Management of cirrhotic ascites in children. Review and recommendations

Part 1: Pathophysiology, diagnostic evaluation, hospitalization criteria, treatment, nutritional management

David F. Bes, M.D.[a], M. Cristina Fernández, M.D.[a], Ivone Malla, M.D.[a], Horacio A. Repetto, M.D.[b], Daniel Buamscha, M.D.[a], Susana López, M.D.[a], Roxana Martinitto, M.D.[a], Miriam Cuarterolo, M.D.[a] and Fernando Álvarez, M.D.[c]

ABSTRACT

Ascites is a major complication of cirrhosis. There are several evidence-based articles and guidelines for the management of adults, but few data have been published in relation to children. In the case of pediatric patients with cirrhotic ascites (PPCA), the following questions are raised: How are the clinical assessment and ancillary tests performed? When is ascites considered refractory? How is it treated? Should fresh plasma and platelets be infused before abdominal paracentesis to prevent bleeding? What are the hospitalization criteria? What are the indicated treatments? What complications can patients develop? When and how should hyponatremia be treated? What are the diagnostic criteria for spontaneous bacterial peritonitis? How is it treated? What is hepatorenal syndrome? How is it treated? When should albumin be infused? When should fluid intake be restricted? The recommendations made here are based on pathophysiology and suggest the preferred approach to its diagnostic and therapeutic aspects, and preventive care.

***Key words**: albumin, hepatorenal syndrome, hyponatremia, portal hypertension, spontaneous bacterial peritonitis.*

http://dx.doi.org/10.5546/aap.2017.eng.385

To cite: Bes DF, Fernández MC, Malla I, et al. Management of cirrhotic ascites in children. Review and recommendations Part 1. *Arch Argent Pediatr* 2017;115(4):385-390.

a. Hospital de Pediatría "Prof. Dr. Juan P. Garrahan", Buenos Aires, Argentina.
b. Department of Pediatrics, School of Medicine, Universidad de Buenos Aires, Buenos Aires, Argentina.
c. CHU-Sainte Justine, Montreal, Canadá.

E-mail address:
David F. Bes, M.D.:
davidfbes@hotmail.com

Funding:
None.

Conflict of interest:
None.

Received: 10-5-2016
Accepted: 12-26-2016

INTRODUCTION

Ascites is defined as the pathological accumulation of fluid in the peritoneal cavity.[1-3] It is the most common complication of cirrhosis; its development is a milestone in disease progression and is associated with an unfavorable course.[4,5] Liver transplantation is the curative treatment approach for cirrhotic patients with ascites.[6,7]

The successful treatment of ascites may improve the course of the disease and relieve symptoms in the cirrhotic patient.[8] There are several evidence-based articles and guidelines for the management of adult patients, but few data have been published in relation to the pediatric population.[2,3,5,6,8-13] Additionally, age-specific considerations make it difficult for pediatricians to rely solely on recommendations extrapolated from the adult population.[2,14] Differences include etiologies of cirrhosis, renal function parameters in relation to the body surface area, water body distribution, fluid and nutritional requirements taking growth into account, creatinine serum levels defining renal failure, and the type of diet with high sodium content and solute-free water.[12,15-17] Likewise, given the present recommendations regarding sodium chloride (NaCl) levels in intravenous maintenance solutions, sodium intake per kg is also higher and may reach 15 mEq/kg/day among infants ≤ 10 kg.[18-23]

The objectives of this consensus of experts are to review the pathophysiology of cirrhotic ascites and make recommendations based on the best available evidence for the management of cirrhotic ascites in patients younger than 18 years.

MATERIAL AND METHODS

Two authors, with experience in the management of pediatric patients with cirrhotic ascites (PPCA), conducted an initial bibliographic

search in MEDLlNE using "cirrhosis" and "ascites" as MeSH descriptors, with no filters applied, between January 1st, 1985 and December 31st, 2015. Bibliographic references of reviewed articles were also analyzed for relevant articles. The analysis of articles that included their assessment based on the GRADE approach (Grading of Recommendations Assessment Development and Evaluation)[24,25] resulted in recommendations which were reviewed and agreed upon with other pediatricians specialized in internal medicine, nephrology, hepatology, and intensive care.

