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IN AND OUT ABOUT SPONTANEOUS BACTERIAL PERITONITIS: SPECIAL MENTION ON RISK FACTORS AND RESISTANCE

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ABSTRACT

Spontaneous Bacterial Peritonitis is a life-threatening complication in cirrhotic ascites increasing mortality by multiple folds. Subdued immunity due to deficient complement system, decreased neutrophilic and reticuloendothelial activity leads to these infections characterized by fever, abdominal pain and leukocytosis. Gram-negative bacteria were originally the main causative agents; the prevalent isolate being Escherichia coli, but gram-positive infections are now on the rise. Cirrhotic patients with low levels of ascitic protein and vitamin-D, those admitted with bleeding episodes and previous episodes of SBP present a higher risk of SBP infection. Effective antibiotic treatment is critical; third-generation Cephalosporins being the first line agents. The constantly changing microbial resistance, with emergence of multi and extent drug-resistant strains are constantly challenging the management. Selection of empirical antibiotic regimen should be driven by infection severity and local resistance patterns. Selective albumin supplementation, withholding of acid suppressants and discontinuation of beta-adrenergic antagonist therapy, considering liver transplantation options and implementing non-antibiotic strategies deserve particular attention. While antibiotic prophylaxis curtails SBP; a cautious selection of high-risk candidates is critical to prevent antibiotic overuse.

INTRODUCTION

In 1826, Laennec coined the term cirrhosis which has its origin from Greek which means orange or twanny. It is a complex condition marked by diffuse liver damage, fibrosis and transition of normal liver cells to structurally irregular nodules. WHO reports that cirrhosis is responsible for 1.1% of all deaths.[1] In day to day clinical practise, Ascites – accumulation of fluid in the abdomen is commonly observed in these patients.[2] Ascites is the first sign of liver decompensation in cirrhotic patients and occurs in about 20% people with cirrhosis.[3] Bacterial infections are a major risk factor in these patients and can lead to serious complications or even death.[4] One such life threatening, infectious complication in patients with ascites is Spontaneous bacterial peritonitis (SBP). The term SBP was coined in 1964 by Harold O Connen to depicit a condition of peritonitis and bacteraemia in cirrhosis with no evident cause of infection.[5] The gradual development of the disease adds to the complexity of earlier chances of diagnosis, but with time it becomes more apparent due to patients deteriorating condition.[6]

EPIDEMOLOGY

SBP occurs in both children and adults. In children it is most prevalent among neonates and those under five years of age and in adults, is a common & ominous complication in cirrhotic patients.[1] The chance for developing SBP in patients with cirrhosis & ascites ranges between 10-30% annually. The In-patient mortality rates in these patients are on the higher side and ranges between 20-40%.[6] In hospital admissions prevalence of SBP varies between 10-27%.[7] The odds of recurrence of SBP after the first hospitalization is fairly high even after a successful medical treatment and therefore the mortality rates in these cases are 70% and 80% respectively after the first and second year of hospital admissions.[8]

BACTERIOLOGY

In hospitalized and non hospitalized patients there is a difference in causative agent responsible for SBP. Gram negative strains (Gns) tops the chart in case of hospitalized infections were as Gram positive strains (Gps) tops the chart in case of Non hospitalized infections.[9] The key causative agents of SBP are Gns. Escherichia coli and Klebsiella pneumonia are the common isolates. E. coli consistently remains the most common isolate till date. There is currently an increase in the incidence of gram- positive infections, with Streptococcus, Staphylococcus and Enterococcus being the common isolates. At present Multi-drug- resistant (MDR) species are the biggest concern. Possible explanations are the widespread use of long term prophylaxis, growing use of invasive procedures, the increased use of broad spectrum antibiotics and broadening of conditions for admission to intensive care units.[10] The emergence of extended spectrum b-lactamase producing (ESBL) Gram negative bacteria(GNB), Methicillin- resistant Staphylococcus aureus(MRSA) , Quinolone-resistant (QR) GNB, Vancomycin-resistant Enterococcus (VRE), Carbapenem-resistant enterobacteria (CR-Eb) and other resistant micro-organisms altered the previous perceptions and management of SBP.[11]

