THE NORTHERN HOSPITAL

SPONTANEOUS BACTERIAL PERITONITIS

A glass laboratory flask used by Louis Pasteur in his experiments in the 1860s, London Science Museum.

...Now there is one property that animals are found to have in common with plants. For some plants are generated from the seed of plants, whilst other plants are self-generated through the formation of some elemental principle similar to a seed; and of these latter plants some derive their nutriment from the ground, whilst others grow inside other plants, as is mentioned, by the way, in my treatise on Botany. So with animals, some spring from parent animals according to their kind, whilst others grow spontaneously and not from kindred stock; and of these instances of spontaneous generation some come from putrefying earth or vegetable matter, as is the case with a number of insects, while others are spontaneously generated in the inside of animals out of the secretions of their several organs..

Aristotle, "History of Animals", Book V, Part 1, Fourth Century, B.C

I have removed from it, the only thing that it has not been given to man to produce ....I have removed life, for life is the germ, and the germ is life. Never will the doctrine of spontaneous generation recover from the fatal blow that this simple experiment delivers to it"

Louis Pasteur, Lecture at the Sorbonne, 7th April 1864.

From at least the Fourth century, B.C it was well recognized that life arose from parents, eggs or seeds in some way, but in many cases, life it appeared to arise from none of these sources, a case in point being that of fungal growth arising from dead or decaying organic matter, or maggots seemingly arising from rotting inanimate meat. Aristotle in his "History of Animals" articulated the prevailing view of many that life could also arise, "spontaneously" that is from non-living matter. This was a remarkably resilient orthodoxy that persisted for well over two millennia. Life could, under certain circumstances, it was held, arise from non-life. Debate over the theory of spontaneous generation" as it was called raged into the mid-Nineteenth century.

In centuries subsequent to Aristotle, it came to be believed that even large creatures such as mice, eels or even crocodiles could arise spontaneously out of the mud of the Nile. The theory of spontaneous generation was taken up by the authorities of the Church, who held that the classical ancients had firmly established all worldly knowledge. Augustine of Hippo discussed spontaneous generation in "The City of God" and applied it to the literal meaning of Genesis, citing Biblical passages such as "Let the waters bring forth abundantly the moving creatures that have life" (Genesis 1:20) Life in other words could spontaneously arise in seawater, as well as the mud of the Nile.

But by the Seventeenth century Leeuwenhoek in the Netherlands and Robert Hooke in England had discovered the world of microscopic animals, and doubts began to be raised about the theory of spontaneous generation. In the Nineteenth century Robert Koch discovered the existence of bacteria. By this time it was believed that all larger organisms arose from their parents, eggs or seeds. Fungi could arise from spores, but the question remained one of the "chicken and the egg". Where did microscopic spores or bacteria come from. In these the idea of spontaneous generation still held sway. By now it was known that boiling water could kill microorganisms and render a "broth" sterile. But when left to sit and cool the broth soon once again became cloudy. Debate

raged as to whether microorganisms arose spontaneously in the broth or where introduced from the external atmosphere. It would be left to the brilliant French scientist Louis Pasteur to settle the issue of spontaneous generation once and for all. Though Pasteur did not originate germ theory, he did provide sufficient experimental evidence to convince most of the scientific community that it was true. He also demonstrated the importance of heat treatment of milk, beer and wine that would kill bacteria, a process that become known as "pasteurization" which was named in his honor. The pasteurization of milk greatly reduced the risk of contracting tuberculosis. On the question of spontaneous generation, Pasteur sterilized a series of beef broth solutions in specially designed "swan neck" flasks. He then demonstrated that those flasks that were exposed to air and dust soon became cloudy once more due to microbial growth, but in other flasks that had been sealed from the environment, no microbial growth was seen. When the seals were broken, microbial growth occurred. By these experiments he essentially showed that all bacteria originated from other bacteria, and at the same time disproved the theory of spontaneous generation. He famously declared at the Sorbonne on 7th April 1864; "I have removed from it, the only thing that it has not been given to man to produce (i.e. microbes)… I have removed life, for life is the germ, and the germ is life. Never will the doctrine of spontaneous generation recover from the fatal blow that this simple experiment delivers to it"

One famous flask that was sealed by Pasteur remains today the in the science Museum in London. After well over a century and a half, it remains sterile!

