This guidance is based on LTHT guidelines for the management of Spontaneous Bacterial Peritonitis and was proposed and accepted by the network in 2010. It is intended for the guidance of hospital departments.

Summary/Quick reference guide

Diagnosis

History
The most common symptoms and signs of SBP are: fevers, increased confusion, diffuse abdominal pain and vomiting.
Determine previous history of liver disease and previous episodes of SBP.

Examination.
The most common signs in patients with SBP are pyrexia, confusion, ileus and other features of a systemic inflammatory response or severe sepsis, measure MEWS score.

SBP may be suspected on clinical grounds but confirmation and classification is a laboratory diagnosis.

Investigations

A routine diagnostic paracentesis should be performed PRIOR to starting antimicrobial therapy within 6 hours in all patients:
With a clinical suspicion of SBP
With cirrhosis and ascites on hospital admission,
on the development of ascites,
suffering gastrointestinal haemorrhage
with cirrhosis on the development of any local (abdominal pain, reduced motility) or systemic symptoms (fever, sepsis) or signs (encephalopathy, renal impairment).

<table>
<thead>
<tr>
<th>Test</th>
<th>Tube</th>
<th>Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (WCC) and differential</td>
<td>EDTA tube</td>
<td>Haematology</td>
</tr>
<tr>
<td>Culture &amp; susceptibility.</td>
<td>Universal container &amp; blood culture bottles</td>
<td>Microbiology</td>
</tr>
<tr>
<td>Protein, albumin, LDH, pH (amylase)</td>
<td>Li-Hep Yellow tube or universal container</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>Cytology</td>
<td>Universal container</td>
<td>Pathology</td>
</tr>
</tbody>
</table>

Table 1. Ascitic fluid tests required.
Consider ascitic fluid neutrophil count ≥ 250/mm³ (or 0.25 x10⁹/l) diagnostic for SBP in an appropriate clinical situation.

When culture unexpectedly yields an organism known to cause SBP in a patient without clinical signs of infection or with a low ascitic WCC, repeat ascitic tap.

When an ascitic culture yield a potential contaminant (e.g. coagulase-negative staphylococcus or "diphtheroid") repeat the ascitic tap.

If mixed organisms are seen on Gram-stain or cultured – (particularly anaerobes and Candida species). Consider a surgical cause or sampling from gut lumen.

Consider secondary bacterial peritonitis if ascitic fluid neutrophil count is climbing despite 48 hours of antibiotics.

Paracentesis may be repeated after 48 hours of treatment to assess the response to antibiotics.

**Non-antimicrobial management**

Urgent radiology (US/S if serum creatinine > 150 mmol/l, CT if normal renal function) and surgical review is mandatory for secondary SBP.

Early recognition and treatment of SBP is essential to preserve renal function. If creatinine raised send urine sodium. Urine sodium < 20 mmol/l suggests HRS.

If hypovolaemic give 1.5mg/kg body weight of albumin within 6 hours of the first antibiotic dose.

**Day 3** – If hypovolaemic repeat human albumin dose of 1mg/kg.

**After day 3** - Consider large volume paracentesis e.g. if diaphragmatic splinting or variceal haemorrhage – seek expert help.

**Antimicrobial treatment**

The literature supports the use of 3rd generation cephalosporins but many trusts around the region have limited the use of these antibiotics. For the guidance of the region, LTHT is recommending piperacillin/tazobactam 4.5g 8-hourly iv. However, network members are advised to discuss this with their microbiology departments to ensure it fits with infection prevention and control policies locally.

If genuine penicillin allergy LTHT is recommending – vancomycin 1g 12-hourly iv plus aztreonam 1g 8-hourly iv OR tigecycline 100mg loading followed by 50mg 12-hourly*. *Child Pugh C liver disease reduce to 25mg 12-hourly iv. However, network members are advised to discuss this with their microbiology departments to ensure it fits with infection prevention and control policies locally.

Discuss ongoing treatment with microbiology.

For directed therapy regimens, duration of treatment, switch to oral agent(s) see full guideline
Diagnosis and Management of Spontaneous Bacterial Peritonitis

Full guideline

Aims

To improve the diagnosis and management of spontaneous bacterial peritonitis.