PATHOPHYSIOLOGY

The term Spontaneous was used initially, as the source of infection was not clear, but it became more clear over time but still scholars are of the assumption that it is due to the imbalance of intestinal bacterial growth and distribution.[12] Intestinal and Extra intestinal bacteria also causes infections less frequently. The most frequent isolates being E.coli, K.pneumonia, Streptococcus, Staphylococcus, Enterococcus and other Enterobacteriaceae.[1] The mechanism of SBP is hypothesized as

1. Small Intestinal Bacterial Overgrowth
2. Increased Intestinal Permeability
3. Bacterial Translocation
4. Immunosuppression
5. Ascitic Fluid Defence Mechanism[13]

Small Intestinal Bacterial Overgrowth: Approximately 20%-60% cirrhotic patients are affected by bacterial overgrowth. In a healthy individual, the host and the intestinal flora co-exist in a symbiotic relationship, but with the progression of cirrhosis, the flora begins to cause a deleterious effects on host. The frequent isolate of SBP are significantly different from the flora of the intestinal lumen but Intestinal bacterial overgrowth leads to conditions favourable for the colonization and dissemination of the common isolates. In cirrhotic patient's bacterial overgrowth is favoured mainly due to reduced intestinal passage, malnutrition, hypochlorhydria and an aberration in bile secretions.[1,14]

***Increased Intestinal Permeability*:** Increased Intestinal Permeability plays a contributory role in development of SBP in cirrhotic patients. Severity of Portal Hypertension has a direct impact on Intestinal Permeability. In Cirrhotic patients with Portal Hypertension, edema, vascular congestion and increased interepithelial cell space are often seen and paves the way for structural abnormalities. Meanwhile Chronic elevation in portal pressure leads to an increased Intestinal water flux. Consequence of all this being an Increased Intestinal Permeability, leading to an impaired function of the Intestinal barrier that facilitates bacterial translocation and contributes to sepsis.[1,13,15]

Bacterial Translocation: Bacterial Translocation is characterized as the movement of living organisms and their toxic products via the mucosal epithelial layer to lamina propria mucosae by active/passive means. It is possible only if there is a high bacterial population of up to 10^8 in 1 gram of faeces.[16] Among the healthy individuals, bacteria that colonise lymph nodes are destroyed by local immune defences. Nevertheless, after cirrhosis many mechanisms of immune deficiency promote the transmission of bacteria to the blood.[13] Translocation is unique to the organisms, on comparison Gns translocate more efficiently than the Gps and could be the plausible explanation behind higher incidence of gram negative infections.[17]

***Immuno suppression*:** In healthy individuals, bacteria entering the blood stream are coated by the complement system and then engulfed and killed by neutrophils. Due to deficit bactericidal system in cirrhotic patients and reduced bacterial clearance contributes to invasion of bacteria in the bloodstream and the ultimate consequences is the prolongation of bacteraemia and dissemination to locations such as ascitic fluid.

Ascitic Fluid Defence Mechanism: The advent of bacteria to the ascitic fluid doesn't guarantee the onset of SBP. Ascitic fluid is capable of self-defence, humorally. Therefore progression of SBP is only noticed in patients who doesnot have an adequate activity of this vital bactericidal system and viceversa.[13]

CLINICAL PICTURE:

