RECENT GUIDELINES IN PERIOPERATIVE IMMUNONUTRITION IN LIVER TRANSPLANT PATIENTS AND THEIR EFFECT ON OUTCOME

Essay

Submitted for Partial Fulfillment of the Master Degree in Anesthesia

By

Ayman Mohamed Habashy Hasan

M.B., B.Ch, Ain Shams University

Under supervision of

Prof. Raafat Abdel-Azim Hammad

Professor of Anesthesia, Intensive Care and Pain Management
Faculty of Medicine, Ain Shams University

Dr. Reeham Saied Botrous

Assistant Professor of Anesthesia and Intensive Care
Theodor Bilharz Research Institute
Ministry of Scientific Research

Dr. Diaa Eldin Shalaby Alawady

Lecturer of Aesthesia, Intensive Care and Pain Management
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2017

بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا

إلا ما علمتنا إنك أنت

العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to ALLAH, the Most Gracious and Most Merciful.

*I'd like to express my respectful thanks and profound gratitude to **Prof. Raafat Abdel-Azim Hammad,** Professor of Anesthesia, Intensive Care and Pain Management - Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

*I am also delighted to express my deepest gratitude and thanks to **Dr. Reeham Saied Botrous,** Assistant Professor of Anesthesia and Intensive Care - Theodor Bilharz Research Institute - Ministry of Scientific Research, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

*I am deeply thankful to **Dr. Diaa Eldin Shalaby Alawady,** Lecturer of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, for his great help, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Ayman Mohamed Habashy Hasan

List of Contents

Title	Page No.

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
AAAs	*Aromatic amino acids*
ADH	*Alcohol dehydrogenase*
ALF	*Acute liver failure*
ARG	*Arginine*
BCAA	*Branched-chain amino acids*
BEE	*Basal energy expenditure*
BIA	*Bioelectric impedance analysis*
BMI	*Body mass index*
BTR	*BCAAs/tyrosine ratio*
CT	*Computed tomography*
CYP	*Cytochrome p450*
DEXA	*Dual x-ray absorptiometry*
EN	*Enteral nutrition*
ESLD	*End-stage liver disease*
GLN	*Glutamine*
HE	*Hepatic encephalopathy*
HOMA	*Homeostasis model assessment*
HWP	*Hydrolyzed whey peptide*
IgA	*Immuno globulin A*
IGF-1	*Insulin-likegrowth factor*
IL6	*Interleukin 6*
IMD	*Immunomodulation diet*
LC	*Liver cirrhosis*
LCFA	*Longchain fatty acids*
LDL	*Low density lipoprotein*
LDLT	*Living donor liver transplantation*
LT	*Liver transplantation*
MAC	*Mid-arm circumference*
MAFA	*Mid-arm fat area*

List of Abbreviations (Cont...)

Abb.	Full term
MAMA	*Mid-arm muscle area*
MAMC	*Mid-arm muscle circumference*
MCFA	*Medium-chain fatty acids*
MEOS	*Microsomal ethanol-oxidising system*
MRI	*Magnetic resonance imaging*
NO	*Nitric oxide*
NPO	*Nil per os*
npRQ	*Non-protein respiratory quotient*
OLT	*Orthotropic liver transplantation*
PBC	*Primary Biliary Cirrhosis*
PEM	*Protein energy malnutrition*
PN	*Parenteral nutrition*
POD	*Post operative day*
SBD	*Selective bowel decontamination*
SGA	*Subjective global assessment*
SMM	*Skeletal muscle mass*
TEI	*Total energy intake*
TNF- a	*Tumor necrosis factor alpha*
TSF	*Triceps skinfold thickness*
VCO_2	*Production of carbon dioxide*
VLDL	*Very low density lipoprotein*
VO_2	*Oxygen consumption*

INTRODUCTION

The liver plays an important role in the turnover of carbohydrates, lipids, proteins, vitamins, and trace minerals and also plays an important role in the immune system. Malnutrition in patients with end stage liver disease (ESLD) may be due to underlying etiology of liver damage or declining liver functions regardless the type of liver disease. Both primary and secondary factors contribute to poor nutritional status ***(Plank et al., 2015).***

Malnutrition in patients with ESLD is usually due to:

1) Dietary insufficiency from the anorexia, nausea, vomiting, reflux disease due to ascites and abnormal gut motility.
2) Malabsorption due to pancreatic insufficiency and cholestasis
3) Metabolic disturbances as:
   a) Hypermetabolism during infections, hemorrhage and ascitic decompensation
   b) Protein catabolism due to inflammation and impaired liver synthesis
   c) Impairment of glucose homeostasis, increased lipolysis, enhanced lipid oxidation and release of pro inflammatory cytokines as tumor necrosis factor alpha (TNFα), interleukins and leptin.
   d) Iatrogenic due to protein restriction during periods of encephalopathy ***(Riggio et al., 2003)***.