To modern sensibilities, the question of the "spontaneous generation" of life is now debated on a far more sophisticated level. Though we accept that all life is the result of generation from a preceding parental life form, there must have been some point in deep geological time that the first "life" did in fact arise - by untold steps over untold eons- from a "broth" of non-life chemicals. The point at which non-life chemicals suddenly became life is obscure, and perhaps is ultimately merely a point of semantics! Either way we do believe that life arose in the sea - giving a modern poignancy to Genesis's - "Let the waters bring forth abundantly the moving creatures that have life". But even if life did arise from non-life - the basic question still remains, where did the non-life arise from? 21st Century quantum physicists now tell us that matter arose "spontaneously" from "quantum fluctuations" - out of nothing - if so then this "truth" is even stranger than crocodiles arising spontaneously from the mud of the Nile!

The entity known as "Spontaneous bacterial peritonitis" remains somewhat of a mystery to us. It was so named on account of the apparent "spontaneous" appearance of pathogenic bacteria within the ascitic fluid of cirrhotic patients. Of course we have known since the time of Louis Pasteur, that bacteria do not arise spontaneously, it is more of a question of how they are translocated from the gut.

SPONTANEOUS BACTERIAL PERITONITIS

Introduction

Spontaneous bacterial peritonitis (SBP) is defined as an ascitic fluid infection without evidence of an intra-abdominal surgically-treatable source, (hence the appellation, "spontaneous").

It is usually a complication of **large volume ascites** in patients with **chronic cirrhotic liver disease** of any cause.

Generally, no *source* of the infecting agent is easily identifiable, however, contamination of dialysate solutions or improper aseptic technique can cause the condition among those receiving **peritoneal dialysis.**

SBP should be considered in any patient with ascites whose clinical state deteriorates.

A high index of suspicion must be maintained for patients with chronic cirrhotic liver disease and ascites, particularly those with any **acute clinical deterioration.**

The diagnosis is confirmed by a **positive ascitic fluid bacterial culture** and an ascitic fluid **absolute polymorphonuclear leukocyte count $\geq$ 250 cells/mm^3.**

A main challenge will be to distinguish SBP from a surgical condition such as GIT perforation. Both conditions have high mortality if missed. SBP patients have high mortality if they undergo needless laparotomy. Perorated GIT patients have very high mortality if they are not operated on.

History

Dr. Harold O. Conn first recognized the SBP in the 1960s.

When the phrase spontaneous bacterial peritonitis was coined in 1964, the descriptor "spontaneous" was used simply because the origin of the infection was unknown.

Pathology

The exact mechanism of bacterial migration from the GI tract into ascites fluid is unclear.

Hematogenous transmission in combination with an impaired immune system is one current theory.

Organisms:

The majority of cases are caused by a single organism.

Pathogens most associated with SBP include: [1]

1. Gram-negative bacilli:
    - Escherichia coli
    - Klebsiella species
2. Streptococcal species

Less commonly:

3. Enterococci
4. Anaerobes

Causes:

1. Generally no clear source of infection is found
2. Patients receiving peritoneal dialysis:
    - Contamination of dialysate solutions
    - Improper aseptic technique

Risk factors:

These include:

1. Chronic liver disease with cirrhosis
2. Large volume ascites
3. Peritoneal dialysis patients
4. Patients with low protein levels in ascitic fluid (< 1 gram/dL) have a 10 fold higher risk of developing spontaneous bacterial peritonitis than those with a protein level greater than 1 gram/dL.
5. Previous episode of SBP.
6. Low complement levels.

Clinical features

The presence of SBP almost always occurs in patients with **cirrhosis** and **ascites.**

It is suspected because of suggestive features of acute illness as listed below:

1. Abnormal vital signs:
    - **Fever**
    - Tachycardia
    - Tachypnea
    - Hypotension
2. Altered mental status: confusion/ clouded conscious state.
3. Abdominal pain
4. Abdominal tenderness:
    - This may range from no tenderness to a frankly peritonitic picture mimicking an acute surgical emergency.
    - Note however that the signs and symptoms of both SBP and surgical peritonitis in the presence of ascites can be masked.

      Ascites may prevent the development of a rigid abdomen by separating the visceral from the parietal peritoneal surfaces. Thus, even with frank perforation of the colon a classic "surgical abdomen" may not develop.
5. Diarrhea
6. Worsening or new-onset renal failure.
7. Unexplained ileus.

If unrecognized and untreated, death may result from **septic shock** and/ or renal failure from **hepatorenal syndrome.**

Differential diagnoses:

The principle ones will be from

1. An acute surgical problem including:
    - Bowel obstruction
    - Bowel perforation - with **secondary bacterial peritonitis.**
    - Intraabdominal abscess

2. Acute alcoholic hepatitis.

SBP versus Secondary bacterial peritonitis:

The distinction of secondary bacterial peritonitis from SBP is crucial because the former usually requires antibiotics and surgical treatment, whereas the latter only requires antibiotics.

