

Role of Clinical Pharmacist in Evaluating Risk factors for Multidrug Resistant Bacteria after Living Donor Liver Transplantation

Thesis

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Dedication

To the resting soul of

Prof. Dr. Abd El-Hamid El Shamy

Thank You



Approval Sheet

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Table of Contents

Content	Page number
Abstrat	vi
Introduction	1
• Liver Transplantation	3
○ Historical background	3
○ Selection of candidates	4
○ Indication for transplantation	5
▪ Acute liver failure	6
▪ Chronic viral hepatitis	7
▪ Cholestatic liver disease	8
▪ Hepatobiliary malignancy	8
▪ Alcholic liver disease	9
▪ Metabolic disease	9
▪ Vascular disease	11
▪ Miscellaneous	11
○ Contraindication for liver transplantation	11
○ Evaluation of candidates for liver transplantation	12
○ Living Donor liver transplantation	12
▪ Selection of living donor	12
▪ Phases of living donor evaluation	13
▪ Preoperative complication in LDLT	17
▪ Postoperative complication in LDLT	18
○ Post LDLT infections	20
▪ Sources and risk factors	21
▪ Phases of post LDLT infection	21
• Early phase	21
• Opportunistic infections	23
• Late infection	23
• Immunology at glance	25
○ Definition of immunology	25
○ Types of immune response	25
▪ Non specific immune response	26
▪ Specific immune response	26
○ Characteristics of immune response	28
○ Host pathogen interaction	29

Content	Page number
▪ Innate immune response	32
▪ Humoral immune response	37
▪ Cell mediated immunity	39
• Immunosuppression	42
○ Induction therapy	44
○ Maintenance therapy	45
▪ Calcineurin inhibitors (CNI)	46
▪ mTor inhibitors	49
○ treatment of rejection episodes	50
• Antimicrobials	51
○ Classification of antimicrobials according to mechanism of action	53
▪ Antimicrobials that inhibit cell wall synthesis	53
▪ Antimicrobials that interfere with membrane integrity and function	58
▪ Antimicrobial that inhibit nucleic acid synthesis	59
▪ Antimicrobial that inhibit protein synthesis	61
• Antibiotic resistance	66
○ Mechanism of antibacterial resistance	68
▪ Genetic mechanism	68
▪ Biochemical mechanism	69
▪ Adaptive resistance	73
▪ Non specific resistance	74
○ Types of antimicrobial resistance organisms	76
▪ Pencillin resistant pneumococci (PRP)	76
▪ Vancomycin and methicillin resistance	77
▪ Multidrug resistance of P. aeruginosa	78
▪ Third generation cephalosporin's resistant E. coli	78
▪ Fluroquinolone resistant gram negative pathogens	79
▪ Vancomycin resistant enterococci	79

Content	Page number
○ Risk factors for antimicrobial resistance	80
• Role of clinical pharmacist in antimicrobials management	82
○ Clinical pharmacist activities	83
▪ Active participation in ward round	83
▪ Medication information provider	83
▪ Checking and monitoring patients prescription	83
▪ Patient counselling and education	84
▪ Therapeutic drug monitoring	84
▪ Active participation in clinical audit	84
○ Skills needed for clinical pharmacy practice	85
○ Antimicrobial pharmacist: A growing need for new speciality	86
▪ General role for antimicrobial selection	89
▪ General principles	90
▪ Roles of antimicrobials pharmacist	90
Aim of work	92
Subjects and methods	93
Results	98
Discussion	121
Summary and conclusion	128
Recommendations	131
Reference	132
Appendix	147
Arabic summary	-

List of Abbreviations

Abbreviation	Meaning
6- APA	: 6 amino penicillimic acid
AA	: Amino acid
AAH	: Acute alcoholic hepatitis
ABC	: ATP Binding capacity
ACR	: Acute cellular rejection
AIH	: Auto immune hepatitis
AKI	: Acute kidney injury
ALD	: Alcoholic liver disease
ALF	: Acute liver falliure
ANA	: Anti nuclear antibody
AP	: Alkaline phosphatas
APC	: Antigen presenting cell
APRAC	: Antibiotic resistance prevention and control
AST	: Antibiotic support team
ATG	: Anti thyno globulin
BMI	: Body mass index
CCA	: Cholangio carcinoma
CD	: Culture of differentiate
CIA	: Cyclosporin A
CMV	: Cytomegalovirus
CNI	: Calcineurin inhibitors
CT	: Computed Tomography
CTP	: Child Turcotte pugh
DM	: Diabetes Mellitus
DRI	: Donor risk index
EARSS	: European anti microbial surveillance system
EBV	: Epestien Barr virus
ECG	: Electro cardio gram
ENT	: Ear, Nose and throat
ERCP	: Endoscopic retrograde cholangio pancreastography
ESBL	: Extended sectrum B- lactamas
EVR	: Evrolimus
FFP	: Freash frozen plasma
GGT	: Gamma glutamyl transferase
HAT	: Hepatic arter thrombosis
HBV	: Hepatitis B virus
HCC	: Hepato cellular carcinoma
HCV	: Haptitis c virus
HLA	: Human Leukocute antigen
IL	: Interleukim
IMPDH	: Inosine monophosphate dehydrogenese
INH	: Isonicotinic acid hydrazine
IQR	: Interquartile range
IST	: Immunosuppression therapy
LTCF	: Long term care facility
m. Tor	: Mamliam target of rapamycin
MAC	: Membrane attack complex

List of Abbreviations (Cont.)