Over the ages there was a widespread misconception that SBP was an infrequent complication in cirrhotic patients with ascites but in fact it is the most common infectious complication representing about 31% of all bacterial infectons.[13] Only around half of the SBP episodes are diagnosed on admission and the remaining are acquired during hospitalization.[18,19] The suspected SBP index is higher in patients with ascites, hepatic encephalopathy (HE), compromised kidney and liver function combined with clinical deterioration.[20] The clinical manifestation of SBP vary greatly from a minor asymptomatic bacterial infection to a potentially lethal sepsis.[21] Most patients are symptomatic, but around 13% are asymptomatic. Most common clinical manifestation are fever (50-70%), abdominal pain (27-72%), abdominal tenderness (30-40%). The other signs are impaired mental sensorium (50%), diarrhoea (32%), chills (16–29%) and nausea/vomiting (8-21%), ileus (31%) and renal dysfunction (30-34%). Although abdominal tenderness is frequent in patients, rebound tenderness is seen only in a few.[18,22,23,24,25] Fever is a classic sign since most cirrhotic patients are hypothermic.[20] Sepsis is uncommon but fatal.[18]

RISK FACTORS

Severity of disease: The incidence of SBP is on the higher side in case of cirrhotic patients with end-stage disease. Serum bilirubin is a reliable factor in determining the extent of disease since it's the key criteria used in both Child Pugh and Meld scoring systems. Higher the serum bilirubin, higher the risk of infection. It thus confirms why all these SBP patients have a higher Meld score and are Child Pugh class C. Patients with elevated bilirubin level (>2.5mg/dl) and meld score (≥18) often pose greater risk.[26,27]

Ascitic fluid protein concentration: Low protein levels in ascitic fluid are an independent risk factor, and often predispose to SBP. But the concentration of ascitic fluid protein doesn't vary with initiation of SBP. There is a direct correlation between the antimicrobial activity of the ascitic fluids and its protein concentration. Higher the protein levels, greater will be the magnitude of the antimicrobial activity and vice versa. In patients with protein value <1g/dl there is an absolute deficit of anti-microbial activity and are at higher risk of infections (10 times more prone to SBP).

Recommendations: The level of protein and anti-microbial activity of ascitic fluid tends to increase on diuresis[28]. They are advised for Norfloxacin prophylaxis either for life time or until liver transplantation.[29]

***Vitamin D*:** Vitamin D boosts our normal and adaptive immune responses and thereby protects us from bacterial infections. Its deficiency is associated with higher auto-immunity and increased vulnerability to infections especially in cirrhotic patients. Low Vitamin D levels (<10 ng/ml) is often

associated with an increased mortality rate in SBP patients.[30]

Gastrointestinal (GI) bleeding: GI bleeding is a severe complication in cirrhotic patients and often predisposes to infections.[31] In cirrhotic patients with acute bleeding, 20% are infected at the time of admission and 30-40% are infected during the hospital stay. The mortality rate is about 30-40%.[13] The infections are predominant in patients with failure to control bleeding. Invasive surgical treatments, increased intestinal bacterial translocation and dysfunction of the reticulo-endothelial network lead to the increased rate of infections.[31]
Recommendations: Antibiotic prophylaxis should be started immediately in cirrhotic patients with bleeding and maintained for up to 7 days.[10]

Previous episodes of SBP: Since SBP is a progressive disease, there is a higher chance of re-infection.[8] In patients without any prophylaxis, the incidence rates are as high as 70% and in case of patients on prophylaxis the incident rates are 20%. Following an initial episode of SBP the life expectancy is very low with 1 & 2 year survival chances at around 30-50% and 25-30% respectively.
Recommendations: Continuous Antibiotic prophylaxis is recommended and since survival chances are very low they are considered for liver transplantation[32]

Proton pump inhibitors (PPI): Although the connection between PPI therapy and SBP infection risk remains controversial, the possibility of modest increase in SBP risk cannot be excluded. Gastric acidity is a crucial defence line against pathogens yet the use of PPI inhibitors supresses gastric acid production and boosts bacterial overgrowth, translocation and colonization which predispose to SBP.[33]
Recommendations: Use of Lansoprazole and Pantoprazole are highly discouraged in patients with cirrhosis. Omeprazole / Esomeprazole / Rabeprazole are recommended for CTP A and CTP B cirrhotic patients and Esomeprazole in case of CTP C cirrhotic patients.[34]