Differences can be summarized thus:

Feature	**SBP**	**Secondary bacterial peritonitis**
Definition	Ascitic fluid infection without evidence of an intra-abdominal surgically-treatable source	Ascitic fluid infection in which there is a surgically-treatable intra-abdominal source of infection
Ascitic fluid glucose	Generally > 2.8 mmol/L	Generally < 2.8 mmol/L
Serum protein - ascitic protein **Total ascitic protein**	**> 1.1 grams /dL**, the patient has portal hypertension and SBP more likely Total protein < than 1 gram/dL	**<1.1 g/dL**, portal hypertension is not present and SBP is unlikely. Total protein > than 1 gram/dL
LDH		Lactate dehydrogenase above the upper limit of normal for serum
Organism types	Usually single organism	Multiple organisms
Radiological imaging CXR/AXR/ CT scan	No abnormality	Obstruction, perforation, abscess formation detected.

Investigations

The diagnosis of SBP is essentially established by a positive ascitic fluid bacterial culture and an elevated ascitic fluid absolute PMN count $\geq$ 250 cells/mm^3.

Definitive diagnosis therefore cannot be established in the ED, when culture results are not available, and treatment is initially presumptive based on the index of clinical suspicion as well as supportive investigation results.

Blood tests:

1. FBE:
    - There may be an elevated WCC
2. CRP:
    - May be elevated
3. U&Es/ glucose
4. LFTs, including albumin.
5. Coagulation profile
6. Blood cultures:
    - Blood culture results are positive for in as many as 33% of patients with spontaneous bacterial peritonitis and can help guide antibiotic therapy. [3]

Diagnostic Paracentesis

This should ideally be done before any antibiotics are given, unless the patient is particularly unwell/ septic.

About 20 mls of fluid is generally sufficient for testing.

In peritoneal dialysis patients with a peritoneal catheter, fluid can be withdrawn from the catheter with a sterile technique.

In the vast majority of patients, a paracentesis can be safely carried out *despite* an elevated international normalized ratio (INR). [2]

Ultrasonography may aid paracentesis if ascites is minimally detectable or its presence is uncertain.

Fluid is tested for:

1. Gram stain microscopy and culture, (aerobic and anaerobic).
    - Gram stain is notoriously insensitive for detecting SBP and is associated with a high false-positive rate

However, a Gram stain can help differentiate SBP from secondary bacterial peritonitis due to gut perforation. In the latter, the Gram stain may show **multiple different bacterial species.** A single organism is usually the cause of SBP.

- If tuberculous peritonitis is suspected, additional fluid should be obtained for acid fast bacteria smear and Mycobacterial culture, however yield is low.

  If there is high suspicion, peritoneoscopy with mycobacterial culture and histology of a biopsied tubercle will be required to confirm the diagnosis.

2. Total cell count and differential: [1]

   Diagnostic results include:

   - A total white cell count **> 500/mm^3**

   And/or

   - A neutrophil count **> 250/mm^3**

3. Biochemistry:

   - Albumin

     ♥ To enable a serum-ascites albumin gradient to be determined.

     The vast majority of patients with SBP have advanced cirrhosis with portal hypertension.

     The serum-ascites albumin gradient indirectly measures portal pressure.

     It is helpful in the diagnosis of SBP because, with the exception of patients with nephrotic syndrome, SBP rarely develops in patients who do not have portal hypertension.

     The ascitic fluid value is subtracted from the serum value to obtain the gradient.

     If the *difference* (**not the ratio**) is **> 1.1 grams /dL**, the patient has portal hypertension, (with 97 % accuracy).

     If the difference is **< 1.1 grams/dL**, portal hypertension is not present and **SBP is unlikely.**

- Protein:
  - ♥ Total protein > 1 gram /dL (10 g/L) makes secondary bacterial peritonitis the more likely diagnosis.
  - ♥ Ascitic fluid total protein concentration correlates inversely with the risk of developing SBP.

    Patients with the most dilute ascites (i.e protein concentration < 1 gm/dL) have the lowest concentration of opsonins in the ascitic fluid and are at the highest risk of getting SBP.
- Glucose: [2]
  - ♥ Neutrophils can consume large quantities of glucose.

    Thus, the concentration of PMNs in ascitic fluid and their degree of stimulation have a rough inverse correlation with the glucose concentration.

    The glucose concentration generally remains above **2.8 mmol/L** in SBP but frequently falls below this level in secondary bacterial peritonitis.

    This difference may be related to the fact that patients with SBP typically have lower ascitic fluid PMN counts than patients with secondary bacterial peritonitis. In the setting of gut perforation, the ascitic fluid glucose concentration may fall to near zero
- Lactate dehydrogenase (LDH):
  - ♥ Lactate dehydrogenase in ascitic fluid is released from PMNs that have lysed.