Abbreviation	Meaning
MAR	: Multiple Antibiotic resistance
MATE	: Multidrug and toxic compounds extrusion
MEX	: Multidrug resistance efflux
MFS	: Major Facilitator superfamily
MHC	: Major histocompatibility complex
MIC	: Minimum Inhibitory concentration
MPA	: Mycophenolic Acid
MRT	: Magnetic resonance imaging
MS	: Moderate sensitivity
NDM -1	: New Delhi metallo B- lactamase
NK	: Natural Killers
OKT	: Ortho Clone
OPRM	: Outer membrane porin
P. RBC'S	: Packed Red blood cells
PABA	: Para amino benzoic acid
PBC	: Primary biliary Cirrhosis
PBP	: Penicillin Binding protein
PELD	: Pediatric end stage liver disease
PNFG	: Primary non functioning graft
PRP	: Penicillin resistant Pneumococci
PSC	: Primary sclerosing cholangitis
PTLD	: Post transplant lymphoproliferative disorder
PVT	: Portal vein thromboses
R	: Resistant
RMD	: Resistance modulation division
RNA	: Ribonucleic acid
S	: Sensitive
SD	: Standard deviation
SHV	: Sulfhydryl variable
SMR	: Small multidrug resistance
SRL	: Sirolimus
TAC	: Tacrolimus
TCR	: T-Cell receptor
TDM	: Therapeutic drug monitoring
TEM	: Temoneira
TMP	: Trimethoprim
TMP – SMX	: Trimethoprim sulfamethoxazole
TNF	: Tumor necrosis factor
UNOS	: United Network of organ sharink
UV	: Ultra violet
VZV	: Varicella Zoster virus

List of Tables

Table	Title	Page
1	Show different types of antibodies and their classifications	37
2	Show the activity of penicillins to different organisms	55
3	Summay of antibacterial spectrum of some amino glycosides	63
4	Comparison between cases and controls as regard personal and medical data	102
5	Comparison between cases and controls as regard preoperative medical history	103
6	Comparison between cases and controls as regard intraoperative medical data	104
7	Comparison between cases and controls as regard post transplantation medical data	105
8	Comparison between cases and controls as regard duration of: Urinary catheter, central line insertion, ICU and total hospital stay	106
9	Multivariate regression to study independent risk factors for developing resistant infection after liver transplantation	106
10	Description of sensitivity of tested antibiotics	107
11	Description of isolated organisms	108
12	Description of sensitivity of tested antibiotics according to isolated organisms	109
13	Description of sensitivity of tested antibiotics according to isolated organisms	147

List of Figures

Fig.	Title	Page
1	Summary of the different indications of liver transplantation	6
2	Segmental anatomy of liver using the Couinaud segments	16
3	Flow chart, Illustrate the possible complication post LDLT	29
4	The common infection period post LDLT	20
5	Shows the types of immune Response.	26
6	The production of antibody in response to antigen	29
7	The innate immune response to control infection	32
8	Different phases of phagocytosis.	33
9	Illustration of the complement system	34
10	The difference between different pathways of complement activation	35
11	Show antibody structure	38
12	Different defense mechanism exerted by antigen antibody complex	39
13	Illustrate the activity of innate immune response and adaptive immune response.	41
14	Illustration of actions of different immunosuppression	46
15	Summary of the antimicrobial discovery years	52
16	The possible biochemical resistance mechanisms of bacteria to antimicrobials	69
17	Model pathway for improving antimicrobial prescribing practice in hospitals using AST	89
18	Show a model BD bactic 9050 instrument	69
19	Recipients rabbits in study groups	113
20	Pretransplant prevalence of DM and other comorbidities in study groups	113
21	prevalence of pretransplant abdominal and pleural paracentesis in study groups	114
22	Prevalence of pretransplant hospital admission in study groups	114
23	prevalence of pretransplant abdominal surgery and PVT in study groups	115

List of Figures (Cont.)

