Ascites

- Most common complication of decompensation in cirrhosis
  - Develops in 5–10% of patients with compensated cirrhosis per year
- Significant impact on patients
  - Impairs patient working and social life
  - Frequently leads to hospitalization
  - Requires chronic treatment
  - Direct cause of further complications
  - Poor prognosis (5-year survival, ~30%)
- Ascites can be uncomplicated or refractory
  - Ascites is uncomplicated when not infected, refractory or associated with impairment of renal function

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Uncomplicated ascites: evaluation and diagnosis

- Cirrhosis is responsible for 80% of cases of ascites
- Initial patient evaluation:
  - History
  - Physical examination
  - Abdominal ultrasound
  - Laboratory assessment
    - Liver and renal function, serum and urine electrolytes, analysis of ascitic fluid
- Ascites is graded based on amount of fluid in the abdominal cavity

Grading of ascites*	
Grade 1	Mild ascites: only detectable by ultrasound examination
Grade 2	Moderate ascites: manifest by moderate symmetrical distension of abdomen
Grade 3	Large or gross ascites: provokes marked abdominal distension

*Ascites recurring on ≥3 occasions within a 12-month period despite dietary sodium restriction and adequate diuretic dosage are considered recurrent

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Uncomplicated ascites: evaluation and diagnosis

- Diagnostic paracentesis is indicated in:*
  - All patients with new-onset grade 2 or 3 ascites
  - Patients hospitalized for worsening ascites or any complication of cirrhosis

Recommendation	Grade of evidence	Grade of recommendation
Neutrophil count and culture of ascitic fluid culture† should be performed to exclude **bacterial peritonitis** • Neutrophil count >250 cells/µl denotes SBP	II-2	1
Ascitic total protein concentration should be performed to identify patients at higher risk of developing SBP‡	II-2	1
The SAAG should be calculated when the cause of ascites is not immediately evident, and/or when conditions other than cirrhosis are suspected§	II-2	1
Cytology should be performed to differentiate malignancy-related from non-malignant ascites	II-2	1

*Grade of evidence II-2, grade of recommendation 1; †Bedside inoculation blood culture bottles with 10 ml fluid each;
‡A total protein concentration <1.5 g/dl is generally considered a risk factor for SBP;
§SAAG ≥1.1 g/dl indicates that portal hypertension is involved in ascites formation with an accuracy of about 97%
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Uncomplicated ascites: management

- **Grade 1** or mild ascites
  - No data on evolution and not known if treatment modifies natural history
- **Grade 2** or moderate ascites
  - Hospitalization not required
  - Correct sodium imbalance:
    - Dietary restriction and increased renal excretion with diuretics

Recommendation	Grade of evidence	Grade of recommendation
Moderate restriction of sodium intake (80–120 mmol/day, corresponding to 4.6–6.9 g of salt) is recommended	I	1
Generally equivalent to a no added salt diet with avoidance of pre-prepared meals. Adequate nutritional education of patients on how to manage dietary sodium is also recommended	II-2	1
Very low sodium diets (<40 mmol/day) should be avoided	II-2	1
Prolonged bed rest cannot be recommended	III	1

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Uncomplicated ascites: recommended diuretics

- Mainstay of medical treatment are anti-mineralocorticoid drugs*
- Loop diuretics may be added in patients with long-standing ascites

Recommendation	Grade of evidence	Grade of recommendation
First episode of grade 2 ascites • Anti-mineralocorticoid drug alone (from 100 mg/day with 100 mg stepwise increased every 72 hours to a maximum of 400 mg/day if no response to lower doses)	I	1
In **patients who do not respond to anti-mineralocorticoids**† or who develop hyperkalaemia, furosemide should be added (from 40 mg/day with 40 mg stepwise increases to a maximum of 160 mg/day)	I	1
Long-standing or recurrent ascites • Combination of an anti-mineralocorticoid drug and furosemide (dose increased sequentially according to response)	I	1
Torasemide can be given in patients exhibiting a weak response to furosemide	I	2

*Spironolactone, canrenone or K-canrenoate; †Body weight reduction <2 kg/week

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Uncomplicated ascites: monitoring of patients receiving diuretics

- Loop diuretics can lead to potassium and magnesium depletion and hyponatraemia
- Muscle cramps can impair quality of life in patients receiving diuretics

Recommendation	Grade of evidence	Grade of recommendation
Frequent clinical and biochemical **monitoring** during the first weeks of treatment (particularly on first presentation)	I	1
Recommended **maximum weight loss**: 0.5 kg/day in patients without oedema, 1 kg/day in patients with oedema	II-2	1
Once ascites have largely resolved, the dose of diuretics should be reduced to the lowest effective dose	III	1
Discontinue diuretics in case of severe hyponatraemia,* AKI, worsening hepatic encephalopathy, or incapacitating muscle cramps	III	1
Discontinue **furosemide** for severe **hypokalaemia** (<3 mmol/L) Discontinue **anti-mineralocorticoids** for **hyperkalaemia** (>6 mmol/L)	III	1
Albumin infusion or baclofen administration† are recommended in patients with muscle cramps	I	1

