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

Thesis
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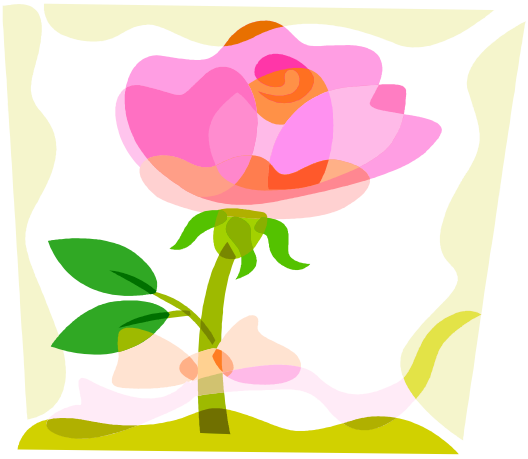
Dedication

To the resting soul of

Prof. Dr. Abd El-Hamid El Shamy

Thank You



Approval Sheet

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*First, thanks are all due to **Allah** for Blessing this work until it has reached its end, as a part of his generous help throughout our life.*

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S. A. Osman

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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	: Alcholic 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 Anibiotic resistance
MATE	: Multidrug and toxic compounds extrusion
MEX	: Mutidrug resistance efflux
MFS	: Major Facilitator superfamily
MHC	: Major histocambatapility complex
MIC	: Minimum Inhibitory concentration
MPA	: Mycophenolic Acid
MRT	: Magnetic resonance imaging
MS	: Moderate sensitivity
NDM -1	: Newdelhi metalo B- lactanase
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 scelerosing cholangtis
PTLD	: Post transport lymphoproliferative disorder
PVT	: Portal vein thrombesses
R	: Resistant
RMD	: Resistance modulation division
RNA	: Ribo neuclic acid
S	: Sensitive
SD	: Standard deviation
SHV	: Sulfhydryl variable
SMR	: Small multidrug resistance
SRL	: Sirolimus
TAC	: Tacrolimus
TCR	: T-Cell receptor
TDM	: Therapeulic drug monitoring
TEM	: Temoneira
TMP	: Trimethoprime
TMP – SMX	: Trimethroprim sulfamethoxazole
TNF	: Tumor necrosis factor
UNOS	: United Network of organ sharink
UV	: Ultra violet
VZV	: Varicilla Zoster virus

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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 devided 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 signicant contribution to the occurrence of post transplant infection with multi drug resistant bacterial strains. Multivariate regression test revealed that prolonged operative time (P=0. 0. 16), 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 auerogenosa (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 developes 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 injur, opportunistic super infection and malignancy (**Zhou et al., 2006)**