Given that almost all the studies were based on the adult population, the evidence was considered indirect, and most pediatric publications were grounded on expert opinions, which do not account for a category of evidence;[24] therefore, the recommendations of this consensus were not classified as strong or weak.

The following questions were posed: 1) How should PPCA be assessed from a clinical and ancillary testing standpoint? 2) When is ascites considered refractory? How is it treated? 3) Should fresh plasma and platelets be infused before abdominal paracentesis to prevent bleeding? 4) What are the hospitalization criteria? 5) What should the treatment be considering on the severity of ascites? 6) What are the most common complications in PPCA? How are they treated? 7) How is hyponatremia corrected? 8) When should spontaneous bacterial peritonitis (SBP) be suspected? How is it diagnosed and how is it treated? 9) How is hepatorenal syndrome (HRS) defined? How is it treated? 10) When should albumin and furosemide be administered? 11) When should fluid intake be restricted?

PATHOPHYSIOLOGY OF ASCITES IN CIRRHOSIS

Understanding how ascites develops is critical for its adequate management; sodium and water retention are key factors in the setting of the development of sinusoidal portal hypertension.[9,26-28]

In cirrhosis there is a loss of sinusoidal permeability, activation of stellate cells, and collagen deposition in liver microcirculation. Fibrosis and nodularity combined with local, dynamic vasoconstriction increase resistance to the venous blood flow through the liver.[29] In addition, there is an increased production of vasoactive substances, such as nitric oxide, carbon monoxide, and endocannabinoids, which cause splanchnic vasodilation, increased blood flow through this area, and a decrease in peripheral vascular resistance.[30] The resulting reduction of the effective arterial volume (EAV) (that is, the blood volume in the heart, lungs, and central arterial tree that is sensed by arterial receptors, which is the main stimulus for renal sodium and water reabsorption),[31,32] together with the increased cardiac output –a compensatory mechanism– are typical of the hyperdynamic state observed in cirrhotic patients. Clinical signs include tachycardia, reduced blood pressure, and hyperkinetic peripheral pulses. At this stage of compensated cirrhosis, patients can manage fluid intake and there is no sodium retention, so no restrictions are required. However, due to the slow and low sodium excretion,[25,33,34] current recommendations regarding sodium in parenteral maintenance solutions[18-22] may cause positive sodium balances, which, together with iso-osmotic water retention, lead to the development of ascites.

In the course of cirrhosis, baroreceptors sense the decrease of EAV and activate the renin-angiotensin-aldosterone and sympathetic nervous systems together with vasopressin to retain sodium and water in the kidneys and induce vasoconstriction of non-splanchnic beds. In spite of renal vasoconstriction, glomerular filtration is usually normal. As hepatic resistance progresses, intravascular volumes in the abdomen and noncentral territories increase,[33,35] portal hypertension develops, and a hydrostatic pressure gradient is developed in the liver and splanchnic microcirculation. Protein-rich and -poor fluids transudate from these two microcirculations, respectively, and mix in the peritoneum.[2,36,37] Pathologic accumulation occurs when the intestinal lymph production exceeds the lymphatic drainage through the thoracic duct. Although low in albumin, ascitic fluid contains proteins and exerts oncotic pressure, which contributes to fluid retention, thus perpetuating ascites formation. In this stage, antidiuretic hormone (ADH) secretion responds to osmotic and non-osmotic stimuli, and iso-osmotic water retention passively follows sodium re-absorption, depending on its balance.