*Serum sodium <125 mmol/L; †10 mg/day, with a weekly increase of 10 mg/day up to 30 mg/day

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Uncomplicated ascites: management of Grade 3 ascites

- **Grade 3** or large ascites
  - LVP, under strict sterile conditions, is the treatment of choice
    - Ascites should be completely removed in a single session*
  - Contraindications to LVP include:
    - Uncooperative patient, abdominal skin infection at puncture sites, pregnancy, severe coagulopathy, severe bowel distention

Recommendation	Grade of evidence	Grade of recommendation
LVP should be **followed with plasma volume expansion**	I	1
Plasma volume expansion should be performed by **albumin infusion** (8 g/L ascites) • For >5 L of ascites: more effective than other plasma expanders • For <5 L of ascites (low risk of PPCD): treat with albumin due to concerns about use of alternative plasma expanders	I III	1 1
After LVP, patients should receive the **minimum dose of diuretics** necessary to prevent re-accumulation of ascites	I	1
When needed, LVP should be performed in patients with AKI or SBP	III	1

*Grade of evidence I, grade of recommendation 1

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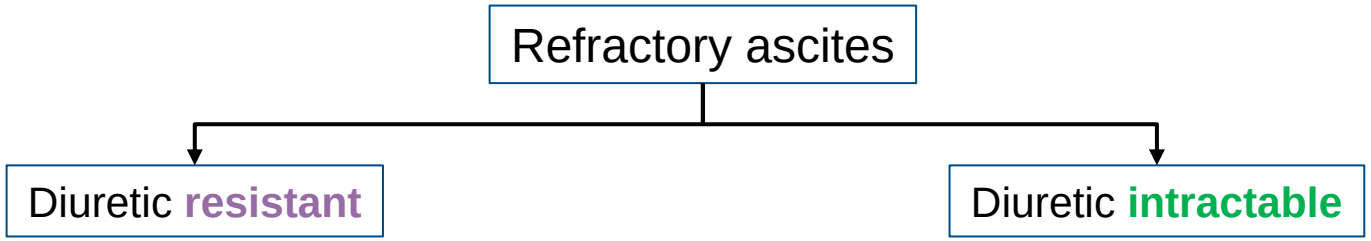
Refractory ascites: definition

- **International Ascites Club**:
  - "Ascites that cannot be mobilized or the early recurrence of which (after LVP) cannot be satisfactorily prevented by medical therapy"



Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a **lack of response to sodium restriction and diuretic treatment**

Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the **development of diuretic-induced complications that preclude the use of an effective diuretic dosage**

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Refractory ascites: management

- LVP is a safe and effective treatment
  - Should be associated with albumin administration to prevent PPCD
- Drug treatments are controversial or inadequately studied

Recommendation	Grade of evidence	Grade of recommendation
Repeated LVP plus albumin (8 g/L of ascites removed) are recommended as first-line treatment for **refractory ascites**	I	1
Diuretics should be discontinued in patients with refractory ascites who do not excrete >30 mmol/day of sodium under diuretic treatment	III	1
Although controversial data exist on the use of NSBBs in refractory ascites, caution should be exercised in severe cases* • High doses of NSBB should be avoided (i.e. propranolol >80 mg/day) • Carvedilol can not be recommended at present	 II-2 I	 1 2

*See also section on gastrointestinal bleeding

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Refractory ascites: indications for TIPS

- TIPS decompresses the portal system*
  - **Short term:** accentuates peripheral arterial vasodilation
  - **Within 4–6 weeks:** improves effective volaemia and renal function to increase renal sodium excretion

Recommendation	Grade of evidence	Grade of recommendation
Patients should be **evaluated for TIPS** insertion when: • There is **refractory or recurrent ascites** • Paracentesis is ineffective	I III	1 1
TIPS insertion is recommended in patients: • With **recurrent ascites** as it improves survival • With **refractory ascites** as it improves the control of ascites	I I	1 1
The use of **small-diameter PTFE-covered stents** is recommended to reduce the risk of TIPS dysfunction and hepatic encephalopathy	I	1
After TIPS insertion, continue the following until ascites resolution: • Diuretics and salt restriction • Close clinical follow-up	II-2 III	1 1

*By shunting an intrahepatic portal branch into a hepatic vein

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Spontaneous bacterial peritonitis: diagnosis

- Diagnosis is based on diagnostic paracentesis
- 50% of SBP episodes are present at hospital admission
  - **Signs/symptoms of peritonitis**: abdominal pain, tenderness, vomiting or diarrhoea, ileus
  - **Signs of systemic inflammation**: hyper- or hypothermia, chills, altered WBC count
  - **Worsening liver function**, **HE**, **shock**, **renal failure**, **GI bleeding**

