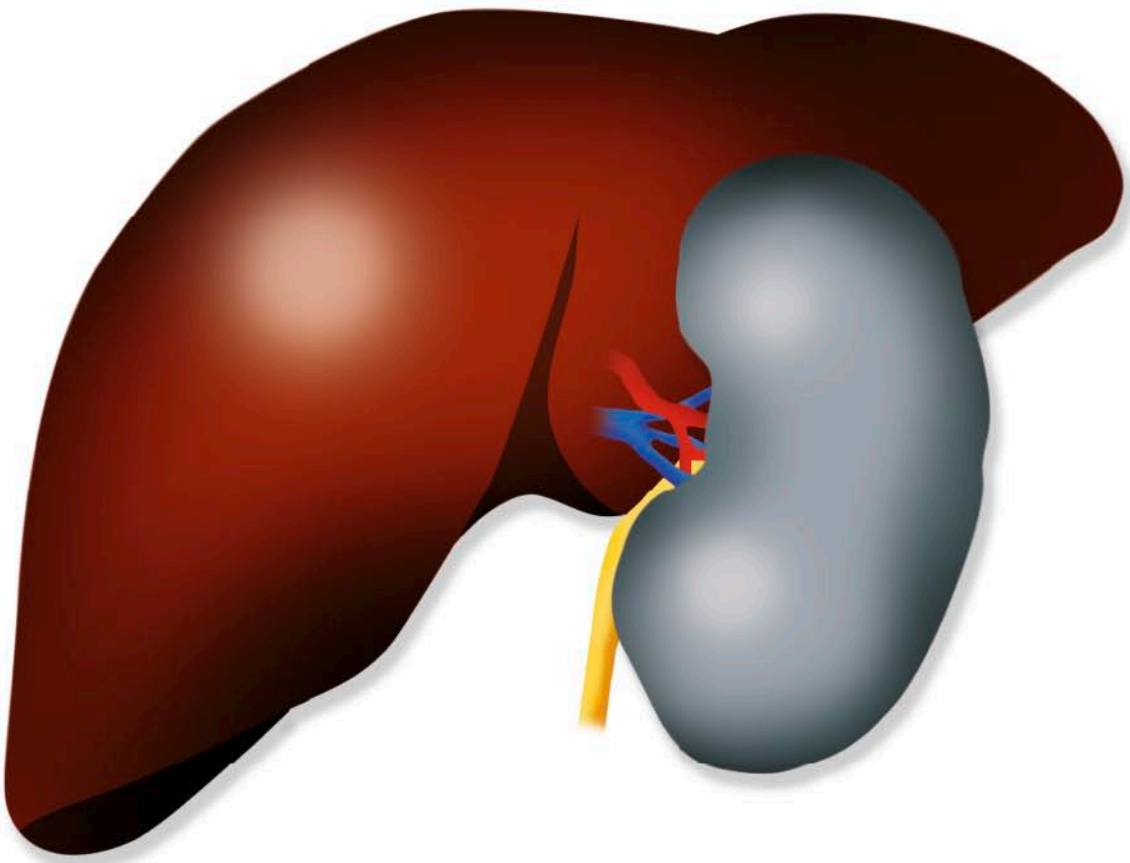
Frontiers of Gastrointestinal Research
Editor: M.M. Lerch
Vol. 28

Ascites, Hyponatremia and Hepatorenal Syndrome: Progress in Treatment

Editor
A.L. Gerbes



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Frontiers of Gastrointestinal Research

Vol. 28

Series Editor

Markus M. Lerch Greifswald

Ascites, Hyponatremia and Hepatorenal Syndrome: Progress in Treatment

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Alexander L. Gerbes Munich

23 figures and 31 tables, 2011

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Frontiers of Gastrointestinal Research
Founded 1975 by L. van der Reis, San Francisco, Calif.

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Library of Congress Cataloging-in-Publication Data

Ascites, hyponatremia, and hepatorenal syndrome : progress in treatment / volume editor, Alexander L. Gerbes Munich.
p. ; cm. -- (Frontiers of gastrointestinal research, ISSN 0302-0665 ; v. 28)
Includes bibliographical references and indexes.
ISBN 978-3-8055-9591-9 (hard cover : alk. paper) -- ISBN 978-3-8055-9592-6 (e-ISBN)
1. Liver--Cirrhosis--Complications--Treatment. I. Gerbes, A. L. (Alexander L.) II. Series: Frontiers of gastrointestinal research ; v. 28. 0302-0665
[DNLM: 1. Liver Cirrhosis--complications. 2. Liver Cirrhosis--therapy. 3. Ascites--therapy. 4. Hepatorenal Syndrome--therapy. 5. Hyponatremia--therapy. W1 FR946E v.28 2011 / WI 725]
RC848.C5A83 2011
616.3'624--dc22

2010032384

Bibliographic Indices. This publication is listed in bibliographic services, including Current Contents®.

www.karger.com
Printed in Switzerland on acid-free and non-aging paper (ISO 9706) by Reinhardt Druck, Basel
ISSN 0302–0665
ISBN 978–3–8055–9591–9
e-ISBN 978–3–8055–9592–6

Contents

Preface

In patients with cirrhosis of the liver treatment focuses on the therapy of complications.