Non-selective beta blockers (NSBB): In accordance to the current guidelines, NSSB treatment usually referred as "Hepatologist's Aspirin" is prescribed mainly for preventing the onset of variceal haemorrhage or re-bleeding in cirrhotic patients. Recent studies put forth the need of a therapy window for the safe use of NSSB in cirrhotic patients with SBP onset defined as the end point. The mortality rate of SBP patients on NSSB therapy is high at around 58% as there is high chance for the onset of Hepatorenal Syndrome (HRS), Acute Kidney Injury (AKI) and deteriorating Cardiac output.
Recommendations: The use of NSSB is contraindicated in patients for first six months after the SBP development owing to the deleterious effects. Whether to permanently discontinue or to restart the NSSB therapy after resolving the SBP episode is a question with no clear answer till date.[35]

***Bacteriuria*:** It is a condition characterized by the presence of bacteria in the urine and is a major risk factor for SBP, since it often predisposes to AF infections (in females).
Recommendations: SBP development can be significantly reduced by implementing Urinary Tract Infection (UTI) treatment even in the absence of symptoms and through routine screening of these patients. Catheterization in these patients should also be reduced.[13]

DIAGNOSIS:
Recognition of SBP and associated sepsis in patients is frequently troublesome as the signs concurs and are general characteristics in cirrhotic patients mainly decreased PMNL count tally because of hypersplenism, raised pulse due to hyperdynamic circulation, hyperventilation owing to HE.[20,36] Therefore, a high level of doubt is essential to maintain a strategic distance from symptomatic pitfalls, particularly since the death pace of untreated patients approaches nearly 50%.[37] Individuals who pose potential risk for sudden SBP onset

- Patients with perfect indications of contamination like fever, abdominal pain.
- All Cirrhotic patients with ascites.
- New beginning ascites.
- Ascitic patients with GI bleeding.
- Ascitic patients who develops indications for sepsis, HE and altered GI motility.
- Recent unexplained clinical deterioration.

- Impeded hepatic or renal capacity.

Regardless of utilizing highly sensitive culture techniques nearly 40% of cases with potential clinical traits of SBP and elevated ascitic Polymorphonuclear leucocyte (PMNL) counts are still culture negative.[38] The other significant setback is that these culture methods take at any rate 24 to 48 hours to convey the results.[13] Besides, commencement of treatment can't be postponed while anticipating results as the demise pace of untreated patients is on the higher side.[38] On account of these inadequacies, paracentesis, when used to get an ascitic fluid cytologic tap, remains the absolute most significant test for recognizing and evaluating SBP. Of all the data gathered from the ascitic fluid cytologic tap, the PMN count remains the best test for making a possible determination of SBP.[13,39,14]

Abdominal Paracentesis: In the past worry of intricacies during paracentesis had held " analytic taps" to minimal. Anyway time and progressions in clinical sectors diminished such concerns and also identified a security profile. It is generally realized that examining a sample of ascitic fluid is the ideal method to detect an episode of SBP. Abdominal paracentesis is a medical procedure that punctures the transabdominal needle at a vascular infra umbilical midline or ideally at the lower left quadrant to extract ascitic fluid and also extracts a sample for analysis.[40] Delay in analysing ascitic fluid in SBP patients undergone paracentesis has culminated in a 2.7 fold increased risk of in-hospital mortality. Diagnostic paracentesis should be performed before the use of antibiotics and within 6 hours of patient evaluation but in patients with septic shock sampling should be done quickly as antibiotics should be started within 45 minutes.[6,41] SBP is confirmed based on a PMNL count >250 cells/mm^3 in the ascitic fluid, which is a sign to prescribe antibiotics.[42] The cut off value of 250 cells/mm^3 offers greatest sensitivity, meanwhile 500 cells/mm^3 provides greatest specificity. Nonetheless, the most sensitive cut off value ought to be utilized for diagnosis, as it is significant not to miss cases of SBP.[43] On the off chance if patient is diagnosed haemorrhagic ascites (i.e. ascitic red blood cells > 10 000/mm^3), 1 PMNL should be subtracted for every 250 red blood cells to get the actual ascitic PMNL count.[38]

