ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 11, Issue 4, 2018

Online - 2455-3891
Print - 0974-2441

Reserach Article

# A COMPREHENSIVE INFORMATIVE NOTE ON ASCITES

**NAVNEET SINGH[1]*, SAZAL PATYAR[2], NAVEEN CHANDRA TALNIYA[1]**

**[1]Department of Chemistry, School of Chemical Engineering and Physical Science, Lovely Professional University, Phagwara, Punjab, India.**
**[2]Departmentof Pharmaceutical Sciences, School of Pharmaceutical Science, Lovely Professional University, Phagwara, Punjab, India.**
**Email: drnavneet10@gmail.com**

*Received: 05 October 2017, Revised and Accepted: 27 December 2017*

**ABSTRACT**

Ascites impairs both the physical and mental dimensions of quality of life in patients. The patients due to unawareness do not report to medical practitioners in the early stage of disease, and also in few cases, medical practitioners due to lack of adequate expertise face difficulty to ensure the early stage detection for causes of ascites, i.e., due to cirrhosis, cancer, congestive heart failure, mycobacterium tuberculosis, or others. Ascites is a symptom of progression of single disease or multiple diseases. Gross collection of fluid in peritoneal cavity may initiate a series of problems such as spontaneous bacterial peritonitis and an increase in abdominal distension and discomfort and hinder the mobility of the patient and dullness and loss of appetite. In the present review, a detail study over the ecology of ascites has been done with emphasizing on diagnosis by history and physical examination, clinical examination, and imagining techniques followed by management of treatment through general guidelines, and various available therapies are covered.

**Keywords:** Ascites, Malignant, Benign, Imaging techniques, Peritoneal, Ascetic fluid.

 DOI: http://dx.doi.org/10.22159/ajpcr.2018.v11i4.22948

## INTRODUCTION

The diagnostic paracentesis is usually a clinical tool to find and confirm ascites, but abdominal sonography helps to detect an amount of fluid as little as 100 ml [1]. Normally, 50 ml of fluid in peritoneal cavity gives lubrication, but the accumulation of at least 1500 ml of fluid may be required for clinic evidence. Ascites is known to be the cause of various diseases. Ovarian, endometrial, breast, esophageal, gastric, colorectal, lung, pancreatic, hepatobiliary, and primary peritoneal carcinomas are cancer-related cases which cover 10% of all cases of ascites [2-4]. The identification of subclinical metastases through cytological investigation of peritoneal fluid was first proposed in 1956 [5]. Thereafter, peritoneal fluid cytology was included in protocol for the staging of ovarian cancer by recommendation of the International Federation of Gynecologists and Obstetricians [6]. However, both false-negative and false-positive rates of peritoneal fluid cytology are high [7]. In general, clinically evident malignant ascites has an association with poor prognosis, regardless of factors [8]. It is not a trusted prognostic indicator, with reported median survival time ranging from 1 to 4 months [9]. Therefore, it is an urgent need for incorporating new diagnostic methods in protocol to detect microscopic disease in peritoneal cavity.

In the present study, an effort has been made to write a comprehensive information note on ascites by incorporating various aspects related to diseases born ascites, possible cause, clinical tests, and management of treatment and role of chemotherapeutic agents.

## DIAGNOSIS OF ASCITES

Ascites may be one of the revelations of a primary disease or symptom of a complication of disease. Simple test(s) and analysis on ascitic fluid (AF) or serum can be of immense help in differentiating benign and malignant causes of ascites. Lots of expertise is required to discriminate malignant from benign causes of ascites. The differential diagnosis of ascites is of paramount importance because therapy and management of two groups are radically different. The protocol for diagnosis of ascites is established according to Fig. 1.

### History and physical examination

Proper investigation of physical examination and patients' lifestyle reveals possible cause of ascites. Mild AF may not reflect any symptoms. Abdominal distension and weight gain are generally observed in case of moderate ascites. Whereas, symptoms such as abdominal discomfort and hindering mobility in patients are produced in case of a large amount of fluid accumulated in peritoneal cavity.

Cirrhosis of liver may be correlated by intensive examination of patient's habits and lifestyle related to alcohol intake, drug abuse, blood transfusions, or hepatitis. Patient may be prone to complications related to liver disease, including refractory ascites, SBP, hyponatremia, or hepatorenal syndrome if they have cirrhosis and ascites [10]. Cardiac ascites may be correlated with heart failure and pericardial disease in patients. A history of malignancy, for example, ovaries, breast, prolonged fever, and chronic pancreatitis may indicate malignant, tubercular etiology, and pancreatic ascites, respectively. Refractory ascites may be correlated with inability to mobilize ascitic fluid or multiple early recurrences of ascites despite giving medical therapy in patients [10, 11].