Objectives

To provide evidence-based recommendations for the diagnosis and appropriate investigation of spontaneous bacterial peritonitis (SBP).
To provide evidence-based recommendations for appropriate empirical or directed antimicrobial therapy of SBP.
To standardise non-antimicrobial management of SBP.
To recommend appropriate dose, route of administration and duration of antimicrobial agents.
To advise in the event of antimicrobial allergy.
To set-out criteria for referral to specialists.

Background (there will be a direct link to this section on LHP)

Spontaneous bacterial peritonitis (SBP) is the infection of ascitic fluid in the absence of any intra-abdominal, surgically treatable source of infection (Conn et al., 1971) and in the absence of medical devices such as ventriculoperitoneal shunts or continuous ambulatory peritoneal dialysis catheters.

SBP is therefore sometimes referred to as “primary bacterial peritonitis” but the term SBP is used throughout this guideline.

SBP can occur at any age but this guideline concerns adults, in whom cirrhosis is the most common predisposing condition.

Current British Society of Gastroenterology (BSG) guidelines on the management of ascites in cirrhosis highlight the effect of early diagnosis and prompt treatment of SBP with a reduction of in-hospital mortality from 90% to less than 20% (Garcia-Tsao 2001).

Classification

Bacterial infection of ascitic fluid can be classified in the table below based on (Koulaouzidis, 2007).
Diagnosis and Management of Spontaneous Bacterial Peritonitis

<table>
<thead>
<tr>
<th>Category</th>
<th>Ascitic fluid analysis</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous bacterial peritonitis (SBP)</td>
<td>PMN ≥250/mm³</td>
<td>Single organism</td>
</tr>
<tr>
<td>Culture-negative neutrocytic ascites</td>
<td>+</td>
<td>negative</td>
</tr>
<tr>
<td>Monomicrobial non-neurocytic bacterascites</td>
<td>-</td>
<td>Single organism</td>
</tr>
<tr>
<td>Polymicrobial bacterascites</td>
<td>-</td>
<td>multiple</td>
</tr>
<tr>
<td>Secondary bacterial peritonitis</td>
<td>+</td>
<td>Multiple organisms</td>
</tr>
</tbody>
</table>

Table 2. Classification of ascitic fluid infection.

Alternative causes of neutrocytic ascites should be considered:
- Peritoneal tumour deposits
- Pancreatitis
- TB
- Connective tissue disease
- Haemorrhage into ascitic fluid.

Incidence

The reported incidence in patients with ascites varies from 7 to 30% per annum (Rimola et al., 2000, Sherlock 2002, Soares-Weiser et al., 2005, Wong 2005). Patients with cirrhosis can also develop similar spontaneous infection of the pleural fluid (Arroyo et al., 2000). SBP occurs primarily in patients with pre-existing ascites in the setting of cirrhosis. It is less common in those with sub-acute liver disease e.g. alcoholic hepatitis.

Risk factors for developing SBP include:
- Prior episode of SBP – (two-thirds develop a recurrence within a year)
- GI bleeding (variceal haemorrhage)
- Ascitic total protein < 1.0 g/dl
20% of patients with cirrhosis who have a variceal haemorrhage develop SBP at the time of admission and 50% of these develop SBP during the admission. Infections are associated with higher rates of rebleeding and a higher mortality (Garcia-Tsao 2004).

**Pathogenesis**

Bacterial seeding of ascitic fluid is the common denominator of ascitic fluid infections. However the route of bacterial entry is controversial. Two theories of the initial step in pathogenesis are proposed, the first being the currently favoured model:

**Translocation.** Bacterial translocation is the passage of bacteria from the gut lumen into mesenteric lymph nodes and thereafter into the blood stream and other extra-intestinal sites (Guarner 2005). Translocation is promoted by abnormal gut flora, mucosal oedema and altered gut permeability. Bacterial overgrowth in association with impairment of the intestinal barrier, alterations of local immune defences, slow motility of the bowel, and reduced opsonic activity may precede the episodes of bacterial translocation (Cirera et al., 2001, Guarner 2005). Interestingly the gut microflora of animals with cirrhosis contains an increased proportion of Gram-negative bacteria (Guarner et al., 1997). Furthermore Frances et al. (2004) described bacterial DNA in 30% of peritoneal macrophages isolated from patients with cirrhosis and ascites. These macrophages exhibited an activated phenotype.