Asctic Fluid Culture: Traditional bacterial culture methods fail to identify microbes in under half of ascites samples with an elevated PMN count (>250/mm^3). It is therefore advised to inoculate the ascitic fluid into blood culture bottles near patient's bedside in order to expand the sensitivity of the bacterial culture even with these strategies, positive outcomes for ascitic cultures are 40–70% only. Patients with negative culture display a clinical presentation like that of culture positive SBP therefore these patients are sorted as having culture negative SBP and ought to be treated in a similar way as those with culture-positive SBP.[20,42,43]

Laboratary Parameters: Leukocyte esterase reagent strips (LERS) have sensitivity of 45% - 100% and specificity of 81% -100% but overall negative predictive value over 95% makes it a unreliable diagnostic method. Measuring lactoferrin & interleukin 6 level in the ascitic fluid with a cut-off point ≥242 ng/ml & 5.0 ng/mL has a sensitivity of 96% &100% respectively. Estimating serum procalcitonin (PCT) has a sensitivity of 86% to 95% and a specificity of 80%.[1] Recommendations: Myeloperoxidase (MPO) and Neutrophil gelatinase associated lipocalin (NGAL) may play a role as promising parameters in the diagnosis of SBP. MPO is a heme containing enzyme that is found in PMN and is secreted from stimulated WBCs and implicated in host defence during inflammation. NGAL appears to be upregulated in cell under stress as in infection as it mediates an immune response to bacterial infection. Studies uncovers with cut off esteems for MPO and NGAL as 1189 ng/mL and 25 ng/mL individually shows high sensitivity and specificity to distinguish SBP from those without SBP. Subsequently we can say that MPO and NGAL can fill in as a delicate and explicit test for diagnosing of SBP and in deciding the reaction to anti-infection treatment in SBP patients.[44]

EMPIRICAL ANTIBIOTIC THERAPY:

Upon diagnosis (PMNL count than 250/mm3), empirical antibiotic regimen should be started immediately, or when there is a high SBP suspicion (fever, abdomen pain and tenderness,

altered sensorium). The empirical antibiotic should be effective against most likely species with an excellent ascitic fluid penetration capacity and ought not impede renal capacity.[6,45]European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines recommends cefotaxime, ceftriaxone or any other third-generation cephalosporin as the drug of choice for SBP.

Aminoglycosides: Owing to the risk of nephrotoxicity they have no place in the empirical treatment of SBP.[32]

Cephalosporins: Third-generation, broad-spectrum cephalosporins are preferred drug of choice for SBP therapy due to their efficacy and minimal side-effect with very low risk of nephrotoxicity. Empirical treatment is now paired with a beta lactamase inhibitor due to an increase in the occurrence of drug-resistant organisms[19,46,47]

Categories	Cefotaxime	Cefotriaxone
Recommendation	First line of choice	Second line of choice
Dose	2 gm/ 8 hrs	2 gm/ 24 hrs
Contraindications	Penicillin allergy	Severe penicillin allergy
Side Effects	Pseudomembranous colitis	Biliary sludging
Special Points	Resolution in 85% cases Low toxicity High ascitic fluid penetration	Resolution in 75 %cases Low toxicity High ascitic fluid penetration

Newer Generation Cephalosporins: Ceftolozane/ tazobactam and Ceftazidime/ avibactam are the newer generation cephalosporins and may also be integrated into SBP management, but no clinical data on their use are available as of now.

***Amoxicillin Plus Clavulinic Acid*:** Intravenous amoxicillin + clavulanic acid (1000 / 200 mg) 8-hourly supplemented by oral amoxicillin + clavulanic acid (500 /125 mg) 8-hourly was given to patients with SBP for 14 days. On Comparison amoxicillin + clavulanic acid formulation was as effective as cefotaxime with no significant side effects. There is no change in efficiency on switching to oral therapy.