At later cirrhosis stages, EAV continues reducing, and non-osmotic stimuli overcome the suppressive effects of hypo-osmolality, stimulate ADH secretion, and cause hypervolemic hyponatremia (HH). Most of the volume expansion in HH occurs in noncentral

vascular territories, mainly the splanchnic area.[33,35] In addition, combined ADH and renin-angiotensin secretion leads to renal and peripheral vasoconstriction, prevents further EAV contraction maintaining blood pressure close to normal, although at the expense of reducing renal perfusion.[38] Management at this stage is difficult because water balance is less dependent on sodium balance. If oral intake is contraindicated, hypotonic intravenous fluids should not be administered due to the kidneys' impaired ability to excrete free water.[39] HRS develops in the end stages.[29]

From the above, it follows that, although hypoalbuminemia may worsen ascites, it is not its main cause.[9,29] Pathological fluid accumulation, mainly located in the abdomen, is secondary to splanchnic vasodilation, which increases the splanchnic blood flow in this area and, in the presence of sinusoidal portal hypertension (hepatic venous pressure gradients > 12 mmHg), results in fluid transudation into the peritoneal cavity.[35,40,41] Such hypervolemic state contrasts the edematous state in primary nephrotic syndrome, where extravascular fluid accumulation is the result of the reduction of oncotic pressure due to hypoalbuminemia, which induces intravascular volume contraction.[42] Although albumin infusion is not the main treatment for cirrhotic ascites, there are good levels of evidence of its use in this clinical setting.[8,13,43-45]

DIAGNOSTIC EVALUATION

1. Classification

The International Ascites Club classifies ascites according to its severity and response to diuretics.[6,9]

a) *Severity.* Grade 1 (mild): ascites is detectable by ultrasound. Grade 2 (moderate): the patient suffers from moderate abdominal distension and there is clinical evidence of ascites. Grade 3 (severe): the patient has tense ascites and/or respiratory distress due to a restrictive respiratory disability.

b) *Response to diuretics.* 1) refractory ascites, which fails to respond after 7 days of adequate treatment, defined as a maximum dose of spironolactone and furosemide combined with a low-sodium diet (1.5 mEq/kg/day) or when fluid reaccumulates within one month of treatment initiation; 2) resistant, when weight loss is < 0.8 kg (adults) and diuresis is lower than fluid intake; and 3) intractable, when diuretics are contraindicated due to adverse effects: encephalopathy, hyponatremia (reduction in blood sodium level ≥ 10 mEq/L to blood sodium level < 125 mEq/L), renal failure (doubling of blood creatinine level), hypo- or hyperkalemia (< 3 mEq/L or > 6 mEq/L).[8,9]

Ascites complications are classified into electrolyte and nonelectrolyte disturbances (the latter include SBP and HRS).

2. Physical examination

It includes weight, body temperature, vital signs, presence of peripheral edema and bleeding, abdominal palpation, waist circumference measurement at the level of the umbilicus, and neurological examination (screening of encephalopathy). Physical examination should be done at the time of diagnosis, during each outpatient visit, and on a daily basis for hospitalized patients.

3. Ancillary testing

Lab tests: white blood cell count, platelet count, hemoglobin, hematocrit, liver function tests (total and direct bilirubin, glutamic-oxaloacetic transaminase [GOT], glutamic-pyruvic transaminase [GPT], alkaline phosphatase, gamma-glutamyl transpeptidase [GGT]), coagulation tests (prothrombin time, activated partial thromboplastin time [aPTT], and international normalized ratio [INR]), electrolytes, and acid-base status (may be venous), kidney function tests (blood urea, blood creatinine, urine electrolytes, urine density, urine osmolality) and, if paracentesis is performed, ascitic fluid cytochemistry. In pediatrics, the etiology of ascites is usually determined based on the case history and physical examination; in case of uncertainty, a serum albumin-ascitic fluid albumin gradient ≥ 1.1 g/dL will be helpful in the diagnosis of portal hypertension.[3,5,8,9,46]

Imaging tests: an abdominal ultrasound is useful to confirm the presence of ascites, establish its severity, and detect signs of portal hypertension (splenic size, omentum:aortic diameter ratio [normal: < 1], collateral circulation), and cavernous transformation of the portal vein.