The exact diagnosis of ascites-based diseases is a challenge to the medical practitioners. The experienced gastroenterologists may diagnose mild and moderate ascites with a probability of 50% through physical examination [12]. It reveals distended abdomen, flank dullness, shifting dullness, and fluid thrill. Flank dullness is the most critical physical sign and has been reported by 90% of patients, but shifting dullness is more specific. Large ovarian or hydatid cyst, pregnancy with hydromnias, and focal ascites may be the other cases responsible for fluid thrill other than ascites.

### Clinical investigations

#### *Abdominal paracentesis and analysis of AF and non AF*

The diagnosis resulted from physical examination and history is further verified by the outcome of the clinical investigation. The different diagnosis of ascites as displayed in Fig. 2 can be predicted effectively by the help of different clinical methodologies as outlined in Fig. 3.

Medical practitioners may evaluate a patient in an early stage by adopting a protocol for abdominal paracentesis and a careful analysis of AF. An investigation under few reported parameters such as physical investigation (peritoneal fluid), serum protein, serum ascites albumin

gradient, cell count and cytology, AF glucose, ascetic fluid lactate dehydrogenase, serum cholesterol, serum ferritin, and cancer antigen may provide useful information about the possible cause of ascites. Literature findings reveal that peritoneal fluid examination may lead to suggest conventional diagnostic procedures for primary ovarian cancer if molecular abnormalities are detected in peritoneal fluid [13]. By convention, total protein content in peritoneal fluid gives information about exudate or transudate which may further explore pleural fluid and different processes of fluid formation [14]. The cutoff values are generally used in a range between 25 and 30 g/L [15-17]. The exudate/transudate concept in ascites evaluation has, however, associated with many problems and exceptions. Therefore, exudates/transudate-based classification was proposed to be discontinued more than 15 years ago [18]. Peritoneal fluid collected from patient with reported ascites of unknown origin may be examined for tests as presented in Table 1 [11,19-23].

However, AF cytology is positive only in validating of peritoneal carcinomatosis. 96.7% sensitivity of cytology has been reported in detecting peritoneal carcinomatosis if three samples (from different paracentesis procedures) are collected and processed promptly; the first sample is positive in 82.8%, and at least 1 of 2 samples is positive in 93.3% [24]. In addition to that, the aim of abdominal paracentesis should be to provide immediate relief to the patient while at the same time, preventing complications such as paracentesis-induced circulatory dysfunction (PICD). It may occur after large-volume paracentesis (>5–6 L) and result in faster reaccumulation of ascites, hyponatremia, renal impairment, and shorter survival [25]. Large-volume paracentesis may lead up to 80% incidences of PICD without additional therapeutic management; further, the cases may be reduced to 15–35% with volume expanders [26].

**Role of imaging**

Radiologic studies are a boon in the management of ascites because it has been quite successful in detecting a small amount of ascetic fluid as well as helpful in assessing etiology of ascites as shown in Fig. 4.

The possible outcome of physical examination and clinical investigation undergoes intensive cross-examination by the imaging techniques. Abdominal sonography may be used to detect as little as 100 ml of intraperitoneal fluid. Few imaging technique has been listed in Table 2 [27].

**Laparoscopy**

Laparoscopy may prove useful technique for direct visualization of peritoneum and other organs if no clear perception for diagnosis is made. In the extreme cases, definite diagnosis may be sorted with biopsies.

**MANAGEMENT OF ASCITES**

In the present era of modern technology and advanced drugs, exact diagnosis of ascites is still put a question mark, and exact treatment with efficacy and less toxicity is still undergoing research and study. The management of ascites depends on the possible cause. The protocol to be followed requires intensive screening of factors such as medical practitioners' understanding about patient's health, ascites type, disease, and the stage.

**General guidelines for the treatment**

The general guidelines for the treatment of ascites are discussed with the help of Table 3 [28-30].

**Medication for ascites**

Apart from dietary sodium restriction, diuretic, and antibiotic, paracentesis should not be considered as first-line therapy in ascites management. The common drugs used for management of ascites are listed in Table 4. The specific treatment with medication is only possible, once the actual causes and type of ascites are confirmed, clinically.