***DURATION OF THERAPY*:**
Recent studies have shown that the length of therapy is primarily focused on signs and the extent of PMNL count reduction after initiation of antibiotic therapy. Recent studies have shown no significant differences in resolution and mortality rate of SBP patients irrespective of 5 or 10 days of treatment.[48,49]
Recommendation: In order to combat adverse events, including the emergence of resistant bacteria 5 days should be made as the standard duration and may be extended up to 10 days if the therapeutic response is slow.

SUPPORTIVE THERAPY
Diet: Patients with advanced cirrhosis are hypermetabolic, experiences malnutrition which incline to SBP now and then.[50] Patients ought not devour crude nourishment relating to the chance of microbes in them, ought to take 4–6 little continuous meals per day with a bedtime starch rich diet and about 1.2–1.5 gm of protein intake/day. It is also advised to limit dietary sodium intake.[51,52]

Lifestyle: Lifestyle modifications don't have much role at all.[53]

Probiotics: Probiotics are live microorganisms that are beneficial for you particularly your gut. They are generally utilized for intestinal flora re equilibration, in favour of anaerobic defensive microscopic organisms.[54] For instance, Lactobacillus & Bifidobacterium are typical occupants of the gut and improves hepatic capacity and lessens liver catalysts in cirrhotic patients and aids in prevention of SBP. When coupled with Antioxidants like vitamin C and glutamate lessens endotoxemia. Continuous research into the use of probiotic agents has showed marked decrease in cytokine release and improved neutrophil function.[55]

***SWITCH THERAPY*:**
Recent studies suggest an Iv to Oral switch in patients who after a short Iv course show improvement. Changes to oral therapy is advised only when patients are rapidly improving, on being afebrile and when a drop in inflammatory markers is seen..[56] Oral forms

of fluroquinolones, co-amoxiclav and 3rd generation cephalosporins showed same efficacy on comparison to Iv therapies and no significant difference either in mortality, resolution rate or presence of adverse effects was seen but was more cost effective.[57] *Recommendation:* In patients initiated on Iv piperacillin/tazobactam, oral Co-amoxiclav 625mg 8-hourly is fitting for switch therapy unless culture results suggests otherwise.

EMERGING THERAPY:

***Albumin therapy*:** Albumin is a protein synthesised in the liver.[58] The main uses of albumin being:(i) bind's & transfer toxins to elimination sites; (ii) builds up protein in AF which aids in boosting its anti-bacterial activity; (iii) increases blood volume. In advanced liver disease cases, their synthesis and function are impaired and are associated with increased morbidity and death.[36] Therefore, in addition to antibiotics, in select patients with SBP albumin is indeed a key therapy. The SBP is linked with high potential for Liver failure (LF), AKF, HE, HRS and death, and will increase circulatory deterioration in spite of appropriate and early antibiotic treatment.[59] It still has 20% hospital mortality following infection control.[11] Recent trials involving SBP patients receiving a combination of empirical antibiotics and albumin (1.5 gm/kg within 6 h of diagnosis, followed by 1 gm/kg on day 3) observed a significant decrease in renal impairment (33% to 10%) , HRS (30% to 10%) , had lower mortality rate both during hospitalisation (29% to 10%) and at 3-month follow-up (41% to 22%).[60] Patients ought to be carefully screened for albumin infusion, in light of the fact that those in danger for renal disability [i.e. serum creatinine > 1 mg/dL, bilirubin > 4 mg/dL, BUN > 30 mg/dL] have plainly indicated benefit. Chronic renal disease patients with SBP must receive albumin therapy independent of dialysis dependency.[61]

Note:

- The proposal was also made to restrict the albumin infusion to 100 gm per dose.
- In patients with moderate LF, with no AKF and no evidence of HE, albumin treatment is not essential.