Abdominal paracentesis: using a sterile technique, a puncture is made on the lower left abdominal quadrant with an Abbocath catheter gauge 21. Specimens are collected for cytochemistry (0.05-0.1 mL in a tube with anticoagulant for white blood cell and neutrophil differential counts) and for culture. To increase microorganism rescue, 10 mL of ascitic fluid should be immediately

inoculated to culture tubes for anaerobic and aerobic bacteria.[9] Severe bleeding is a rare, potentially life-threatening complication, but abdominal paracentesis is considered to be a safe and cost-effective procedure.[47,48] Given that in cirrhotic patients coagulation tests do not reflect bleeding tendencies,[49-53] coagulopathy and thrombocytopenia are not considered contraindications for paracentesis except in the case of primary fibrinolysis or disseminated intravascular coagulation. In general, the infusion of fresh plasma or platelets is not recommended; platelets may be considered in the case of a platelet count < 40 000/mL, especially in the setting of renal failure.

HOSPITALIZATION CRITERIA

These include severe ascites, suspected SBP or evaluation of an infectious process with or without fever, electrolyte disturbances, gastrointestinal bleeding, failure of diuretic treatment, and suspected HRS.

TREATMENT

Treatment depends on the clinical picture and the severity of ascites. The main goal is to achieve a negative sodium balance. The initial treatment is largely dependent on sodium restriction. As ascites progresses, antialdosterone agents and, eventually, loop diuretics should be added to increase sodium excretion. Diuretics should be discontinued in case of electrolyte disturbances and/or hypovolemia or low sodium excretion in spite of maximum doses. Refractory ascites is treated with large-volume paracentesis.

Grade 1 ascites: low-sodium diet (1-2 mEq/kg/day).[2,3,5,6,8,9]

Grade 2 ascites: In addition to the above-mentioned treatment, 2-4 mg/kg of spironolactone once daily are added. The most reversed urinary sodium:potassium ratios should start with the highest doses (up to 100 mg). Given spironolactone prolonged half life, doses are increased every 3-4 days, up to 9 mg/kg/day[54,55] (up to 400 mg). Daily examination of hospitalized patients includes hydration status, sodium and water balance, and weight. During the first weeks of treatment, lab tests should be conducted every 48 or 72 hours, including blood and urine electrolytes, blood urea, and blood creatinine levels.

If there is still no response to maximum doses of spironolactone, then furosemide may be added, initially at 1 mg/kg/day (up to 40 mg), then increasing the dose up to 12 mg/kg/day (up to 80 mg for patients ≤ 12 years and 120 mg for patients aged 12-18 years).[56]

To prevent blood potassium alterations, the spironolactone:furosemide dose ratio should be maintained at 2.5:1,[3,5] and both may be administered once daily. Experience with the use of amiloride in pediatrics is limited.

An adequate treatment response consists of weight loss and edema resolution, waist circumference reduction, and increased diuresis. The goal is to reduce body weight by 0.5-1% (300-500 g/day for older patients) each day until ascites is gone, and to prevent reaccumulation of ascites.[2] An inadequate response indicates that negative sodium balance was not achieved, and the patient should be considered to have poor compliance with low-sodium diet and/or unnoticed sodium intake (parenteral solutions and/or antibiotics). Urine sodium excretion helps to assess diet compliance and diuretic response; however, given that excretion is not consistent throughout the day, 24-hour urine specimens may be more indicative than isolated specimens. Daily weight loss should contemplate that peripheral edemas[2,4,5] are more rapidly reabsorbed. In the absence of edema, if diuresis exceeds ascitic fluid reabsorption, intravascular volume contraction will occur with increased blood urea and creatinine levels, and reduced blood sodium levels. Once ascites is resolved, diuretics should be reduced to half the dose.[3]