The literature review suggested that prescription of few treatment regimens should be addressed with utmost care due to negative impacts in patients. Drugs which function toward inhibition of vasoconstrictors such as vasopressin, angiotensin, and aldosterone would be expected to lower blood pressure [53]. Lowering blood

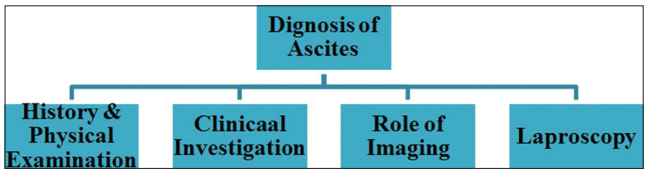


**Fig. 1: Protocol for diagnosis of ascites**

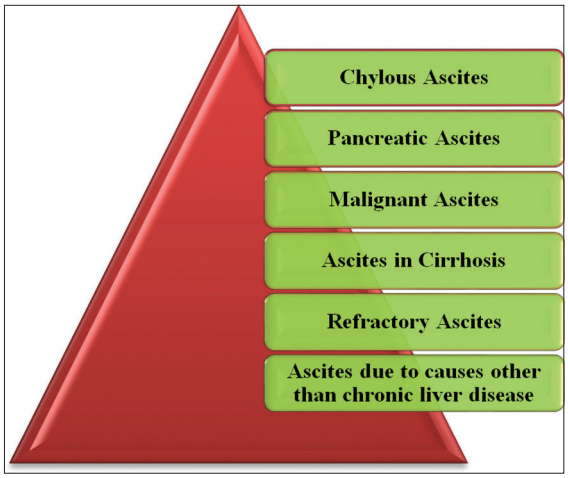


**Fig. 2: Classification of ascites**


**Fig. 3: Clinical methodologies for the diagnosis of ascites**

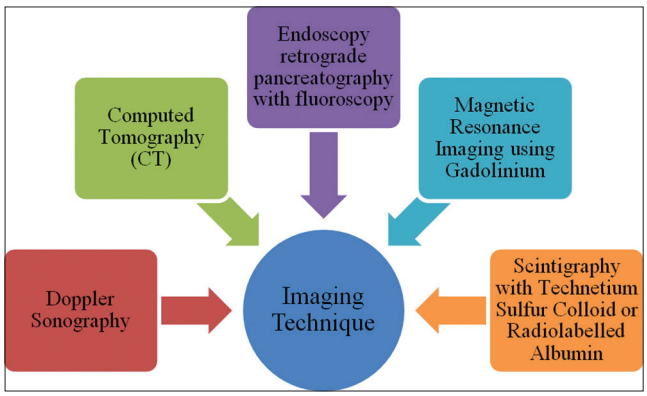


**Fig. 4: Imaging techniques**

**Table 1: Test for the diagnosis of ascites**

| Test | Observation | Possible cause of ascites |
|---|---|---|
| Physical investigation (peritoneal fluid) | Clear or straw color | Portal hypertension and hypoalbuminemia |
| | Turbid | Ascites due to infection |
| | Milky due to lymphatic obstruction | Chylous ascites |
| | Dark brown fluid | presence of bile |
| | Hemorrhagic effusion | Malignancy, tuberculosis, pancreatitis and recent abdominal tapping |
| Serum protein | TP content of AF >2.5 g/dl (exudates) | Tuberculosis, Malignancy, pancreatitis, and myxedema |
| | TP content of AF <2.5 g/dl (transudate) | portal hypertension or hypoalbuminemia |
| SAAG | SAAG >1.1 g/dl (high gradient) | Cirrhosis, alcoholic hepatitis, cardiac failure, massive liver metastases, myxedema, acute fatty liver of pregnancy, and mixed ascites |
| | SAAG <1.1 g/dl (low gradient) | Peritoneal tuberculosis, peritoneal carcinomatosis, pancreatic ascites, biliary ascites, nephrotic syndrome, bowel obstruction or infarction, serositis |
| Serum creatinine | Increases more than 100% from baseline to a final level of greater than 2.5 mg/dl (221 mol/l) | Conventionally, type 1 HRS is only diagnosed. Type 2 HRS occurs in patients with refractory ascites, and there is a steady but moderate degree of functional renal failure, often with avid sodium retention |
| Cell count and cytology | WBC count >500/cmm | Malignant ascites and tubercular ascites |
| | Neutrophils count >250/cmm | Ascites due to bacterial infection |
| Other tests | Ascetic fluid glucose <40–70 mg/dl | Malignant ascites and tubercular ascites |
| | Ascetic fluid amylase >40–70 mg/dl | Pancreatic ascites |
| | Stained fat globules with increased triglyceride content | Chylous ascites |
| AF LDH | ideal cutoff 422 U/l | Malignant ascites/non-malignant |
| AF cholesterol | ideal cutoff 67 mg/dl | Malignant ascites |
| AF ferritin | ideal cutoff 95 mg/ml | Malignant ascites |
| Serum LDH | ideal cutoff 474 U/l | Malignant ascites |
| Serum cholesterol | ideal cutoff 164 mg/dl | Malignant ascites/non-malignant |
| Serum ferritin | ideal cutoff 266 mg/ml | Malignant ascites/non-malignant |
| CA 125 | ideal cutoff 35 | Ascites due to ovarian cancer and closely related cancers, such as fallopian tube and primary peritoneal cancer |
