

STUDY OF ASCITIC LACTOFERRIN IN
CIRRHOTIC PORTAL HYPERTENSIVE
PATIENTS WITH SPONTANEOUS BACTERIAL
PERITONITIS

*Thesis submitted in partial Fulfillment
of M. Sc. Degree in Internal Medicine*

Presented By

Shereen Abou Bakr Abdel Rahman Saleh
M. B, Ch.,

Supervisors

Prof. Dr. Nabil Aziz Shoukry

*Professor of Internal Medicine
Faculty of Medicine
Ain Shams University*

Prof. Dr. Abd El-Ghany Shawkat

*Professor of Internal Medicine
Faculty of Medicine
Ain Shams University*

Prof. Dr. Sayed Abd El-Naby Shalaby

*Professor of Internal Medicine
Faculty of Medicine
Ain Shams University*

**Faculty of Medicine
Ain Shams University
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دراسة عن الاكتوفيرين فى استسقاء البطن
فى مرضى تليف الكبد المصحوب بارتفاع
ضغط الوريد البابى والذين يعانون من
التهاب الغشاء البريتونى البكتيرى التلقائى

رسالة توطئة للحصول على درجة الماجستير

مقدمة من:

الطبيبة/ شيرين أبوبكر عبد الرحمن صالح
بكالوريوس الطب والجراحة العامة

تحت إشراف

أ.د/ نبيل عزيز شكرى

أستاذ الباطنة العامة
كلية الطب . جامعة عين شمس

أ.د/ عبد الغنى شوكت

أستاذ الباطنة العامة
كلية الطب . جامعة عين شمس

أ.د/ سيد عبدالنبي شلبى

أستاذ الباطنة العامة
كلية الطب . جامعة عين شمس

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List of Abbreviations

*A.F.alb.	: Ascitic fluid albumin.
*A.F.Glu.	: Ascitic fluid glucose.
*A.F.Iron	: Ascitic fluid Iron.
*A.F.LDH	: Ascitic fluid Lactate dehydrogenase.
*A.F.prot.	: Ascitic fluid protein.
*ADCC	:Antibody dependent cell mediated cytotoxicity.
*AIDS	: Acquired immunodeficiency syndrome.
*ALT	: Alanine Transaminase.
*ANCA	: Anti-neutrophil cytoplasmic Antibodies.
*ANP	: Atrial Natriuretic peptide.
*AST	: Aspartate Transeaminase.
*BA	: Bactericidal activity.
*bLF	: Bovine Lactoferrin.
*BT	: Bacterial translocation.
*C	: complement.
*C.B.C.	: complete blood count.
*CD	: cluster of differentiation.
*CD4	: Antigenic marker of helper T cells.
*CD8	: Antigenic marker of cytotoxic T cells.
*CFU-GM	:Colony Forming unit-granulocyte-macrophage.
*CH-C	: Chronic Hepatitis C.
*CIF	: colony inhibitory factor.
*CINF	: consensus Interferon.
*CMV	: cytomegalovirus.
*CR	: complement recptor.
*CYP1A2	: cytochrome P450 1 A2.
*D.Bil.	: Direct Bilirubin.
*DNA	: Deoxyribonucleic acid.
*E.coli	: Escherichia coli.

- *EABV : Effective arterial blood volume.
*ECF : extra-cellular fluid.

List of Abbreviations (Cont.)

- *ELISA : enzyme linked immunosorbent assay.
*eNOS : endothelial nitric oxide synthase.
*GFR : glomerular filtration rate.
*GM-CSF : Granulocyte-macrophage colony-stimulating factor.
*gp : glycoprotein.
*HB : Haemoglobin.
*HbsAg : Hepatitis B surface antigen.
*HBV : Hepatitis B virus.
*HCV : Hepatitis C virus.
*HCVAb : Hepatitis C virus antibody.
*HIV : Human immunodeficiency virus.
*hLF : Human Lactoferrin.
*HRP : horseradish peroxidase.
*HRS : Hepatorenal syndrome.
*HS : Heparan sulphate.
*HSV : Herpes simplex virus.
*HTL-V1 : Human T-cell Leukemia virus 1.
*IBO : Intestinal bacterial overgrowth.
*IFN : Interferon.
*Ig A : Immunoglobulin A.
*Ig G : Immunoglobulin G.
*IL : Interleukin.
*iNOS : Inducible nitric oxide synthase.
*LAL : Limulus ameocyte lysate.
*Lf : Lactoferrin.
*Lfcin : Lactoferricin.
*LPS : Lipopolysaccharide.
*LTA : Lipoteichoic acid.
*LTF : Lactoferrin.
*Mab : Monoclonal antibody.

- *MHC : Major Histocompatibility.
*MLNs : Mesenteric lymph nodes.

List of Abbreviations (Cont.)

- *NK : Natural Killer cell.
*NO : Nitric oxide.
*OA : Opsonic activity.
*OMPs : outer membrane proteins.
*OPD : *o*-phenylenediamine.
*PG : prostaglandin.
*RNA : Ribonucleic acid.
*Rnase : Ribonuclease.
*SA : Sterile ascites.
*SAAG : Serum Ascites Albumin gradient.
*SBP : Spontaneous bacterial peritonitis.
*T.Bil : Total Bilirubin.
*Th : T helper cells.
*TMB : Tetramethyl-benzidine.
*TNF : Tumor Necrosis Factor.
*VIP : Vasoactive intestinal peptide.
*WBCs : White blood cells.