Recommendation	Grade of evidence	Grade of recommendation
Diagnostic paracentesis should be carried out in: • Patients with cirrhosis and ascites, **at admission**, to rule out SBP • Patients with GI bleeding, shock, fever or other signs of systemic inflammation, worsening liver and/or renal function, and HE	II-2	1
SBP diagnosed by a neutrophil count in ascitic fluid >250/mm^3 • Neutrophil count is determined by microscopy or flow cytometry • **No clear evidence** to support routine use of **reagent strips**	II-2	1
Ascitic fluid culture positivity is not a prerequisite for SBP diagnosis*	II-2	1

*Culture should be performed to guide antibiotic therapy (Grade of evidence II-2, grade of recommendation 1)

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Management of SBP: empirical antibiotics

- Empirical IV antibiotics should be started immediately following diagnosis*
- Several factors should guide empirical antibiotic use†
  - Environment (community acquired vs. nosocomial)
  - Local bacterial resistance profiles
  - Severity of infection

Recommendation	Grade of evidence	Grade of recommendation
Third-generation cephalosporins are recommended as first-line antibiotic treatment for **community-acquired SBP** in countries with **low rates of antibiotic resistance**	I	1
• In countries with **high rates of antibiotic resistance** piperacillin/tazobactam or carbapenem should be considered	II-2	1
Antibiotic resistance is more likely in **healthcare-associated** and **nosocomial SBP** • Piperacillin/tazobactam: in areas with low prevalence of MDR bacteria • Carbapenem: in areas with high prevalence of ESBL-producing *Enterobacteriaceae* • Carbapenem + glycopeptides, daptomycin linezolid in areas with high prevalence of gram-positive MDR bacteria	I	1

*Grade of evidence II-2, grade of recommendation 1; †Grade of evidence I, grade of recommendation 1

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Management of SBP: empirical antibiotics

- Antibiotic therapy should be carefully controlled and monitored

Recommendation	Grade of evidence	Grade of recommendation
Severe infections by **XDR bacteria may require antibiotics** known to be highly **nephrotoxic in patients with cirrhosis** (e.g. vancomycin or aminoglycosides) • In these cases, patients' plasma levels should be monitored in accordance with local policy thresholds	III	1
De-escalation according to bacterial susceptibility based on positive cultures is recommended to **minimize resistance** selection pressure	II-2	1
Antibiotic **efficacy** should be checked with a **second paracentesis at 48 hours** from starting treatment • Suspect failure of first-line antibiotic if worsening clinical signs and symptoms and/or increase, or no marked reduction in leucocyte count (at least 25%) in 48 hours	II-2	1
The duration of treatment should be **at least 5–7 days**	III	1
Spontaneous bacterial empyema should be managed similarly to SBP	II-2	2

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Management of SBP: use of albumin

- In patients with SBP treated with a third generation intravenous cephalosporin antibiotic, albumin significantly decreased the incidence of type-1 hepatorenal syndrome and reduced mortality[1]

Recommendation	Grade of evidence	Grade of recommendation
The administration of albumin is recommended in patients with SBP • 1.5 g/kg at diagnosis and • 1 g/kg on Day 3	I	1

1. Sort P, et al. N Engl J Med 1999;341:403–9;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

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Management of SBP: primary prophylaxis

- Patients with cirrhosis and low ascitic fluid protein concentration (<10 g/L) and/or high serum bilirubin levels are at high risk of developing a first episode of SBP[1]

Recommendation	Grade of evidence	Grade of recommendation
Primary prophylaxsis with norfloxacin (400 mg/day) is recommended in patients with: • Child–Pugh score ≥9 and serum bilirubin level ≥3 mg/dl, and • Either impaired renal function or hyponatraemia, and • Ascitic fluid protein lower than 15 g/L	I	1
Norfloxacin prophylaxis should be stopped in patients with long-lasting improvement of their clinical condition and disappearance of ascites	III	1

1. Wiest R, et al. Gut 2012;61:297–310;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

Management of SBP: secondary prophylaxis

- In patients who survive an episode of SBP, the cumulative recurrence rate at 1 year is approximately 70%[1]

Recommendation	Grade of evidence	Grade of recommendation
Prophylactic norfloxacin (400 mg/day, orally) is recommended **in patients who recover from an episode of SBP**	I	1
At present, rifaximin cannot be recommended as an alternative to norfloxacin for secondary prophylaxis of SBP • At present, no recommendation can be given to guide prophylaxis of SBP among patients already on rifaximin for the prevention of recurrent HE	I	2
Patients who recover from SBP have a poor long-term survival and **should be considered for LT**	II-2	1
PPIs may increase the risk for the development of SBP, their use should be **restricted to those with a clear indication**	II-2	1

1. Rimola A, et al. J Hepatol 2000;32:142–53;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024