| CA125/CEA ratio | more than 25 | Epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer |
| Vascular Endothelial Growth Factor - A (VEGF-A) | The average levels of VEGF-A are 361 pg/ml, 528 pg/ml, and 2136 pg/ml among the benign, borderline, and malignant subsets, respectively. VEGF-A higher than~900-1000 pg/ml in their ascites was marked for aggressive disease and earlier recurrence (recurrence within 2 years from debulking surgery and primary line of treatment) | Epithelial ovarian cancer |
| Diuretic-resistant ascites | Lack of response to sodium restriction and diuretic treatment | Refractory Ascites |
| Diuretic-intractable ascites | Development of diuretic-induced complications that preclude the use of an effective diuretic dosage | |
| Treatment duration | Intensive diuretic therapy for at least 1 week and on a salt-restricted diet of less than 90 mmol/d | |
| Lack of response | Mean weight loss of<0.8 kg over 4 days and urinary sodium output less than the sodium intake | |
| Early ascites recurrence | Reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization | |
| Diuretic-induced complications | An increase of serum creatinine by>100% to a value >2 mg/dl (177 µmol/l), a decrease of serum sodium by >10 mmol/l to a serum sodium of<125 mmol/l, a change in serum potassium to<3 mmol/l or>6 mmol/l | |

TP: Total protein, SAAG: Serum-ascites albumin gradient, AF: Ascitic fluid, LDH: lactate dehydrogenase, CA: Cancer antigen

pressure might raise survival issues. Cirrhosis and ascites patient should not be prescribed angiotensin-converting enzyme inhibitors and angiotensin receptor blockers or advised with utmost caution. The European Association for the study of the liver practice guideline on ascites recommends that "they should generally not be used in patients with ascites" [54]. Beta blockers may pose challenges like

**Table 2: Imaging technique for diagnosis of ascites**

| Imaging technique | Application of detecting | Cause of malignancy |
|---|---|---|
| Doppler sonography | Thrombosis of the portal or hepatic veins | |
| CT | Appearance of liver | Cirrhosis |
| | Pancreatic pseudo cyst | Pancreatic ascites |
| | Intra-abdominal tumors | Carcinomatosis |
| | Thickening of mesentery and bowel wall, matting of bowel loops, and presence of mesenteric lymph nodes | Tuberculosis peritonitis |
| | Peritoneal lining by contrast-enhanced CT scan | Carcinomatosis or inflammatory peritonitis |
| Magnetic resonance imaging using gadolinium | Peritoneal lining | Carcinomatosis or inflammatory peritonitis |
| Endoscopy retrograde pancreatography with fluoroscopy | Leakage of pancreatic juice from the pancreatic duct | Pancreatic ascites alone or associated with liver cirrhosis |
| Scintigraphy with technetium sulfur colloid or radiolabelled albumin | Intraperitoneal origin of the thoracic fluid | Cirrhosis and large hydrothorax |