**Haematogenous.** 50% of episodes of SBP are accompanied by bacteraemia (Friedman et al., 2004). The organism is identical to that cultured from ascitic fluid and can sometimes be isolated from urine or sputum. This suggests haematogenous seeding of the ascitic fluid might be the initial key step in pathogenesis.

**Microbiology**

The microorganisms isolated from patients with SBP are most commonly members of the normal microbial flora of the gastrointestinal tract including *Escherichia coli* (70%), *Klebsiella* species (10%), *Proteus* species (4%), *Enterococcus faecalis* (4%), *Pseudomonas* species (2%) and others (6%) (Arroyo et al., 2000). Beta-haemolytic streptococci and *Streptococcus pneumoniae* are also an important cause in a small number of patients.

The cultures results of all ascetic fluid samples that grew a single organism in Leeds during the 3 years 2006-2008 are shown in Figure 1. The raw data are presented without an assessment of clinical significance, the large number of coagulase negative staphylococci (CNS) cultured suggests a high rate of sample contamination with skin flora.
Figure 1. Results of ascitic fluid cultures that grew a single organism from samples sent January 2006-December 2008. 1875 samples were sent. CNS=coagulase negative staphylococci.

Prognosis

Mortality for an episode of SBP remains high at 20 to 40%. Patients with cirrhosis who survive an episode of SBP have a 40 to 70% chance of recurrence within 12 months (Wong et al., 2005). Patients who recover from an episode of SBP should be considered as potential candidates for liver transplantation (Rimola et al., 2000). Guidance on prevention of subsequent episodes of SBP will be provided in LTHT prophylaxis guideline (link) currently under development. The environment in which a patient acquires SBP (nosocomial or community) does not appear to affect either the short or long term survival (Song et al., 2006).
Clinical diagnosis  (there will be a direct link to this section on LHP)

History

The most common symptoms and signs in patients with SBP are: fevers, increased confusion, diffuse abdominal pain and vomiting.

Determine previous history of liver disease and previous episodes of SBP.

Examination.

The most common signs in patients with SBP are pyrexia, confusion, ileus and other features of a systemic inflammatory response or severe sepsis.

<table>
<thead>
<tr>
<th>Symptoms &amp; signs</th>
<th>SBP (%)</th>
<th>Bacterascites (%)</th>
<th>CNNA (%)</th>
<th>Secondary peritonitis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>68</td>
<td>57</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>49</td>
<td>32</td>
<td>72</td>
<td>67</td>
</tr>
<tr>
<td>Tenderness</td>
<td>39</td>
<td>32</td>
<td>44</td>
<td>59</td>
</tr>
<tr>
<td>Rebound</td>
<td>10</td>
<td>5</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>54</td>
<td>50</td>
<td>61</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 3. Adapted from Sleisenger’s & Fordtran’s Gastrointestinal & Liver Disease, 7th Ed, Elsevier.

Many of the features of liver failure make the recognition of sepsis difficult. For example, the reduced peripheral neutrophil count due to hypersplenism, elevated basal heart rate and relative hypotension due to the hyperdynamic circulation and basal hyperventilation due to encephalopathy (Wong et al., 2005). A high index of suspicion must be maintained.  [Evidence level C]

SBP may be suspected on clinical grounds but confirmation and classification is a laboratory diagnosis (see investigations below).

(Initial) Investigations  (there will be a direct link to this section on LHP)

SBP can only be diagnosed by examining a sample of ascitic fluid. Abdominal paracentesis (ascitic tap) is safe (Runyon 1986, Lin et al., 2005).