Ascites is the most frequent and hepatorenal syndrome the most lethal complication of liver cirrhosis. Fortunately, major progress has been made in recent years in providing effective treatment and thus reducing mortality in these patients. Therefore, the topics of ascites, hyponatremia and hepatorenal syndrome are very well suited to be presented as a book in the *Frontiers in Gastrointestinal Research* series.

Consequently, this project highlights and critically appraises recent achievements and novel advances. It also provides the background needed to grasp the novel concepts, but is not intended to represent an encyclopedic textbook. Contributions are provided by the most renowned experts at the forefront of clinical research. Their state of the art contributions provide up-to-date references and conclude with a bullet point summary.

Just to pick some of the hot topics that are elaborated in this book. The Transjugular Intrahepatic Portosystemic Shunt (TIPS) and paracentesis, respectively have been introduced into clinical routine, but several pitfalls need to be observed. Chapters deal with the most relevant issues of complications of paracentesis, the right choice of plasma expanders, and selection of patients who will experience survival benefit from TIPS. Beneficial effects of albumin infusion independent of its properties as a plasma expander are discussed.

There is a broad spectrum of acute kidney injury in cirrhosis. Hepatorenal syndrome was considered as a terminal renal failure in cirrhosis until recently. Now, drug treatment can improve renal function and prolong survival – a clinical breakthrough. However, important issues for clinical outcome are still under debate, such as predictors of response and ways to reduce the incidence of side effects of vasoconstrictor therapy. The role of combined kidney-liver transplantation versus conventional liver-only transplantation is considered.

Finally, hyponatremia, an indicator of poor prognosis in cirrhosis can now be addressed with vaptans, new pharmaceutical compounds. The role of vaptans for treating patients with ascites is still a matter of controversy.

I gladly accepted the invitation by Markus Lerch, the series editor, to design and organize this volume, and am very grateful that a highly selected group of international experts has contributed to this book. I do appreciate that despite their extremely busy agenda they took the time to share their knowledge and expertise. They come from the Americas and from Europe and thus provide a truly universal perspective.

It is my hope that this book provides practical advice for practitioners and clinicians who care for patients with cirrhosis. Furthermore, clinicians and scientists working in the field should find the latest data and inspiration for future research.

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Gerbes AL (ed): Ascites, Hyponatremia and Hepatorenal Syndrome: Progress in Treatment.
Front Gastrointest Res. Basel, Karger, 2011, vol 28, pp 1–10

Differential Diagnosis of Ascites

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Abstract

Approximately 80–85% of causes of ascites are related to portal hypertension; however, malignancy-related ascites, cardiac failure and tuberculosis and other less common causes should always be considered. If ascites is suspected the patient should be carefully evaluated, including clinical history and physical examination. Diagnostic paracentesis should be performed routinely to determine the cause of ascites and spontaneous bacterial peritonitis. Basic tests include a cell count with differential and total protein concentration in ascitic fluid. Culture and other optional tests like the serum ascites albumin gradient can be performed based on clinical suspicion. New tests have been developed especially for the diagnosis of spontaneous bacterial peritonitis such as measurement of lactoferrin concentration in ascitic fluid or detection of bacterial DNA. These tests still need to be evaluated further.

Ascites is defined as accumulation of fluid in the peritoneal cavity. It is a common complication of cirrhosis, indicating portal hypertension which occurs in 80–85% of patients with ascites [1]. Nearly 60% of patients with compensated liver cirrhosis develop ascites within 10 years after onset of the liver disease. Once patients have developed ascites their prognosis is poor; nearly half of them die within 2–3 years [2]. However, other less common causes of ascites should be evaluated in the differential diagnosis of ascites. Other causes of ascites are, for example, malignancy (10%), cardiac failure (5%) and abdominal tuberculosis (2%) (table 1) [3].

Clinical Work-Up and Problems

In patients where cirrhosis is not the cause of ascites, a clinical work-up should be elicited for other causes of ascites. Furthermore, in approximately 5–10% of patients there is more than one cause of ascites [1].