Grade 3 ascites: The treatment of choice is large-volume paracentesis with complete drainage of ascites.[3,57,58] Following the abdominal tap, a bag is connected for gravity drainage over 4-6 hours with periodic vital sign monitoring. Adult volumes ≥ 5 L[4,5,8,33] or ≥ 50 mL/kg of dry body weight in PPCA[2,58] require 20-25% albumin infusion to prevent postparacentesis circulatory dysfunction.[2,58] Although this alteration is asymptomatic, it may be associated with hyponatremia, renal failure, and increased mortality.[34,45] Albumin infusion should be administered at the same time or immediately after a large-volume paracentesis over 4 hours. No pediatric dosage has been established, but the recommendation is 6-8 g per drained liter or 1 g/kg of dry body weight.[2,5,58]

Refractory ascites: The treatment of choice is large-volume paracentesis with complete drainage of ascites.[3,8]

NUTRITIONAL MANAGEMENT

Nutritional status assessment is critical because it is related to post-transplantation outcome.[60] This topic has been discussed in several publications.[14,60-63] Patients have hypermetabolic state and high energy requirements (130-150% for infants, up to 170% for older children).[60-63] Fasting or low intake should be prevented in PPCA because low glycogen content results in rapid protein catabolism, and advantage should be taken while function is adequate so that the nutritional support also favors growth. Even though this may result in a sodium intake higher than recommended, nutrient intake should prevail, and diuretics should be administered when ascites develops. In children with chronic liver disease, it is critical to assess the actual nutrient intake at each outpatient visit and frequently during hospitalization. ■