Recommendation: A routine diagnostic paracentesis should be performed PRIOR to starting antimicrobial therapy within 6 hours in all patients:

- with a clinical suspicion of SBP
- with cirrhosis and ascites on hospital admission,
- on the development of ascites,
- suffering gastrointestinal haemorrhage
- with cirrhosis on the development of any local (abdominal pain, reduced motility) or systemic
Diagnosis and Management of Spontaneous Bacterial Peritonitis

A number of ascitic fluid parameters have been evaluated for the diagnosis of SBP. The highest accuracy for a diagnosis of SBP can be made from a pH ≤ 7.34 or a blood-ascitic fluid gradient ≥ 0.10 in combination with an ascitic fluid neutrophil count > 500/mm$^3$ (Stassen et al., 1986). An ascitic fluid neutrophil count ≥ 250/mm$^3$ is consistent with a diagnosis of SBP (Garcia-Tsao 1992, Arroyo et al., 2000). The total white cell count can also be used to diagnose SBP. Runyon et al. (2006) suggest a WCC > 500/mm$^3$ is diagnostic, irrespective of the differential. The ascitic cell count and differential is performed by automated techniques in the laboratory.

Recommendation: Samples of ascitic fluid should be routinely sent to haematology for a differential white cell count [Evidence level B].

Recommendation: an ascitic fluid neutrophil count ≥ 250/mm$^3$ (or 0.25 x 10$^9$/l) should be considered diagnostic for SBP in an appropriate clinical situation. [Evidence level B]

Leukocyte esterase reagent strips have a high sensitivity (64 to 100%) and specificity (92.5 to 100%) in the detection of an elevated ascitic fluid neutrophil count (Castelote et al., 2002, Sapey et al., 2005). Although these are cheap, rapid and readily available on wards (urine dipsticks) microscopy is an absolute requirement so bedside testing will not alter management and is not therefore recommended.

Recommendation: use of Leukocyte esterase reagent strips is not recommended for the diagnosis of SBP. [Evidence level D]

The yield of ascitic fluid culture can be increased from ~45% to more than 80% by inoculating ascitic fluid samples into blood culture bottles (Bobadilla et al., 1989). At least 10ml of fluid is required.

Recommendation: 10ml ascitic fluid should be inoculated directly into both an aerobic and anaerobic blood culture bottle according to Standard operating procedure. [Evidence level D]

Recommendation: When an ascitic culture unexpectedly yields an organism known to cause SBP in a patient without clinical signs of infection or with a low ascitic WCC the ascitic tap must be repeated to reassess the neutrophil count and re-culture (Rimola et al., 2000). [Evidence level C]

Recommendation: When an ascitic culture yield a potential contaminant (e.g. coagulase-negative staphylococcus or “diphtheroid” the ascitic tap should be repeated to reassess the neutrophil count and re-culture (Rimola et al., 2000). [Evidence level C]

Recommendation: If mixed organisms are seen on Gram-stain or cultured – (particularly anaerobes and Candida species). Consider a surgical cause or sampling from gut lumen. [Evidence level C]

Recommendation: consider secondary bacterial peritonitis if ascitic fluid neutrophil count is climbing despite 48 hours of antibiotics. [Evidence level C]

Paracentesis may be repeated after 48 hours of treatment to assess the response to antibiotics. [Evidence level C]
Non-Antimicrobial Treatment (there will be a direct link to this section on LHP)

Secondary bacteria peritonitis is suggested by an ascitic fluid neutrophil count ≥250/mm³ and multiple gut organisms on Gram-stain and culture.

Secondary bacteria peritonitis is suggested from the ascitic fluid analysis by:

- Total protein > 1.0g/dl
- Glucose < 50mg/dl (2.78 mmol/l)
- Raised LDH (Rimola et al., 2000, Wong et al., 2005).

Recommendation: Urgent radiology (US/S if serum creatinine > 150 mmol/l, CT if normal renal function) and surgical review is mandatory for secondary bacterial peritonitis. [Evidence level B]

Patients with SBP are at risk of hepatorenal syndrome (HRS). Bacteria and their endotoxins trigger a systemic inflammatory response with vasodilatation, hypotension and a hyperdynamic circulation. The development of renal impairment in SBP carries a poor prognosis (Ruiz-del-Arbol et al., 2003).

Recommendation: Early recognition and treatment of SBP is essential to preserve renal function. If Creatinine raised send urine sodium. Urine sodium < 20 mmol/ suggests HRS.