CT: Computed tomography

**Table 3: General guidelines for the treatment of ascites**

| Ascites type | General guidelines for the treatment |
|---|---|
| Ascites due to causes other than chronic liver disease | Appropriate chemotherapy is needed for infective causes. |
| Chylous ascites | A low-fat diet with medium-chain triglycerides substituted for normal long-chain triglycerides may help decrease triglycerides content of AF. |
| Pancreatic ascites | Somatostatin infusion may help by reducing pancreatic exocrine secretion. Occasionally, surgical or endoscopic intervention may be needed. |
| Malignant ascites | If AF has malignant cell and no residue of intra-abdominal tumor masses is found, repeated therapeutic paracentesis may be required. Intraperitoneal injection of appropriate cytotoxic drug may help to some patient with chemosensitive malignancies for achieving palliation. PVS may prove a valuable technique to control resistant ascites in patient without malignant cells in AF. |
| Ascites in Cirrhosis | Sodium restriction, bed rest, and use of diuretics are mainstay of therapy. For a patient with mild-to-moderate ascites, spironolactone, an aldosterone antagonist is preferred as initial diuretic. It decreases sodium reabsorption in distal tubule. Addition of a loop diuretic (furosemide) to spironolactone potentiates the effect of both drugs and reduces the risk of developing hyperkalemia. Patients with severe or tense ascites who are refractory to diuretic should be treated with LVP. Paracentesis associated with intravenous albumin infusion (about 8 g of albumin per liter of AF removed) is considered to be the treatment of choice in patients with tense ascites. |
| Refractory ascites | Repeated LVP at intervals of 2–3 weeks depending on the severity of sodium retention and the amount of fluid removed each time. PVS or LeVeen shunt - this technique produces a marked increase in plasma volume and inhibits renin, aldosterone, noradrenaline, and ADH concentrations leading to an increase in diuresis, natriuresis, and free water clearance. Surgical portosystemic shunts - they relieve portal hypertension and are effective in clearing ascites. TIPS - the procedure is most commonly used for the treatment of recurrent esophageal variceal bleeding and refractory ascites. In addition to that, TIPS has been reported to improve renal function in patients with Type 1 HRS. However, the applicability of TIPS in this setting is very limited because many patients have contraindications to the use of TIPS. CART - this process is executed in four steps - paracentesis, removal of cell components from ascites by filtration, and concentrating ascetic fluid and reinfusion of fluid obtained through this process to gastric cancer patients with refractory ascites. |

CART: Concentrated ascites reinfusion therapy, TIPS: Transjuglar intrahepatic portosystemic shunts procedure, HRS: Hyponatremia or hepatorenal syndrome, ADH: Antidiuretic hormone, PVS: Peritoneovenous shunt, LVP: Large volume paracentesis

shorten survival in refractory ascites. Propranolol has been found to shorten survival in patients with refractory ascites in a panorama study [55]. It may be related with a negative impact on blood pressure and increase in rate of PICD in patients who rely on propranolol intake for management of refractory ascites [56]. In addition to said drugs, different plant-derived extracts are also reported to have anticancer activity in related ascites [57,58].

## CONCLUSION

This study exposes various aspects of ecology of ascites and indicates that the role of history and physical examination, clinical investigation, and imaging techniques followed by laparoscopy is equally important to search possible cause of ascites based diseases. This comprehensive information note provides a wide spectrum of guidelines through

**Table 4: Drugs for the treatment of ascites**

| Treatment regimen | Drugs | Reference |
|---|---|---|
| Diuretic | Spironolactone and furosemide | [31,32] |
| | Amiloride | [33] |
| | Triamterene, metolazone, and hydrochlorothiazide | [34-36] |
| | Midodrine | [37] |
| | Cephalosporin plus vancomycin or cloxacillin | [38,39] |
| Antibiotic | Norfloxacin | [40-46] |
| | Trimethoprim Sulfamethoxazole | |
| | Cefotaxime, ampicillin plus tobramycin | [47] |
| VAPTANS | Tolvaptan | [48,49] |
| | Satavaptan | [50] |
| Chemotherapeutic agents | Carboplatin and gemcitabine | [51] |
| | Paclitaxel, carboplatin, and liposomal doxorubicin | [52] |

VAPTANS: Vasopressin receptor antagonists

which ascites may be diagnosed. The successful management of ascites depends on the successful diagnosis of the cause. The study further presents a panorama of treatment and therapies in an array of benign and malignant ascites.

**ACKNOWLEDGMENT**

The authors express sincere gratitude to the patients for sharing their experiences during treatment of their disease. Authors also express their regard to Dr. Lalit Kumar Professor and HOD, Dr. Anita, and other doctors, Department of Medical Oncology, Dr. B. R. Ambedkar Institute-Rotary Cancer Hospital, AIIMS, New Delhi, India, and also other medical experts in this field for their esteem guidance.

**AUTHOR CONTRIBUTIONS**

Dr. Navneet Singh: Study design, planning, interpretation of data, manuscript writing and approval of the version to be published. Dr. Sazal Patyar and Dr. Naveen Chandra Talniya: Interpretation of data and approval of the version to be published.

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

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