Table 1. Causes of ascites

Cirrhosis
Alcoholic hepatitis
Partial nodular transformation
Fulminant hepatic failure
Hepatocellular carcinoma (usually with cirrhosis)
Cardiac disease
Congestive heart failure
Valvular disease
Constrictive pericarditis
Cardiomyopathy
Malignancy
Vascular disease
Hepatic vein obstruction (Budd-Chiari syndrome)/sinusoidal obstruction syndrome
Portal vein occlusion (thrombosis, tumor)
Peritoneal tuberculosis
Nephrotic syndrome
Ovarian disease (like Meigs syndrome, struma ovarii of ovarian overstimulation syndrome)
Pancreatic ascites
Rupture of pseudocyst
Leak from pancreatic duct
Bile ascites
Gallbladder rupture
Traumatic bile leak
Chylous ascites
Rupture (traumatic, surgical) of abdominal lymphatics
Obstructed lymphatics
Rare causes
HIV-related ascites
Peritoneal vasculitides
Myxedema
Whipple's disease
Sarcoidosis
Gynecologic lesions
Malnutrition
Hypoalbuminemia
Protein-losing enteropathy

History and Physical Examination

Ascites is rarely the sole physical finding. Evidence of liver disease must be considered (jaundice, spider angiomata, palmar erythema, caput medusae, muscle wasting, splenomegaly, gynecomastia). Hepatomegaly may be absent if cirrhosis exists, possible causes of hepatomegaly with ascites include Budd-Chiari syndrome, cardiomyopathy with congestive heart failure or liver metastases. Edema of the lower extremities or significant proteinuria may suggest a nephrotic syndrome as the cause of ascites due to, for example, glomerulonephritis, collagen diseases or diabetes. Jugular venous distention, pathologic heart sound, pulmonary crackles, dyspnea and peripheral edema imply right-side heart failure. Clinical tests for ascites include inspection for bulging flanks and flank dullness and the fluid wave test. If the volume of ascites is low, these techniques are not helpful; 1,500 ml of fluid must be present before shifting dullness can be detected [4].

Diagnostic Imaging Techniques

Abdominal ultrasonography is a cost-effective technique to confirm ascites and to detect potential causes such as liver disease and should be performed first. It may help confirm the presence of ascites and differentiate it from other conditions such as pregnancy or ovarian cysts [4].

Small amounts of ascites (<100 ml) and the best possible location to perform paracentesis can be detected by ultrasound.

A CT scan of the abdomen should be performed to determine the presence of primary malignancy of the gastrointestinal tract or peritoneal carcinomatosis and other structures in the abdomen.

To rule out congestive heart failure, further cardiac work-up can be performed.

Diagnostic Paracentesis and Ascitic Fluid Analysis

A diagnostic paracentesis should be performed during the initial evaluation of ascites to determine its cause and to diagnose spontaneous bacterial peritonitis (SBP) [5].

It should be performed in (a) all patients with new onset of ascites, (b) patients who are admitted to hospital because of cirrhosis-related complications, and (c) in patients with clinical signs or laboratory abnormalities suggestive of infection [5].

For the diagnostic approach, 20–40 ml of ascitic fluid must be obtained.

In patients with new-onset ascites, the fluid should be evaluated for:

- macroscopic appearance
- cell count and differential
- total protein

– (optional) cultures
– (optional) ascitic and serum albumin for SAAG
– (optional) other parameters.

Macroscopic Appearance of Ascites

Ascitic fluid is transparent. In jaundiced patients it is slightly yellow due to the presence of bilirubin.

Ascitic fluid may be cloudy due to the presence of neutrophils >5,000/mm^3, while it appears pink due to red blood cells >10,000/mm^3. Bloody ascites is usually due to traumatic puncture. Causes of nontraumatic bloody ascitic fluid include peritoneal tuberculosis or malignancy. Approximately 20% of malignant ascites are bloody. The ascitic fluid of patients with cirrhosis and hepatocellular carcinoma is bloody in up to 50% of the cases [6].

Chylous or 'milky' ascites is often due to the presence of a high concentration of triglycerides (a triglyceride concentration >200 mg/dl establishes the diagnosis of chylous ascites) and is often found in malignancy-related ascites. However, in 20% of patients with cirrhosis ascites is chylous [7]. Another cause of chylous ascites is disruption of the lymphatic system due to abdominal surgery.

Diagnostic Tests for Ascites

Following diagnostic paracentesis of ascites, it has to be decided which tests should be performed and which parameters should be analyzed.