Sort et al. (1999) described the use of human albumin solution as a plasma expander in SBP. The use of albumin improved the mortality rate in SBP from 29 to 10%. The study had no control plasma expander. However albumin may play an additional role to simple plasma expansion: It may bind endotoxin, improve opsonisation within ascitic fluid and stabilise the vascular endothelium.

Recommendation: If the patient is hypovolaemic consider the administration of 1.5mg/kg body weight of albumin within 6 hours of the first antibiotic dose. A repeat dose of 1mg/kg may be given on day 3. [Evidence level B]

The role of large volume paracentesis in SBP is unclear. Ruiz-del-Arbol et al. (2003) described a higher incidence of renal impairment and hyponatraemia following paracentesis. However this was not statistically significant. Anecdotal evidence suggests that ascites rapidly reaccumulates during SBP making paracentesis during acute infection worthless. More clinical data is required.

Recommendation: routine use of large volume paracentesis is not recommended for the treatment of SBP. [Evidence level B] Paracentesis may still have a role if diaphragmatic splinting or variceal haemorrhage – seek expert help.

Empirical antimicrobial treatment (there will be a direct link to this section on LHP)

The initial decision to treat suspected ascitic fluid infection is based on an elevated fluid neutrophil count
and/or the clinical setting. A high index of suspicion is essential. CNNA and SBP have comparable mortality rates so similar management is warranted.

LTHT is recommending empirical regimen for SBP with piperillin/tazobactam 4.5g 8-hourly iv. However, due to the introduction of local antibiotic policies, departments around the region are advised to reach local agreement with their microbiology departments. If there is genuine penicillin allergy LTHT is recommending vancomycin 1g 12-hourly iv plus aztreonam 1g 8-hourly iv OR tigecycline 100mg iv loading followed by 50mg 12-hourly iv*. Similarly, due to the introduction of local antibiotic policies, departments around the region are advised to reach local agreement with their microbiology departments. (Evidence level D, the use of cephalosporins is evidenced in the literature).

*Tigecycline requires dosage adjustment in Child Pugh C liver disease to 25mg 12-hourly iv.

**Justification/Evidence review.**

Empirical antimicrobial therapy should be started early after appropriate sampling and have activity against coliforms such as Escherichia coli and Klebsiella species, and Gram positives such as Enterococcus faecalis and streptococci. Nephrotoxic antimicrobials should be avoided if at all possible. The choice of antimicrobial therapy must take into consideration the increasing frequency of hospital acquired infections, for example, a recent audit at Leeds Teaching Hospitals NHS Trust has identified that patients with liver failure are at increased risk of Clostridium difficile infection.

The use of antibiotics for SBP in patients with cirrhosis has been described in the Cochrane Database of Systematic Reviews (2009). Thirteen studies were included in this review. No meta-analysis was performed since each trial compared different antibiotics in their experimental and control groups. These trials looked at the following antibiotics: intravenous (iv)/oral (po) ciprofloxacin, iv ceftazidime, iv cefotaxime, iv amikacin, iv cefotaxime, iv ampicillin-tobramycin, iv/po moxifloxacin, iv/po co-amoxiclav, oral cefixime and oral ofloxacin. The most commonly used antibiotics were 3rd generation cephalosporins although these did not demonstrate superior efficacy over other antibiotics.

Up to 10% of infections are caused by Gram-positive cocci (particularly Enterococcus species). Ampicillin-tobramycin and co-amoxiclav have been used with the assumption that they would provide adequate Gram-positive cover.

The Cochrane review made no firm conclusions from the randomised controlled trials. Although third generation cephalosporins have been established as the standard treatment of SBP in many centres, current concerns about Clostridium difficile infection, selection of extended-spectrum beta-lactamase (ESBL) producing coliforms and adequacy of spectrum have raised questions about the wisdom of this approach.