REFERENCES

1. National Center for Biotechnology Information. MeSH database. Ascites. [Accessed on: July 10th, 2016]. Available at: http://www.ncbi.nlm.nih.gov/mesh/?term=ascites.
2. Giefer MJ, Murray KF, Colletti RB. Pathophysiology, diagnosis, and management of pediatric ascites. *J Pediatr Gastroenterol Nutr* 2011;52(5):503-13.
3. Yachha SK, Khanna V. Ascites in childhood liver disease. *Indian J Pediatr* 2006;73(9):819-24.
4. Moore CM, Van Thiel DH. Cirrhotic ascites review: Pathophysiology, diagnosis and management. *World J Hepatol* 2013;5(5):251-63.
5. Runyon BA. Management of adult patients with ascites due to cirrhosis: Update 2012. Alexandria: American Association for the Study of Liver Diseases; 2012. [Accessed on: January 13th, 2017]. Available at: https://www.aasld.org/sites/default/files/ guideline_documents/adultascitesenhanced.pdf.
6. Moore P, Wong F, Ginés P, Bernardi M, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology* 2003;38(1):258-66.
7. Ginès P, Cardenas A, Arroyo V, Rodés J. Management of cirrhosis and ascites. *N Engl J Med* 2004;350(16):1646-54.
8. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010;53(3):397-417.
9. Moore KP, Aithal GP. Guidelines on the management of ascites in cirrhosis. *Gut* 2006;55(Suppl 6):vi1-12.
10. Suk KT, Baik SK, Yoon JH, Cheong JY, at al. Revision and update on clinical practice guideline for liver cirrhosis. *Korean J Hepatol* 2012;18(1):1-21.
11. Bendtsen F, Grønbaek H, Hansen JB, Aagaard NK, et al. Treatment of ascites and spontaneous bacterial peritonitis - part I. *Dan Med J* 2012;59(1):C4371.
12. Pinto RB, Schneider AC, da Silveira TR. Cirrhosis in children and adolescents: An overview. *World J Hepatol* 2015;7(3): 392-405.
13. Ginès P, Cabrera J, Guevara M, Morillas R, et al. Documento de consenso sobre el tratamiento de la ascitis, la hiponatremia dilucional y el síndrome hepatorrenal en la cirrosis hepática. *Gastroenterol Hepatol* 2004;27(9):535-44.
14. Leonis MA, Balistreri WF. Evaluation and management of end-stage liver disease in children. *Gastroenterology* 2008;134(6):1741-51.
15. Winters RW. Regulation of normal water and electrolyte metabolism. In: Winters RW, ed. The Body Fluids in Pediatrics. Boston: Little, Brown and Company; 1973:95-112.
16. Greenbaum LA. Electrolyte and Acid-Base Disorders. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, et al, eds. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Elsevier; 2011.Pgs.212-42.
17. Lo SF. Reference Intervals for Laboratory Tests and Procedures. In Kliegman RM, Stanton BF, St. Geme JW, Schor NF, et al, eds. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Elsevier; 2011.Pg.2466.
18. Greenbaum LA. Maintenance and Replacement Therapy. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, et al, eds. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Elsevier; 2011.Pgs.242-5.
19. Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: do we have the answers? *Pediatrics* 2011;128(5):980-3.
20. National Patient Safety Agency. Reducing the risk of hyponatraemia when administering intravenous infusions to children [Internet]. [Accessed on: January 17th, 2017]. Available at: http://www.nrls.npsa.nhs.uk/resources/?entryid45=59809.
21. Choong K, Arora S, Cheng JI, Farrokhyar F, et al. Hypotonic versus isotonic maintenance fluids after surgery for children: a randomized controlled trial. *Pediatrics* 2011;128(5):857-66.
22. National Institute for Health and Care Excellence. Intravenous fluid therapy in children and young people in hospital. NICE: 2015. [Accessed on: January 19th, 2017]. Available at: www.nice.org.uk/guidance/ng29.
23. Bes DF, Rosanova MT, Sberna N, Arrizurieta E. Deoxycholate amphotericin B and nephrotoxicity in the pediatric setting. *Pediatr Infect Dis J* 2014;33(8):e198-206.
24. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006;174(5): 605-14.
25. Marzo-Castillejo M, Alonso-Coello P, Rotaeche del Campo R. ¿Cómo clasificar la calidad de la evidencia y la fuerza de las recomendaciones? *Aten Primaria* 2006;37(1):5-8.
26. Gordon FD. Ascites. *Clin Liver Dis* 2012;16(2):285-99.
27. Bernardi M, Santi L. Renal sodium retention in pre-ascitic cirrhosis: the more we know about the puzzle, the more it becomes intricate. *J Hepatol* 2010;53(5):790-2.
28. Rosner MH, Gupta R, Ellison D, Okusa MD. Management of cirrhotic ascites: physiological basis of diuretic action. *Eur J Intern Med* 2006;17(1):8-19.
29. Møller S, Henriksen JH, Bendtsen F. Ascites: pathogenesis and therapeutic principles. *Scand J Gastroenterol* 2009;44(8):902-11.
30. Bernardi M, Maggioli C, Zaccherini G. Human albumin in the management of complications of liver cirrhosis. *Crit Care* 2012;16(2):211.
31. Ginès P, Arroyo V. Is there still a need for albumin infusions to treat patients with liver disease? *Gut* 2000;46(5):588-90.
32. Schrier RW. Decreased effective blood volume in edematous disorders: what does this mean? *J Am Soc Nephrol* 2007;18(7):2028-31.
33. Henriksen JH, Kiszka-Kanowitz M, Bendtsen F. Review article: volume expansion in patients with cirrhosis. *Aliment Pharmacol Ther* 2002;16(Suppl 5):12-23.
34. Arroyo V, Colmenero J. Ascites and hepatorenal syndrome in cirrhosis: pathophysiological basis of therapy and current management. *J Hepatol* 2003;38(Suppl 1):S69-89.