PROPHYLAXIS AND RESISTANCE

As the possibility of relapse is around 40-70% within a year prophylaxis gains utmost importance in prevention of SBP and thereby reducing the mortality rates.[8] As a whole, we agree that SBP occurs as a consequence of bacterial translocation and that the drug of choice must be effective, economical and reliable in removing bacteria from the gut without detrimental effects on the anaerobic defensive flora.. Taking this into account, prophylaxis is preferred to have an oral form of poorly absorbed antibiotics, which can eliminate or diminish GNB without affecting GPB or anaerobes, the alleged Selective Intestinal Decontamination (SID). The use of prophylactic antibiotics should be curtailed to high risk patients only owing to the expense and the potential for resistant strains to emerge.[62] Three high-risk patient groups were identified (1) Patients with GI bleeding on admission (2) Patients with low concentration of ascitic protein and advanced cirrhosis without prior history of SBP (3) Patients who survived an episode of SBP.[63]

***General measures*:** It lays emphasis on Improving the patient's overall health and nutrition status along with abstinence from alcohol and aggressive treatment and annihilation of localized infections before it inclines to bacterial translocation. Diuretic treatment diminishes the AF amount and significantly raise the AF opsonic response assisting in SBP prevention. Utilizing surgical portacaval shunts or trans-jugular intrahepatic portosystemic stent shunts can reduce the risk of bleeding.[13] Checking for oesophageal varices is likewise instructed to diminish the hazard with respect to GI bleeding. Patients with prior SBP episodes are esteemed potential contender for liver transplantation if patients agree.[64]

Primary prophylaxis: Numerous cirrhotic patients, including those with decreased ascitic protein concentration and those admitted with episodes of bleeding, present a higher risk of infection.[45]

1) Low ascitic fluid protein: Either Oral Norfloxacin [400 mg OD] or Oral Ciprofloxacin [500 mg OD] lessens the probability of SBP and improves endurance rates in patients with diminished ascitic

protein levels and advanced cirrhosis without prior SBP episodes.

2) Gastrointestinal haemorrhage: Patients with cirrhosis and upper GI bleeding face a variety of bacterial infections, such as SBP.[65] Oral norfloxacin (400 mg OD) and oral ciprofloxacin (500 mg BID) for 7 days are recommended as per International Ascites Club (IAC) and the British Gastroenterology Society respectively.[32,66] In people with advanced liver disease the benefit was more noteworthy .

***Secondary prophylaxis*:** Patients with prior SBP episode have 40 -70% 1-year probability for recurrence[8]. IAC suggests oral Norfloxacin (400 mg) for patients who rebound from an initial SBP attack until either ascites recovery, transplantation or death. Norfloxacin prophylaxis reduced the SBP recurrence rates from 68% to 20%, with a decrease in SBP due to GNB specifically.[67] Trimethoprim / Sulfamethoxazole is a reliable alternative for patients who are resistant to quinolones.[68]

EMERGING CONCERNS:

1) Increase in antibiotic resistant organisms
   Advanced healthcare facilities lead to better health services and longer survival rates but also paved way to a scenario with even more severe end-stage liver disease and bacterial resistance.[69] Globally, the most important antibiotic-related problem is the growth of antibiotic resistance.[70] ESBL species contain enzymes such as ESBLs (extended-spectrum beta lactamases) that can break down the active ingredients in antibiotics and make them inefficient. For now, ESBLs are associated with GNB only. The specific classes of bacteria being E. coli, K.pneumoniae, P.aeruginosa and Enterobacter. MDR bacteria are by nature immune to three or more types of antibiotics.[70] ESBL GNB, QR GNB, MRSA, Vancomycin-susceptible Enterococcus (VSE) and VRE, (CR-Eb), Meropenem-Resistant organisms and as of late discovered Extensively Drug Resistant Bacteria (XDR), for example, Carbapenemase delivering K.pneumonia.[71,72] Thereforth a high prevalence of MDR and XDR infections is reported in patients. In addition to improving attributes of bacterial strains, the effectiveness of the clinical regimens previously prescribed has ceased to be adequate.[73]
2) Increase incidence of Gram-positive infections
   Classically, GPB accounted around 20 % of SBP infections, but towards the start of the new era this shifted and the incidence of GPB infections rose, to about (30-45 %). On basis of origin of infection, GNB tops the list in case of CA infections (60%), whereas GPB tops the list in case of Nosocomial infections (60%).[71,74]