    The concentration is increased in SBP and is even further elevated in secondary bacterial peritonitis

    The upper limit of normal for LDH varies by laboratory. In *sterile* ascitic fluid in the setting of cirrhosis, the LDH is generally in the range of 20 - 60 units/L.
- Amylase/ lipase:
  - ♥ These are elevated in **GIT perforation** or **pancreatitis.**
- Bilirubin: [2]

♥ An elevated bilirubin concentration in the ascitic fluid suggests perforation of the gallbladder into the peritoneum (choleperitoneum).

The bilirubin concentration should only be measured if the ascitic fluid is dark orange or brown.

Gallbladder perforation is likely if the ascitic fluid bilirubin concentration is:

♥♥ Higher than that of serum, (Ascitic fluid bilirubin concentration averages about 0.7 mg/dL, a value that is approximately one-third of the plasma value)

♥♥ Greater than 6 mg/dL

And

♥♥ Is not associated with an elevated ascitic fluid amylase (which would suggest upper intestinal perforation rather than gallbladder perforation).

Plain radiography/ CT Scan:

CXR/erect and supine films and/or CT scan may be required to rule out possible bowel obstruction or perforation or intraabdominal abscess.

Management

Prophylaxis: [1]

Secondary Prophylaxis:

After a **first episode** of spontaneous bacterial peritonitis the use of **secondary antibiotic prophylaxis** to prevent subsequent episodes of SBP in patients with **ascites due to cirrhosis** is now well established.

Use:

- **Trimethoprim + sulfamethoxazole** 160 + 800 mg (child 1 month or older: 4 + 20 mg/kg up to 160 + 800 mg) orally, daily.

If trimethoprim + sulfamethoxazole is contraindicated or has previously failed, use:

- **Norfloxacin** 400 mg (child: 10 mg/kg up to 400 mg) orally, daily.

Primary Prophylaxis:

In patients with ascites due to cirrhosis, **primary** antibiotic prophylaxis for the prevention of SBP is *controversial* and should be considered on an individual patient basis.

The potential clinical benefits of primary prophylaxis may be outweighed by the potential harms, which include the development of **antibiotic resistance** and the risk of ***Clostridium difficile*** infection.

Primary prophylaxis may be *considered* in patients who have **ascites** and ascitic fluid protein concentration < 15 grams/L, and either:

- Impaired renal function (serum creatinine 110 micromol/L or more, serum urea nitrogen 8.9 mmol/L or more, or serum sodium 130 mmol/L or less),

Or

- Liver failure (Child-Pugh score 9 or more and serum bilirubin 50 micromol/L or more).

If primary prophylaxis is considered necessary, use the same regimen as for secondary prophylaxis, above.

Treatment:

1. Analgesia as required.

2. Antibiotics:

   Commence broad-spectrum antibiotics, once ascitic fluid has been taken, unless the patient is septic / unwell, then antibiotics should not be delayed for diagnostic paracentesis.

   Empiric antibiotics include: [1]

   - **Ceftriaxone** 2 grams (child 1 month or older: 50 mg/kg up to 2 grams) IV, daily.

   Or

   - **Cefotaxime** 1 gram (child: 25 mg/kg up to 1 gram) IV, 8-hourly

   For patients with immediate hypersensitivity to penicillins **ciprofloxacin** is an alternative.

   For those on antibiotic prophylaxis with trimethoprim + sulfamethoxazole or norfloxacin

- Streptococcal or enterococcal infection is more common in patients who develop SBP while receiving prophylaxis.

  In these patients use **Tazocin** (i.e piperacillin + tazobactam 4+0.5 grams IV, 8-hourly), because cephalosporins are not active against enterococci.

If signs and symptoms of infection resolve rapidly, treat for **5 days**.

Once a pathogen has been identified antibiotics can be tailored accordingly.

If **secondary bacterial peritonitis** is suspected in the first instance a.dd **Metronidazole**

3. Albumin: [1]

Patients with SBP and chronic liver disease who have renal impairment or jaundice are at high risk of developing hepatorenal syndrome.

Renal failure develops in 30 - 40 percent of patients with SBP and is a major cause of death.

Albumin reduces the rate of renal failure and improves survival in this situation.

Give:

- Albumin 20% 100 mL IV, twice daily for 3 days.

Louis Pasteur (1822- 1895)

References

1. eTG - November 2015.

    - Gastrointestinal Therapeutic Guidelines 5th ed 2011.

2. Bruce A Runyon at al. in Spontaneous Bacterial Peritonitis, Up to Date Website, 4 January 2016.

3. Thomas E Green at al. Spontaneous Bacterial Peritonitis, in eMedicine Website, 1 October 2015.

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