Fig.	Title	Page
24	Prevalence of intraoperative complication events and performed additional procedure in study	115
25	Percentage of intraoperative need for inotropes and use of venous graft in study	116
26	Prevalence of operative time in study groups	116
27	Prevalence of intraoperative Packed RBCs and fresh frozen plasma in study groups	117
28	Prevalence of post transplant biliary and vascular complication in study groups	117
29	Prevalence of posttransplant medical complication and timing of extubation in study groups	118
30	Prevalence of post transplant add/change of antibiotic regimes and radiological intervention in study groups	118
31	Duration of post transplant ICU and total hospital stay in study groups	119
32	Duration of post transplant urinary and central line catheter insertion	119
33	Prevalence of isolated organisms in different infection sites	120
34	Data collection sheet form	166

Abstract

Bacterial infection after liver transplantation is the most common early complication after the operation, reported to be more than 60%-80%. Immunocompromised recipients are target for infection by multidrug resistant bacterial strains because of frequent antimicrobial usage. Understanding risk factors for infection can be used to guide the selection of the diagnostic approach and initial therapy.

The aim of the study is to point out resistant bacterial strain to broad spectrum antibiotics and to identify the primary risk factors for antimicrobial resistance among recipient after living donor liver transplantation (LDLT).

Living donor liver transplantation recipients from 2011 to 2013 were screened at Ain Shams Center for Organ Transplantation (ASCOT) for the presence of risk factors for antimicrobial resistance preoperative, intra-operative or post-operative. Routine cultures were withdrawn on day one post-operatively in the ICU and once again when patient is transferred to the ward and in case of fever, elevated C- reactive protein, changed white blood count (WBC) or elevated procalcitonin.

42 patients, 7 females with mean age of 53 ± 6.4 years were divided into two groups on the basis of the presence of post transplant infection with multi drug resistant bacterial strains (group 1, n=22) or absence of infection (group 2, n=20).

Several pre, intra and post transplant risk factors showed significant contribution to the occurrence of post transplant infection with multi drug resistant bacterial strains. Multivariate regression test revealed that prolonged operative time ($P=0.016$), multiple radiological interventions ($P=0.040$) and multiple antibiotic changes post operatively ($P=0.038$) were the main risk factors for developing infection with MDR.

Upon investigating the type and pattern of multiple drug resistant of isolated bacterial strains, 257 bacterial cultures were analyzed, 70.8% were gram negative poly microbial resistant bacterial strains and 29.2% were gram positive resistant strains to third generation cephalosporin, carbapenems and quinolones. The most common isolated resistant organisms were *Pseudomonas aeruginosa* (25.8%), *Klebsiella* spp (19.5%), MRSA (18%), *Acinetobacter* spp. and *E. Coli* (9.8%). The most common sites of infection were biliary and abdominal drains (49.3%).

The current study concluded that gram negative polymicrobial resistant biliary infection is the most common bacterial infection after LDLT. Careful usage of antibiotics, short operative time and reduced rate of radiological intervention are recommended for better patient outcomes.

Key words: liver donor liver transplantation, posttransplant infection, multiple drug resistant bacteria

Introduction

The discovery and clinical application of antibacterial agents represents one of the shining achievements of medical science in the 20th century. Dozens of effective antimicrobial agents have been discovered during the past sixty years. The clinical use of antimicrobial agents has spawned, as an unwanted consequence, the widespread emergence of bacteria resistant to these valuable drugs (**Moellering, 2007**).

Resistance was defined as misuse and overuse of antimicrobials, it develops when potentially harmful bacteria change in a way that reduces or eliminates the effectiveness of antimicrobials (**Mamalis, 2008**). With the discovery of each new class of antimicrobial agents, beginning with sulfonamides in 1930s and penicillin in 1940s, resistance has developed and has become a truly worldwide problem (**Moellering, 2007**).

Resistance occurs wherever antimicrobials are used in the community, on the farm and in the healthcare settings. In order to minimize the selective pressure of antimicrobials, it is important to make sure that when antimicrobials are used, they are used appropriately (**Levy and Marshall, 2004**).

The young, the elderly and the immunocompromised are all targets for infection by antimicrobial resistant organisms. These are groups in whom antimicrobial usage is greatest and hence where selective pressure for antimicrobial resistance is greatest (**Christiansen, 2007**).

Living donor liver transplantation (LDLT) has been used for end stage liver disease (ESLD) since 1989. LDLT has basically resolved the problem of donor organ shortages. However, early complications postoperatively and long term life quality are issues that still need to be resolved (**Liu et al., 2010**).

Infection after liver transplantation, especially bacterial infection is the main early complication after the operation. It is reported that the rate of bacterial infection is often more than 60%-80% and often at least no less than 2 organs or positions that are infected by bacteria (**Zhou et al., 2006**). Bacteremia has been reported to be the main cause of mortality in liver transplant recipients. The mortality in bacteremic liver transplant recipients has been found to range between 24% and 36% (**Kim et al., 2009**). In addition, the release of cytokines during infection may have other indirect and negative effects, including allograft injury, opportunistic super infection and malignancy (**Zhou et al., 2006**).