Cirrhosis is associated with gut bacterial overgrowth, impaired intestinal motility, and increased permeability, all of which facilitate bacterial translocation. In clinical studies, patients with ascites and encephalopathy have significantly altered intestinal permeability. Bacterial translocation can stimulate a cascade of inflammatory cytokine and endotoxin production and lead to severe clinical consequences as exacerbation of the hyperdynamic circulatory state, spontaneous bacterial peritonitis, hepatic encephalopathy, and renal dysfunction ***(Guarner and Soriano, 2005).***

Prebiotics are non-digestible fiber compounds that pass undigested through the upper part of the gastrointestinal tract and stimulate the growth or activity of advantageous bacteria that colonize the large bowel by acting as substrate for them. Prebiotics, dietary elements such as lacto-sucrose, fructo-oligosaccharides, inulin, bran, psyllium, and germinated barley extracts, enhance the growth of protective lactic acid bacteria and the production of essential short chain fatty acids ***(Sartor, 2004)***.

Probiotics (synbiotics) can be defined as living microorganisms that are beneficial to the health of their host. Numerous probiotic microorganisms as Lactobacillus rhamnosus GG, L. and certain strains of L. casei or the L. acidophilus-group are used in probiotic food have also been shown to improve the Child-Pugh score and decrease levels of ammonia, endotoxin and inflammatory cytokines. Prebiotics and probiotics enhance various aspects of intestinal function and reduce pathogenic bacterial overgrowth and lower incidence of life threatening complications ***(Loguercio et al., 2005)***.

Malnutrition affects post-transplant survival rate thus nutritional assessment and management must be an integral part of pre- and post-surgical management. Nutritional supplements should, ideally, be administered enterally, either by oral supplements or, through a gastric or jejunal tube as patients benefit from topical nutritional factors in the gut ***(Plank et al., 2015).***

Total parenteral nutrition (TPN) should be restricted to patients who are unable to eat or those for whom enteral feeding is contraindicated as TPN is associated with higher risks of infection and electrolyte imbalance ***(Riggio et al., 2003).***

Bacterial infections are frequently observed complications during the early postoperative course after liver transplantation ***(Green, 2013)*** leading to increased morbidity and mortality, prolonged hospital stay, and additional costs. There are several reasons for this extraordinary high morbidity: the extensive operation and the immunosuppression given, but also the fact that most of the liver patients are more or less severely malnourished and protein-deficient. Clinical studies have verified a correlation between preoperative malnutrition and postoperative infections, morbidity, and mortality in liver transplant recipients ***(Figueiredo et al., 2000).***

TPN has been shown to be effective in achieving a positive nitrogen balance and to shorten stay in the intensive care unit when compared with no nutritional support. It is obvious that a large proportion of the immune system is localized in the gut. Furthermore, most of pathogens isolated in patients with bacterial infections after liver transplantation are gut-derived. Translocation seems to be the major pathogenic factor for these infections. Translocation is especially facilitated in jaundiced or cirrhotic patients by the inadequate enterohepatic circulation of bile salts with subsequent bacterial overgrowth and leakage of endotoxin from the gut into the general circulation. The endotoxins activate gut and liver macrophages to release inflammatory mediators in abundance, leading to an exaggerated acute phase response and further malnutrition and immune suppression. Progressive endotoxemia during the anhepatic phase of a liver transplantation is also reported to correlate with allograft injury ***(Yokoyama et al., 2007).***

Mucosal atrophy caused by preoperative malnutrition and postoperative fasting or total parenteral nutrition increases the rate of translocation and infections ***(Bengmark et al., 2001)***.

The production of immunoglobulin A (Ig A) by the gut, known to prevent translocation, is drastically reduced during mucosal atrophy. It has been increasingly observed that the protective gut flora is most often reduced or eliminated as a result of antibiotic treatment or malnutrition ***(Dudrick, 2011)***.

Two approaches have been tried to reduce translocation and infections after major abdominal surgery: enteral nutrition and selective bowel decontamination (SBD). Enteral nutrition has shown to stimulate bile flow and gut and liver blood flow, to maintain gut structure and function, and to be efficient in reducing postoperative morbidity ***(Gurusamy et al., 2014).***

Unfortunately so far, mainly fiber-free formulas, which are resorbed in the small bowel and do not reach the colon, have been analyzed in clinical studies. SBD with oral antibiotics has been extensively used after orthotopic liver transplantation (OLT), and most authors report not only a decrease in the incidence of Gram-negative infections but also an increase in Gram-positive infections ***(Hernandez et al., 2015).***

No overall benefit seems to be achieved by this form of treatment. Instead of destroying the gut flora with antibiotics, application of living Lactobacillus appears an attractive alternative. Some Lactobacillus species have been shown to initiate immunoglobulin production, to restore macrophage function, to stimulate apoptosis, and to modulate lymphocyte function ***(Masuda et al., 2013)***.

In addition, they have been shown to influence cytokine release, to increase mucin production, to eliminate toxins, and to stimulate mucosal growth. Lactobacillus has also been reported, at least in experimental studies, to reduce permeability to mannitol in the colon, in sharp contrast to Escherichia coli, Klebsiella species, and Streptococcus viridans, which increase lumen-to-blood clearance of mannitol. The Lactobacillus in the colon needs a regular supply of fibers, which they break down to short-chain fatty acids and other important nutrients, for their survival and function ***(Nagpal et al., 2012).***

AIM OF THE ESSAY

The aim of the present essay is to highlight the importance of sufficient nutritional support and compare different nutritional formulas given entrally or parentrally and the effect of prebiotics, and probiotics on nutritional status, neutrophil count, TNF-α, IL-1β, IL-6, IL-4 and nitric oxide (NO) ruling out their relation to postoperative infection, rejection rate and hospital stay and overall prognosis in liver transplant patients.