The final recommendation were influenced by local epidemiology and resistance patterns which are shown in Figures 1 and 2.
Piperacillin/tazobactam was chosen in order to provide appropriate antimicrobial cover (including enterococci, streptococci, and resistant gram-negative including *Pseudomonas* species) and to avoid the use of cephalosporins, quinolones (whose activity can no longer be relied upon for empirical treatment) and gentamicin (to reduce the risk of toxicity). Vancomycin and aztreonam in combination provides a similar spectrum of activity. Tigecycline has an appropriate spectrum of activity (active against *Staphylococcus aureus*, enterococci and many Gram negatives but not *Pseudomonas*). Tigecycline is licensed for use in intrabdominal infections but data specific for spontaneous bacterial peritonitis are lacking.

N.B. Coamoxiclav susceptibility was not been routinely tested in the laboratory during the review period so data are not available. Cefuroxime can be used as a reasonable marker of co-amoxiclav susceptibility. This antimicrobial is less broad spectrum than piperacillin/tazobactam against Gram-negatives and lacks antipseudomonal activity.

**Directed therapy**

If ascitic fluid culture results are positive then antimicrobials should be changed to optimise effectiveness and reduce adverse effects - this will usually be the most narrow spectrum effective agent available.

Directed therapy should be determined on a case by case basis with discussion with microbiology if required.

**Oral switch**

There is some evidence to support a switch from intravenous to oral antibiotics early in patients who show an improvement after a short iv course. Oral therapy alone may be possible from the start of treatment in those without systemic inflammatory response or renal failure. Oral ciprofloxacin/ofloxacin, co-amoxiclav, and oral 3rd generation cephalosporins demonstrated non-inferiority when compared to iv therapies. Oral ofloxacin was compared with iv cefotaxime in 123 patient with uncomplicated SBP (no encephalopathy, renal failure, vomiting, ileus, shock or GI haemorrhage) - no difference in the number of deaths, resolution of SBP or presence of adverse effects was seen. Two
3rd generation cephalosporins were compared in 38 patients - oral cefixime vs iv ceftriaxone, but no significant differences were found for any of the outcomes provided. No difference in effectiveness or mortality was demonstrated when oral ciprofloxacin was compared to iv ciprofloxacin in 80 cirrhotic patients with SBP.

Recommendation: Switch to oral antimicrobials should be considered when patients are clinically improving, afebrile and inflammatory markers falling. [Evidence level C]

If patients have been commenced on piperacillin tazobactam then oral co-amoxiclav 625mg 8-hourly is appropriate for oral switch unless culture results indicate otherwise. [Evidence level B]

**Duration of therapy**

In most studies the length of treatment was based on disappearance of symptoms and signs. One study demonstrated no difference in either mortality or resolution of SBP with 5 or 10 days treatment with intravenous cefotaxime.

Recommendation: To reduce adverse events including selection for resistant bacteria five days should be the standard duration, extended up to 10 days if clinical response is slow. [Evidence level B]

Provenance: Author name(s) and address(es)

Dr Jason Jennings, Consultant Gastroenterologist, Leeds Teaching Hospitals

Dr Jonathan Sandoe, Consultant Microbiologist, Leeds Teaching Hospitals

Dr Mervyn Davies, Consultant Hepatologist, Leeds Teaching Hospitals

Mr Dan Greer Pharmacist, Lead GI Pharmacist, Leeds Teaching Hospitals

Miss Faye Coxen, Liver Unit, Leeds Teaching Hospitals

Clinical condition- SBP

Target patient group – all adult patients with SBP

Target professional group (clinical competence) all healthcare professional caring for patients with SBP.

Evidence Bases: References


Diagnosis and Management of Spontaneous Bacterial Peritonitis


Sleisenger’s & Fordtran’s Gastrointestinal & Liver Disease, 7th Ed, Elsevier Inc.


Sort P et al. Effects of intravenous albumin on renal impairment and mortality in patients with cirrhosis and


Evidence levels:

A. Meta-analyses, randomised controlled trials/systematic reviews of RCTs
B. Robust experimental or observational studies
C. Expert consensus
D. Leeds consensus. (where no national guidance exists or there is wide disagreement with a level C recommendation or where national guidance documents contradict each other)

**Guideline Provenance:**

As detailed above. Reviewed and accepted at network meeting April 2010. Adopted initially as WYHN guidance, the WEYHN and YHLN guidance with name changes in 2010 and 2012 respectively. Review date October 2013.

Diagnosis and Management of Spontaneous Bacterial Peritonitis