35. Kiszka-Kanowitz M, Henriksen JH, Møller S, Bendtsen F. Blood volume distribution in patients with cirrhosis: aspects of the dual-head gamma-camera technique. *J Hepatol* 2001;35(5):605-12.
36. Levy M. Pathophysiology of ascites formation. In Epstein M, ed. The kidney in liver disease. 2nd ed. New York: Elsevier Biomedical; 1983.Pgs.245-80.
37. Henriksen JH, Møller S. Alterations of hepatic and splanchnic microvascular exchange in cirrhosis: local factors in the formation of ascites. In: Ginès P, Arroyo V, Rodes J, Schrier RW, eds. Ascites and renal dysfunction in liver disease: pathogenesis, diagnosis, and treatment. 2nd ed. Oxford: Blackwell; 2005.Pgs.174-85.
38. Ginès P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009;361(13):1279-90.
39. Moritz ML, Ayus JC. Intravenous fluid management for the acutely ill child. *Curr Opin Pediatr* 2011;23(2):186-93.
40. Casado M, Bosch J, García-Pagan JC, Bru C, et al. Clinical events after transjugular intrahepatic portosystemic shunt: correlation with hemodynamic findings. *Gastroenterology* 1998;114(6):1296-303.
41. Schrier RW, Arroyo V, Bernardi M, Epstein M, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;8(5):1151-7.
42. Pais P, Avner ED. Nephrotic Syndrome. In: Kliegman RM, Stanton B, St. Geme J, Schor NF, eds. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier; 2016. Pgs.2521-8.
43. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol* 2013;11(2):123-30.
44. Sort P, Navasa M, Arroyo V, Aldeguer X, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341(6):403-9.
45. Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. *Hepatology* 2012; 55(4):1172-81.
46. Das B, Acharya U, Purohit A. Comparative utility of sero ascites albumin gradient and ascitic fluid total protein for differential diagnosis of ascites. *Indian Pediatr* 1998;35(6):542-5.
47. Grabau CM, Crago SF, Hoff LK, Simon JA, et al. Performance standards for therapeutic abdominal paracentesis. *Hepatology* 2004;40(2):484-8.
48. Pache I, Bilodeau M. Severe haemorrhage following abdominal paracentesis for ascites in patients with liver disease. *Aliment Pharmacol Ther* 2005;21(5):525-9.
49. Mannucci PM. Abnormal hemostasis tests and bleeding in chronic liver disease: are they related? No. *J Thromb Haemost* 2006;4(4):721-3.
50. Reverter JC. Abnormal hemostasis tests and bleeding in chronic liver disease: are they related? Yes. *J Thromb Haemost* 2006;4(4):717-20.
51. Matsushita T, Saito H. Abnormal hemostasis tests and bleeding in chronic liver disease: are they related? No, but they need a careful look. *J Thromb Haemost* 2006;4(9): 2066-7.
52. Tripodi A, Mannucci PM. Abnormalities of hemostasis in chronic liver disease: reappraisal of their clinical significance and need for clinical and laboratory research. *J Hepatol* 2007;46(4):727-33.
53. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2011;365(2):147-56.
54. BNF for Children 2012-2013. London: BMJ Group; 2012. Pg.81.
55. Tomlin S, ed. Paediatric Formulary. 9th ed. Guy's & St Thomas' NHS Foundation Trust; 2010.
56. BNF for Children 2012-2013. London: BMJ Group; 2012:p.80.
57. Thomsen TW, Shaffer RW, White B, Setnik G. Videos in clinical medicine. Paracentesis. *N Engl J Med* 2006;355 (19):e21.
58. Kramer RE, Sokol RJ, Yerushalmi B, Liu E, et al. Large-volume paracentesis in the management of ascites in children. *J Pediatr Gastroenterol Nutr* 2001;33(3):245-9.
59. Sen Sarma M, Yachha SK, Bhatia V, Srivastava A, et al. Safety, complications and outcome of large volume paracentesis with or without albumin therapy in children with severe ascites due to liver disease. *J Hepatol* 2015;63(5):1126-32.
60. Nightingale S, Ng VL. Optimizing nutritional management in children with chronic liver disease. *Pediatr Clin North Am* 2009;56(5):1161-83.
61. Smart KM, Alex G, Hardikar W. Feeding the child with liver disease: a review and practical clinical guide. *J Gastroenterol Hepatol* 2011;26(5):810-5.
62. Young S, Kwarta E, Azzam R, Sentongo T. Nutrition assessment and support in children with end-stage liver disease. *Nutr Clin Pract* 2013;28(3):317-29.
63. Greer R, Lehnert M, Lewindon P, Cleghorn GJ, et al. Body composition and components of energy expenditure in children with end-stage liver disease. *J Pediatr Gastroenterol Nutr* 2003;36(3):358-63.