Plausible reasons: Increased survival time in cirrhotic patients coupled up with frequent exposure to broad spectrum antibiotics and long-term Norfloxacin prophylaxis are probable reasons for increasing trend in antibiotic resistance.[75] Long-term Norfloxacin prophylaxis pose increased risk of infection with ESBL-producing organisms by 4 times.[76] The diagnostic ability of the existing indicators of bacterial infection in cirrhotic population is minimal and hence many non-infected patients receive antibiotics, thus raising antibiotic pressure on the endogenous flora and causing resistant strains to evolve.[77] This emerging antibiotic resistance among the pathogens is very alarming since it is driving us very fast towards the post antibiotic era.[78] The increased GPB infections is mainly due to the long term prophylactic use of Fluro quinolones, an increase in invasive procedures, and ICU treatment in cirrhotic patients. Fluro quinolone prophylaxis reduces the SBP specifically due to GNB but has far less impact on GPB infections.[71,74]

***Current scenario*:** High antibiotic resistance was seen in antibiotics widely used in SBPs such as quinolones, aminoglycosides and third generation cephalosporin's, approximating about 60% to 70%.[79] The 38% of instances of SBP demonstrate cross-resistance from third generation cephalosporins, amoxicillin / clavulanate and quinolones.[72] It is quite alarming as 3 of the 4 antibiotics of choice for SBP are associated with higher resistance rates and therefore empirical antibiotic treatment requires appropriate modification.[80] Rates of antibiotic sensitivity for piperacillin /

tazobactam, amikacin, and meropenem are higher. Rates of antibiotic resistance for piperacillin/tazobactam and meropenem vary from 10-15%.[78] The current first-line alternative piperacillin/tazobactam combination as per EASL guidelines can be considered as a reliable first-line regimen.[81]

Recommendations:

1) Knowledge of local resistance patterns remains important for directing therapeutic antibiotic regimens or at least to warn clinicians regarding possible loss of effectiveness in some high-risk patients in traditional antibiotic regimes.[82]
2) Antibiotic stewardship programs that restrict excessive use of antibiotics, such as restricting antibiotic prophylaxis to high risk patients, should be implemented.
3) There is an immediate need to develop and implement non-antibiotic strategies based on so-called pathways to infection.[83]
4) Given that monotherapy remains ineffective in a significant proportion of cases, clinical treatment should focus on involving combinations of broad-spectrum antibiotic taking into account the rising trend in resistance.[72]
5) According to the microbiological findings it is also essential to de-escalate antibiotics early to prevent their irrational use.
6) In zones with high prevalence of ESBL, MRSA and VSE and VRE guidelines ought to incorporate the utilization of carbapenems, glycopeptides and linezolid or daptomycin respectively with empirical treatment. [84]

CONCLUSION:

To curtail the incidence of SBP and facilitate early detection, newer diagnostic methods with high efficiency and better detection rates should be established. Empirical regimen should be chosen based on past history and local resistance profiles. Antibiotic de-escalation should be encouraged, in order to reduce antibiotic stress and prevent its overuse. Traditional prophylaxis regime focuses on GNB but, with a spike in GPB infections, there is an immediate need for appropriate prophylaxis modification. Selective albumin therapy, withholding of acid suppressants and discontinuation of beta-adrenergic antagonist therapy and considering liver transplantation options deserve particular attention. Emerging antibiotic resistance is very alarming as it is driving us very fast towards post antibiotic era. New non-antibiotic strategies should be adopted, and treatment services to prevent antibiotic overuse should be facilitated. Broad spectrum antibiotic in combination should be used for managing in areas with high resistance pattern and isolation of such resistant patients is of prime importance to prevent its spreading.

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