While many tests are available, it is neither useful nor cost effective to carry them all out. Further tests can be performed as indicated by the initial specimen (table 2).

As most patients with ascites have liver disease, exclusion of malignancy, tuberculosis or other less common causes is normally not required after the first paracentesis.

Cell Count

Cell count, as a mandatory test, may be performed in an EDTA tube using a small amount of fluid. The average normal total white blood cell count in patients with ascites due to liver disease is 100–500/mm^3. In bloody ascites, the white blood cell count could be misinterpreted: one PMN count per 250 red blood cells can be taken as contamination. In SBP, the total white blood cell count as well as the absolute PMN count are elevated. A PMN count >250/mm^3 is defined as spontaneous bacterial peritonitis (SBP) and indicates initiation of an empiric antibiotic regime [5].

Table 2. Ascitic tests

Mandatory	Optional	Rarely used
Cell count / differential	Albumin (ascitic and blood)	Bilirubin
Total protein	Cytology	Triglycerides
	Culture	Tumor markers
	Cholesterol	LDH
		Glucose
		Amylase

In tuberculous or malignant ascites, lymphocytes dominate in the ascitic fluid [6]. If malignant ascites is suspected, cytology should be performed. If tuberculosis is suspected, microbiological tests and a polymerase chain reaction-based method can be performed.

Cytology

Ascitic fluid cytology should be performed in suspected cases of malignancy-related ascites. The fluid should be examined rapidly after paracentesis – either fresh or fixed. The amount of ascitic fluid should be 50–100 ml.

Cell count is often elevated in malignant ascites. However, in patients with hepatocellular carcinoma ascitic cytology is positive in <10% [8].

Total Protein

Ascites used to be divided into exudative and transudative types using a cut-off value of 2.5 g/dl total protein [9]. Ascites due to secondary abdominal processes like malignancy or abdominal tuberculosis (50%) would be exudates (>2.5 g/dl), whereas ascites due to portal hypertension would be transudates (<2.5 g/dl). However, approximately 20% of cirrhotic patients have an ascitic total protein of >2.5 g/dl and would therefore be categorized incorrectly [10]. Furthermore, patients with cardiac ascites have a high total protein (>2.5 g/dl).

Serum Ascites Albumin Gradient

Calculation of the serum ascites albumin gradient (SAAG) may differentiate the causes of ascites into two groups. It helps determine whether or not ascites is related

to portal hypertension. The gradient can be calculated by measuring the albumin concentration in blood and ascitic fluid and subtracting the ascitic from the serum value. If a patient has portal hypertension, there must be a high oncotic gradient, which means a high albumin gradient between blood and ascitic fluid.

If the SAAG is ≥1.1 g/dl, the cause of ascites is portal hypertension with a reliability of more than 90% [9], another cause could be cardiac disease with a high protein content in ascitic fluid.

While SAAG enables differentiation of ascites into one of two categories, it cannot replace further evaluation. A SAAG of <1.1 g/dl indicates that the patient does not have portal hypertension, but that a process such as peritoneal carcinomatosis, abdominal tuberculosis, pancreatic ascites, nephrotic syndrome, or biliary ascites may be present.

If the gradient has been determined at the initial paracentesis, it is not necessary to repeat this calculation.

Microbiological Culture and Gram Stain

Ascites culture is negative in approximately 40% of patients with SBP [11]. The cultures should be collected at the bedside, including aerobic and anaerobic media with a minimum amount of 10 ml ascitic fluid. Ascitic fluid Gram stain is generally a useless investigation due to the low concentration of bacteria in patients with SBP. Furthermore, an ascites smear for diagnosis of tuberculosis is also not helpful [12]. The sensitivity of fluid culture of mycobacteria is approximately 50%.

Other Ascitic Fluid Tests

Cholesterol

No laboratory test completely distinguishes malignant ascites from ascites associated with cirrhosis. It has been suggested that a fraction of the cholesterol could be derived from a malignant cell [14]. Measurement of total ascitic cholesterol concentration seems to be a rapid and cost-effective diagnostic test for discrimination between ascites of malignant and benign origin. A cholesterol concentration of >45 mg/dl is suspicious for malignant ascites. A cytologic examination should follow [14, 15].

Lactate Dehydrogenase

Lactate dehydrogenase (LDH) as a diagnostic test has little clinical relevance in delineating the cause of ascites. An elevation of LDH is common in SBP, tuberculous peritonitis or secondary bacterial peritonitis with a fluid:serum LDH ratio >0.5, a ratio >1.0 is suspicious of abdominal tuberculosis [16].