الملخص العربى

اجريت هذه الدراسة على ستين مريضا قسموا الى مجموعتين:
المجموعة الاولى: والتي ضمت اربعين مريضا يعانون من تليف بالكبد وارتفاع
بضغط الوريد البابى واستسقاء بالبطن مع وجود التهاب بكتيرى تلقائى بالغشاء
البريتونى.

المجموعة الثانية: وتضم عشرين مريض من مرضى تليف الكبد المؤدى الى
ارتفاع ضغط الوريد البابى واستسقاء بالبطن مع عدم وجود أية اعراض لألتهاب
الغشاء البريتونى البكتيرى التلقائى.

وقد قامت الدراسة على قياس نسبة الاكتوفيرين وذلك فى كل من:

استسقاء البطن بعد عمل عملية بزل لجميع المرضى مع قياس نسب
البروتينات والألبومين والجلوكوز ومادة الأكتات ديهيدروجيناز والحديد فى استسقاء
البطن. وقد تم حساب عدد الخلايا البيضاء ونوعها مع عمل مزرعة بكتيرية
باستخدام زجاجات مزارع الدم المعقمة وذلك لاستسقاء البطن لجميع المرضى.
ما تم قياس نسبة الاكتوفيرين فى الدم لجميع المرضى مع عمل وظائف
كبد وكلى وصورة دم ونسبة الحديد بالدم وموجات صوتية على البطن وتحليل
فيروسات كبدية (فيروس كبدى بى وسى) لجميع المرضى.

وقد اوضحت الدراسة مايلى:

*ارتفاع نسبة الاكتوفيرين بالدم واستسقاء البطن وذلك فى مرضى المجموعة
الاولى وذلك بمقارنتهم بمرضى المجموعة الثانية.

*كما وجد ان نسبة الاكتوفيرين كانت اعلى بكثير فى استسقاء البطن عنها فى الدم وذلك فى مرضى المجموعة الاولى.

*وبقياس نسبة الحديد بالدم واستسقاء البطن وجد عدم وجود اختلاف ذو دلالة احصائية بين مجموعتى البحث.

*كما بينت الدراسة وجود علاقة عكسية ذات دلالة احصائية كبيرة بين الاكتوفيرين والحديد وذلك فى الدم واستسقاء البطن فى مرضى المجموعة الاولى.

*كذلك تم الاستدلال على وجود علاقة عكسية ذات دلالة احصائية بين نسبة الاكتوفيرين ونسبة الاليومين وذلك باستسقاء البطن.

*بالاضافة الى ذلك وجدت علاقة طردية بين نسبة الاكتوفيرين وبعض وظائف الكبد(وهى انزيمات الكبد، ونسبة الصفراء المباشرة والغير مباشرة).

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الاولى تضم المرضى الذين وجد عندهم عدد الخلايا اكبر من 500 خلية بيضاء لكل سم مكعب،

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Introduction

Ascites can be the result of various disease processes, most commonly cirrhosis. It is the most common complication of cirrhotic portal hypertension (compared with bleeding varices and encephalopathy (*Suzanne and Stephen, 2001*)).

Although cirrhosis is the most common cause, a number of other conditions are associated with ascites. These conditions can be divided into those with or without portal hypertension. Examples of portal hypertensive causes are cirrhosis, Budd-Chiari syndrome, portal vein thrombosis, and congestive heart failure. Nonportal hypertensive ascites may be caused by malignancies, myxedema, infections, and renal dysfunction. Nonportal hypertensive etiologies usually can be distinguished from portal hypertensive causes using the serum-ascites albumin gradient (obtained by subtracting the ascites albumin level from the serum albumin level. A serum-ascites albumin gradient (SAAG) of greater than 1.1 is consistent with a portal hypertension cause, whereas a gradient of less than 1.1 is consistent with a nonportal hypertensive cause of the ascites (*Suzanne and Stephen, 2001*)).

The development of renal insufficiency or spontaneous bacterial peritonitis (SBP) in a patient with ascites significantly worsens the prognosis (*Van and Masson. 1976*).

In patients with ascites that is not secondary to cirrhosis, such as nephrogenic or cardiac ascites, SBP occurs infrequently.

Spontaneous bacterial peritonitis (SBP) is considered a bacterial infection of ascitic fluid without any intra abdominal, surgically treatable source of infection (*Frances et al., 2004*).

Multiple alterations in the immune system of cirrhotics contribute to increased infection rates, eg, defective leukocyte chemotaxis, opsonic activity of the fluid, impaired cellular immunity, and hypocomplementemia (*Wakabayashi et al., 2003*).

Decreased clearance of bacteria secondary to intra- and extrahepatic shunting also increases infection risk. The exact mechanism by which ascites fluid becomes infected in patients with cirrhosis is unknown and debated. Studies suggest translocation of bacteria of intestinal organisms from the lumen through the intestinal wall to lymphatics. It was initially thought that the bacteria then passed directly out of the lymphatics and into the ascites, but the bacteria probably become blood-borne prior to seeding the ascitic fluid. SBP is defined as an ascites fluid polymorphonuclear leukocyte (PMN) count of 250 or greater (regardless of culture results, which may be negative).

The majority of SBP is caused by Gram-negative enteric organisms, most commonly *Escherichia coli* and *Klebsiella pneumoniae*. *Streptococcus* species are also common in SBP. Blood cultures are positive in approximately 50% of patients with SBP (*Strauss and Gomes. 2003*).

Lactoferrin, a natural protein fraction present in both cow's and mother's milk, has a number of interesting