Failure					
		Other					
	Renal	AKI not requiring HD**					
		AKI requiring HD					
		Other					
	Pulmonary	Pleural effusion					
			dranied?				
		Thromboembolism					
		Plumonary oedema					
		Other					
	GIT	Biliary (leak, obstruction/c					
		Bleed					
		Hepatic					
		Instetinal- Perf/obstructio					
		Other					
	Neurological	Delirium					
		Other					
	Haematological	Pancytopaenia					
		Other					
	Drug Toxicity	Tacrolimus					
		Other					

Key:*R: recipient, ^D: donor, ^^IVC : inferior vena cava, **AKI not requiring HD: acute kidney injury not requiring haemodialysis

1.4 Ethics Clearance Form

R14/49 Dr Sheetal Chiba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170265

NAME: (Principal Investigator)	Dr Sheetal Chiba
DEPARTMENT:	Internal Medicine Wits Donald Gordon Medical Centre - ICU
PROJECT TITLE:	Early Complications in Adult Liver Transplant Recipients at Wits Donald Gordon Medical Centre
DATE CONSIDERED:	24/02/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Gunter Schleicher
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	27/02/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

0602418x:turnitin_2_edit.docx

ORIGINALITY REPORT

7%	2%	5%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"AMERICAN TRANSPLANT CONGRESS 2012 ABSTRACTS", American Journal of Transplantation, 05/2012 Publication	1%
2	"Poster Abstracts", American Journal of Transplantation, 2016. Publication	1%
3	"Solid Organ Transplantation in Infants and Children", Springer Nature, 2018 Publication	1%
4	"WORLD TRANSPLANT CONGRESS 2006 POSTER ABSTRACTS", American Journal of Transplantation, 8/2006 Publication	<1%
5	Athanasios Tsiouris. "Distal pancreatectomy with or without splenectomy: comparison of postoperative outcomes and surrogates of splenic function : HPB", HPB, 10/2011 Publication	<1%
6	Submitted to University of Witwatersrand	